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ANTINOCICEPTIVE AND OTHER BEHAVIOURAL EFFECTS OF ABNORMAL
VESTIBULAR STIMULATION IN THE RAT

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
Doctor of Philosophy

in

THE FACULTY OF GRADUATE STUDIES

Department of Psychology

We accept this thesis as conforming to the
required standard

THE UNIVERSITY OF BRITISH COLUMBIA

March 1981

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ABSTRACT

Exposure to abnormal motion produces a variety of behavioural effects in both human and non-human species. The general purpose of the present studies was to produce and investigate some of these effects in the laboratory rat.

In the first series of experiments, rats displayed appreciable decreases in reactivity to noxious stimuli presented after exposure to brief periods of different types of motion. This motion-induced antinociception was found to persist for periods of up to 15 min.

A second series of experiments examined the role of the vestibular system in this motion-induced antinociception phenomenon. Rats whose peripheral vestibular apparatus had been rendered insensitive to accelerative stimuli did not exhibit motion-induced antinociception. Subsequent experiments attempted to delineate the role of some individual components of the central vestibular system but no single component investigated was found to play a major role in the production of antinociception. Experiments in this and the preceding series of experiments also demonstrated that the antinociceptive effect could be dissociated from dizziness or acute vestibular dysfunction.

In the third series of experiments, the physiological mechanisms by which vestibular stimulation produces antinociception were investigated. Experiments in this series demonstrated that motion-induced antinociception could be blocked by opiate antagonists and that the motion-induced antinociceptive effect showed cross-tolerance with chronic

morphine administration. These two findings strongly implicate an endogenous opiate peptide (endorphin) system as the underlying mechanism for motion-induced antinociception. The brief duration of the antinociceptive effect and the fact that disruption of the pituitary-adrenal axis did not affect motion-induced antinociception suggested that the opiate peptides involved were the enkephalins rather than B-endorphin.

Other behavioural effects of abnormal motion were reported in the fourth series of experiments. The resemblance between the symptoms of motion sickness and those of opiate administration suggested that endogenous opiate peptides may mediate motion sickness. Although exposure to abnormal motion did produce a substantial conditioned taste aversion (a behavioural assay for motion sickness in the rat), attempts to attenuate the aversion with two different opiate antagonists were unsuccessful. These results suggested that abnormal motion exerts its illness-producing effects through some mechanism other than an endogenous opiate system. In the final experiment, rats that were exposed to a brief period of abnormal motion subsequently exhibited a suppression of defensive burying behaviour that was similar to that produced by anxiolytic drugs.

The results of this study indicate that abnormal vestibular stimulation may have a variety of different behavioural effects in rats. However, it appears that no single mechanism can account for all of these effects.

TABLE OF CONTENTS

ABSTRACT	ii
LIST OF TABLES	vi
LIST OF FIGURES	vii
ACKNOWLEDGEMENTS	ix
INTRODUCTION	1
Behavioural Effects of Abnormal	
Vestibular Stimulation	5
Motion Sickness	6
Signs and Symptoms	6
Biochemical Changes	9
Susceptibility to Motion Sickness	11
Soporific and Drowsiness-Inducing Properties	
of Abnormal Motion	12
Calming or Tranquilizing Effects	
of Abnormal Motion	13
Antinociceptive Effects of	
Abnormal Motion	15
SECTION I - The Antinociceptive Effects of Abnormal Motion	22
Experiment 1	23
Experiment 2	29
Experiment 3	38
Experiment 4	43
Experiment 5	48
General Discussion - Section I	54
SECTION II - Vestibular Mediation of the Antinociceptive	
Phenomenon	59
Experiment 6	60

Experiment 7	69
Experiment 8	82
General Discussion - Section II	92
SECTION III - Mechanisms of Motion-Induced Analgesia	96
Experiment 9	102
Experiment 10	108
Experiment 11	116
Experiment 12	128
General Discussion - Section III	137
SECTION IV - Other Behavioural Effects of Abnormal Motion .	140
Experiment 13	141
Experiment 14	155
Experiment 15	163
GENERAL DISCUSSION	177
Motion-Induced Antinociception	180
Physiological Mechanisms of Motion-Induced	
Antinociception	180
Stress-Induced and Motion-Induced Analgesia .	183
Endogenous Opiate Mechanisms	184
Non-Opiate Mechanisms	185
Applications of the Motion-Induced	
Analgesia Phenomenon	188
Motion Sickness	191
Calming Effects of Abnormal Motion	195
Conclusions	198
REFERENCES	201

LIST OF TABLES

1. Comparison of some signs and symptoms elicited by
opiate (morphine) administration and by exposure
to abnormal motion 144

LIST OF FIGURES

1.	Mean tail movement and tail withdrawal latencies for rats exposed to brief periods of motion or restraint.	18
2.	Mean tail withdrawal latencies for rats exposed to restraint or to one of two different motion conditions in Experiment 1.	28
3.	Schematic representation of the motion device used in Experiment 2.	33
4.	Mean tail withdrawal latencies for rats in Experiment 2.	36
5.	Mean balance beam scores for rats tested in one of the four different motion conditions in Experiment 3.	41
6.	Results of analgesia testing in Experiment 4.	47
7.	Mean tail withdrawal latencies for rats exposed to 5-, 30-, 300-, or 900-sec periods of the motion treatment used in Experiment 5.	51
8.	Effects of peripheral vestibular apparatus lesions on tail withdrawal latencies in Experiment 6.	66
9.	Results of vestibular dysfunction tests in Experiment 6.	68
10.	Histological results for Experiment 7.	74
11.	Results of Experiment 7 depicting the effects of abnormal motion on tail withdrawal latencies in the MVN, LVN, and CER lesion groups.	77
12.	Effects of motion and restraint on balance beam	

scores in the MVN, LVN, CER, and SHAM lesion groups of Experiment 7.	79
13. Locations of the stimulating electrodes in Experiment 8.	86
14. Effects of electrical stimulation in the MVN, LVN, and CER on tail withdrawal latencies in Experiment 8.	89
15. Effects of various doses of naloxone on the motion-induced analgesia phenomenon.	106
16. Differential effects of naloxone on motion, restraint, and cold-water swim treatments in Experiment 10.	111
17. Mean balance scores for rats receiving saline or naloxone in the motion and restraint conditions of Experiment 10.	115
18. Effects of chronic morphine, motion, saline, or restraint treatments in Experiment 11.	121
19. Results of the acute test phase of Experiment 11.	124
20. Effects of adrenalectomy on motion-induced analgesia.	135
21. Mean saccharin preference before and after pairing with abnormal motion.	152
22. Mean saccharin preference after pairing of saccharin and motion in rats pretreated with naltrexone.	159
23. Effects of brief preexposure to motion or shock on defensive burying behaviour.	170

ACKNOWLEDGEMENTS

The author wishes to thank Dr. B.B. Gorzalka for his assistance and encouragement as supervisor of the author's dissertation program. The assistance of the remaining members of the thesis committee, Drs. J.P.J. Pinel and K. Craig is also gratefully acknowledged.

The author also wishes to acknowledge the contributions of a number of other people to this thesis: Lori J. Terlecki for her assistance and encouragement, Sandra Kleinfeld for her invaluable technical support, and H. Umedaly for assistance in performing experiments 1 and 9.

This research was pursued during the author's tenure of a Natural Sciences and Engineering Research Council post-graduate scholarship and a University of British Columbia post-graduate scholarship and was supported by a Natural Sciences and Engineering Research Council operating grant and a Province of British Columbia Youth Employment grant.

INTRODUCTION

The vestibular system is an important and highly complex sensory system that exists in some form in many animal species (Baloh & Honrubia, 1979; Brodal & Pompeiano, 1972; Brodal, Pompeiano, & Walberg, 1962; Clark, 1970; Kornhuber, 1974; Naunton, 1975). This system is highly specialized for the detection and central nervous system integration of accelerative movements of the head that are either generated by the organism or passively experienced (Baloh & Honrubia, 1979; Goldstein, 1974). This specialized capacity for the detection of motion and head movement is intrinsic to the role of the vestibular system in posture and spatial orientation. Although the anatomy and neurophysiology of the vestibular system have been well studied with respect to postural and orienting reflexes (see Howard & Templeton, 1966; Parker, 1980; Roberts, 1967), the involvement of the vestibular system in other forms of behaviour has been largely ignored by psychologists and behavioural neuroscientists.

One difficulty in studying the role of the vestibular system in behaviour lies in the nature of normal vestibular functioning. The vestibular system is unique among sensory systems in that it is essentially 'silent' in the course of its normal functioning (Reason & Brand, 1975, p. 85). That is, vestibular functioning does not enter consciousness in the same manner as do visual, auditory, gustatory, or tactile sensations. The unobtrusive nature of the vestibular system means that any behavioural consequences of vestibular activity are obvious only when some degree of abnormal vestibular activation exists. One

way this abnormal activity may be generated is by exposure to abnormal acceleration (Clark, 1970; Parker, 1980; Reason & Brand, 1975), i.e. acceleration that would not typically be generated by the organism in the course of its normal motor activity. The study of the role of the vestibular system in behaviour then, relies to a great extent on the study of the behavioural consequences of exposure to abnormal motion although abnormal vestibular activity may also be induced pharmacologically (Money & Myles, 1974), or by disease (Hood, 1978).

There are a number of reliable behavioural effects that result from exposure of an organism to abnormal motion. These behavioural consequences include: nausea, vomiting, and a number of related symptoms (motion sickness); depression and dysphoria in humans; and a soporific or tranquilizing effect. Although some aspects of some of these behavioural consequences of exposure to abnormal motion have been well studied (e.g. motion sickness), the study of the behavioural consequences of exposure to abnormal motion has, to the surprise of some authors (e.g. Clark, 1970; Money, 1970; Reason & Brand, 1975), received little attention. Not only is there a paucity of information concerning these behavioural consequences, little information exists concerning the physiological mechanisms that mediate these behavioural consequences. Even motion sickness, perhaps the best known consequence of abnormal vestibular stimulation, is poorly understood in terms of its physiological mechanisms (Money, 1970; Reason & Brand, 1975).

A previously unexplored behavioural consequence of abnormal motion has recently been investigated by Gray (unpublished data,

1979). Following brief periods of abnormal vestibular stimulation, it appears that there is an attenuation of responsiveness to noxious or painful stimuli. This effect has not been extensively studied and is described in more detail below. Study of this antinociceptive effect of abnormal motion could possibly provide some indication of the mechanisms underlying the perception of pain.

The purpose of the present thesis was to investigate some of the behavioural effects of abnormal motion and the possible physiological mechanisms responsible for these effects. Particular emphasis was placed on the nature of the antinociceptive effect described above and the physiological mechanisms underlying it.

Although the behavioural effects of abnormal vestibular stimulation have not been extensively studied in the past, their study would seem to warrant attention for a variety of reasons. One compelling rationale for their investigation is of an applied nature. For example, as society advances in transport technology, the operators and passengers of these vehicles are exposed to a great number of abnormal forces. An understanding of the consequences of exposure to these abnormal forces would seem essential to the safety and success of these operations.

Motion sickness (air sickness, space sickness, sea sickness), for example, is an extremely common response to exposure to abnormal forces (Johnson & Jongkees, 1974; Money, 1970; Reason & Brand, 1975). As will be discussed in greater detail below, motion sickness represents a constellation of behavioural effects including nausea, vomiting, drowsiness,

depression and dysphoria, cold sweating, pallor, and various other behavioural and physiological reactions (Johnson & Jongkees, 1974; Money, 1970; Reason & Brand, 1975). Although perhaps not a life threatening disorder in itself, it is clear that motion sickness could well affect the optimal performance of subjects exhibiting this syndrome. For example, a number of missions in space have been complicated by the motion sickness of the flight crew (see Graybiel, 1980; Reason & Brand, 1975; Schneider & Crosby, 1980). The possibility of impaired performance resulting from exposure to abnormal forces has obvious implications in both military and civilian operations such as troop transport, flight safety, etc.

A second reason for interest in the behavioural effects of vestibular activation concerns the possible mediation of the effects of drugs and toxic substances by the vestibular system. Gutner, Gould, and Batterman (1952) and Money (1970), for example, have suggested that there is a synergistic effect of at least some drug treatments and vestibular activity in producing some of the adverse side effects of these drugs. The nausea and vomiting produced by morphine (Gutner et al., 1952; Jaffe & Martin, 1975) or apomorphine (Money, 1970) are much less evident in patients who remain motionless than in patients who are ambulatory. Treisman (1977) has recently suggested that motion sickness is actually a highly adaptive mechanism for the detection, elimination, and subsequent avoidance of naturally occurring toxic substances. According to this hypothesis, toxic substances can disrupt the usual congruence between the senses used in spatial orientation (i.e. the vestibular, visual, and

proprioceptive systems) to produce a situation that resembles the effects of abnormal vestibular stimulation. One of these effects is vomiting, a behaviour that may hasten the elimination of any remaining toxic substance. Vomiting produced by a toxic substance may cause an organism to avoid that substance in the future; i.e. it may establish a conditioned taste aversion (see Garcia & Hankins, 1977; Gustavson, 1977).

Although the exact nature of the interaction between drugs and the vestibular system is not known, it is clear that at least some drugs exert some of their effects by a direct action on the vestibular system. Money and Myles (1974) for example, have found that alcohol produces the well-known positional alcohol nystagmus (PAN) effect through a direct action on the cupula of the labyrinthine canals. PAN is a repetitive cycle of slow drifting eye movements in one direction followed by a rapid return in the opposite direction, the directions of the slow and fast phases being dependent on head position after ingestion of a moderate amount of alcohol. This effect appears to rely more on the physical properties of the drug (i.e. density) than on a direct pharmacological effect, but nonetheless illustrates that drugs can and do exert some of their effects through vestibular mechanisms. Many drugs produce nausea, dizziness, and vomiting (see Goodman & Gilman, 1975; Rotenberg, 1978), and the vestibular system may prove to play an important role in their etiology.

BEHAVIOURAL EFFECTS OF ABNORMAL VESTIBULAR STIMULATION

From a survey of the literature, it appears that there are at least three kinds of behavioural effects of abnormal motion.

These include: illness induced by motion (motion sickness), a soporific or sleep inducing effect, and a calming or anxiolytic effect. In addition, recent studies in our own laboratory have suggested that exposure to abnormal motion can also have antinociceptive effects. The purpose of the following review is to describe these behavioural effects in greater detail. Although it may seem that a disproportionate amount of discussion is devoted to motion sickness, it should be noted that this disproportionality simply reflects the extent of the relevant literature.

Motion Sickness

Motion sickness is perhaps the best known effect of abnormal vestibular activity. This disorder has been known in humans since the time of the ancient Greeks as sea sickness (Reason & Brand, 1975) and has recently become of great interest because of recent advances in air and space travel. The term motion sickness refers to illness produced by exposure to abnormal force environments that results in a conflict between (Reason, 1978) or an attempt to reintegrate (Treisman, 1977) information from various senses providing spatial information (e.g., cinerama sickness, simulator sickness). Motion sickness is not a unitary phenomenon and actually represents a wide variety of symptoms and signs produced as a result of exposure to abnormal vestibular activity. The most obvious and reliable of these are discussed below.

Signs and symptoms

Nausea and vomiting. Nausea (the feeling of impending emesis) and vomiting (the actual act of emesis) are usually

considered as the endpoint or most severe symptoms of the motion sickness syndrome (Money, 1970; Reason & Brand, 1975). Vomiting is not an inevitable consequence of nausea. In experimentally produced motion sickness, it is possible to adjust the stimulus conditions so that vomiting does not occur, even though subjects report nausea to be present (Kennedy & Graybiel, 1965). The nausea and vomiting seen in motion sickness is indistinguishable from nausea and vomiting produced as a result of the application of other emetic agents (Money, 1970; Reason & Brand, 1975). If the area postrema, a sensitive "trigger zone" for emesis, is removed from the brainstem of an experimental animal, that animal is rendered insensitive to vomiting produced both by centrally acting emetic drugs (Wang & Borison, 1952) and by motion (Brizzee, Ordy, & Mehler, 1980; Money, 1970). Emetic agents, such as copper sulfate, that are thought to exert their emetic actions peripherally, such as copper sulfate, are still effective in inducing emesis in such an animal (Wang, 1965). This fact suggests that abnormal motion exerts its emetic actions through some mechanism in the central nervous system rather than through a peripheral mechanism. The exact nature of this central mechanism however, remains unknown.

Pallor and cold sweating. In addition to nausea and vomiting, the two most commonly observed symptoms of motion sickness are pallor, the result of vasoconstriction of the skin, and cold sweating, which is perspiration in the absence of an adequate thermal stimulus. Although these symptoms can result from activation of the autonomic nervous system, Money (1970) has suggested that autonomic nervous system activation is not

necessarily the cause of pallor and cold sweating in motion sickness but that pallor and cold sweating may be the result of the liberation of some other circulating chemical.

It should be remembered that although pallor and cold sweating often occur during motion sickness, their presence alone is not sufficient to justify a diagnosis of motion sickness. Anxiety, for example, is sufficient to provoke pallor and cold sweating in the absence of unusual motion (Reason & Brand, 1975, p. 44).

Depression and dysphoria. Motion sickness is accompanied by profound dysphoria and a very severe state of depression, apathy, and lethargy in some individuals (Money, 1970; Reason & Brand, 1975). The degree of depression appears to be completely at odds with the actual seriousness of the malady, and persons suffering from motion sickness have often been noted to wish for death (see Reason & Brand, 1975). This depression can be so severe that Money (1970) has suggested that the mechanisms involved in this form of acute depression may also be involved in other forms of pathological depression. However, despite its significance, reports of motion-induced depression have been anecdotal; little or no systematic evidence exists concerning its nature.

Additional signs and symptoms. There are a number of other signs and symptoms that may occasionally result from exposure to abnormal motion conditions.

Increased salivation is frequently noted in conjunction with nausea in both humans and other animals (Money, 1970; Reason & Brand, 1975). In humans, increased salivation is

inferred by more frequent swallowing whereas in other animals saliva may be evident dripping from the mouth.

An increase in respiration rate independent of the presence of other symptoms is sometimes noted (Reason & Brand, 1975), and panting frequently accompanies motion sickness in canines (Babkin, Dworkin, & Schacter, 1966).

Following prolonged exposure to abnormal motion, constipation and loss of gastro-intestinal tone are frequently found, primarily in humans (Reason & Brand, 1975). In addition to decreased gastrointestinal tone, a suppression of urinary output has also been noted (Graybiel, Kennedy, Knoblock, Guedry, Hertz, McCleod, Colehur, Miller, & Fregly, 1965).

Frontal headache is another commonly reported symptom during the early stages of motion sickness, particularly in situations where the provocative stimulus involves cross-coupled angular accelerations (Reason & Brand, 1975). Other symptoms include anorexia, mental confusion, feelings of coldness in the face and extremities, and a feeling of increased overall bodily warmth (Reason & Brand, 1975). A few authors (e.g., Chinn, Noell, & Smith, 1950) have noted that the development of seasickness was associated with electroencephalographic changes. An activation of the alpha rhythm and a slowing of the dominant wave frequency were found in cases of persistent or chronic motion sickness.

Biochemical changes.

There are also a number of biochemical and hormonal changes that result from exposure to abnormal motion environments.

During prolonged (i.e., 12 day) exposure to abnormal

vestibular stimulation in human subjects, decreases in glucose utilization on the first day of rotation were found, followed on subsequent days by a greatly increased glucose utilization rate (Graybiel et al., 1965). Lactic acid dehydrogenase concentrations in blood were found to follow a pattern similar to that found for glucose utilization.

In several studies, levels of hormones typically released in response to stressful stimulation were found to be elevated following exposure to abnormal motion. Increased secretion of adrenal corticosteroids (e.g., cortisol) and their metabolic products has been found to result from abnormal vestibular activity in both humans (Eversmann, Gottsman, Uhlich, Ulbrecht, von Worden, & Scriba, 1978) and other animals (Fox, Kiel, Daunton, Thomsom, Dictor, & Chee, 1980). In addition, increased secretion of the adrenal catecholamines, epinephrine and norepinephrine, has also been noted (Colehour, 1965; Money, 1970; Reason & Brand, 1975). None of these changes was observed in subjects with impaired vestibular sensitivity, suggesting that these hormonal effects depended on the integrity of the vestibular system.

These hormonal and biochemical changes suggest that abnormal motion may act as a stressor. A stressor is usually defined in terms of an activation of the pituitary-adrenal axis (Leshner, 1979; Selye, 1956). Increased secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary results in the increased secretion of steroids from the adrenal cortices whereas adrenal medullary catecholamines are secreted in response to activation of the parasympathetic division of the

autonomic nervous system (Mason, 1968).

The decreased urine production found during motion sickness is thought to result from an increased output of antidiuretic hormone (ADH). ADH, also known as vasopressin, is released from the posterior pituitary and acts to decrease urinary output (Levine, 1972).

Susceptibility to motion sickness

Although individual susceptibility to motion sickness varies, it has been suggested that almost any subject may be made motion sick given the appropriate stimulus conditions (Reason & Brand, 1975). It appears, however, that the vestibular system is a necessary condition for the occurrence of motion sickness; it is difficult, if not impossible, to induce motion sickness in subjects with severely defective vestibular systems (Graybiel, 1965; Money & Friedberg, 1964). A wide variety of species including dogs, cats, horses, sheep, monkeys, seals, birds, cows, and even codfish have been reported to be susceptible (Money, 1970).

Motion sickness has also been reported to exist in the rat, a species that does not vomit (Coil & Garcia, 1977; Hatcher & Weiss, 1923). Because the rat does not exhibit emesis, the most obvious and reliable sign of motion sickness, other techniques have been utilized as assays of motion-induced illness in this species. These techniques include the formation of conditioned taste aversions to novel flavours following a period of abnormal motion (Green & Rachlin, 1973, 1976; Haroutunian & Riccio, 1975; Riccio & Haroutunian, 1976; Roy & Brizzee, 1979); an increased willingness to consume a non-nutritive clay or soil mixture

(pica or geophagia) following abnormal motion (Mitchell, Krusemark, & Hafner, 1977; Mitchell, Laycock, & Stephens, 1977), suppression of drinking following abnormal motion (Haroutunian, Riccio, & Gans, 1976), and decreased motor activity during the period of abnormal motion (Eskin & Riccio, 1966; Riccio & Thach, 1968). Although these studies would seem to suggest that abnormal motion is aversive for the rat, it is not as obvious that all of the behaviours affected by abnormal motion are signs of motion sickness. However, these studies and others (e.g., Weissman & Gottlieb, 1969) do clearly demonstrate that rats are sensitive to abnormal motion and abnormal vestibular activity.

It should be noted that this review does not do justice to the extensive body of literature on motion sickness (e.g., see Johnson & Jongkees, 1974; Money, 1970; Reason & Brand, 1975). It does however, illustrate that there do exist a number of reliable and quantifiable effects of abnormal vestibular stimulation that may be studied in a laboratory situation.

Soporific and Drowsiness Inducing Properties of Abnormal Motion

Drowsiness and sleep in situations that induce motion sickness have been reported in a number of investigations involving both short (Suri, Crampton, & Daunton, 1979) and long-term (Reason & Graybiel, 1971) exposure of humans (Graybiel & Knepton, 1976) and other species (Ordj & Brizzee, 1980; Suri et al., 1979) to abnormal motion. Furthermore, Chinn et al. (1950) found electroencephalographic patterns in seasick individuals that were suggestive of drowsiness.

Although the sleep-inducing effect of abnormal vestibular activity is often found in conjunction with the appearance of

motion sickness, the sleep-inducing and illness-inducing properties of vestibular stimulation appear to represent two distinct phenomena. Graybiel and Knepton (1976) have in fact described the drowsiness-inducing effect of abnormal motion as a distinct syndrome: the Sopite syndrome. Drowsiness is often found in subjects that are otherwise completely unaffected (Graybiel & Knepton, 1976). Furthermore, the sleep-inducing effect of abnormal motion often persists, even after the other illness-inducing effects of abnormal motion have disappeared through adaptation to the continuing stimulus (Reason & Brand, 1975). Recent evidence suggests that abnormal vestibular stimulation is also extremely effective in inducing sleep in human infants (Pederson & Ter Vrugt, 1973; Ter Vrugt & Pederson, 1973). This is particularly interesting in view of the fact that infants are generally reported to be immune to the illness-inducing properties of abnormal motion (Reason & Brand, 1975).

It would seem then, that there exists a sleep-inducing effect of abnormal motion and that this effect, although capable of being induced by the same stimuli that can provoke motion sickness, is a separate and distinct phenomenon. Although Graybiel (1969) has suggested that vestibular activity affects the neural mechanisms for sleep through the ascending reticular formation, the exact nature of this sleep-inducing effect and its physiological mechanisms remain obscure.

Calming or Tranquilizing Effects of Abnormal Motion

A number of authors have suggested that abnormal vestibular stimulation is capable of having a tranquilizing or calming effect.

It should be noted here that there are difficulties in attempting to characterize a particular behavioural effect as a soporific, calming, or tranquilizing effect because the behavioural manifestations of each of these effects may be quite similar (e.g., reduced locomotor activity, reduced vocalization). In no case has an attempt been made to distinguish among these possible effects, and hence it is not clear if these various descriptions of sleep-inducing or calming effects represent the same phenomenon or different phenomena.

Nevertheless, an apparent calming effect resulting from vestibular stimulation has been noted in a variety of experimental situations (Weeks, 1979). Korner and Thoman (1973), for example, compared the relative efficacy of vestibular stimulation (rocking) and other techniques of calming or soothing human infants. Techniques that involved short periods of vestibular stimulation were found to be more effective than the other techniques in reducing the duration of crying and other signs of distress. Pederson and Ter Vrugt (1973) and Ter Vrugt and Pederson (1973) found vertical rocking to be more effective than other forms of vestibular stimulation in calming infants and this calming effect was greater at higher rocking frequencies (up to 72 cycles per minute). At the higher frequencies, the calming effect appeared to greatly outlast the duration of the vestibular stimulation. Recent evidence has also suggested that brief periods of abnormal motion may have some long-term therapeutic value in hyper-kinetic children (Bhatara, Clark, & Arnold, 1978) and in non-paranoid schizophrenics (Bailey, 1978). Exposure of mentally ill

patients to abnormal motion environments as a form of therapy (or management) has a surprisingly long history (Lindzey, Hall, & Thompson, 1975, p. 670). However, the effectiveness of this treatment is yet to be determined.

In animals, vestibular stimulation has been reported to reduce distress in infant rats separated from their mothers (Thoman & Korner, 1971) although the validity of this finding has been questioned by others (LaBarba & Stewart, 1978). Staubli and Huston (1979), in a report concerning a new avoidance learning paradigm, state that rats were swung back and forth at the end of the experimenter's outstretched arm in order to "calm" them before placement in the experimental apparatus. The term "calmed" is not further defined but possibly means that the animal remained motionless when placed in the apparatus. This decrease in motor activity in rats has also been noted in response to exposure to a rotating open field (Eskin & Riccio, 1966).

Although it is not yet clear whether the term "calming" is an adequate label for such effects, the evidence is quite clear that abnormal vestibular activity can reduce an organism's reactivity to its environment.

Antinociceptive Effects of Abnormal Motion

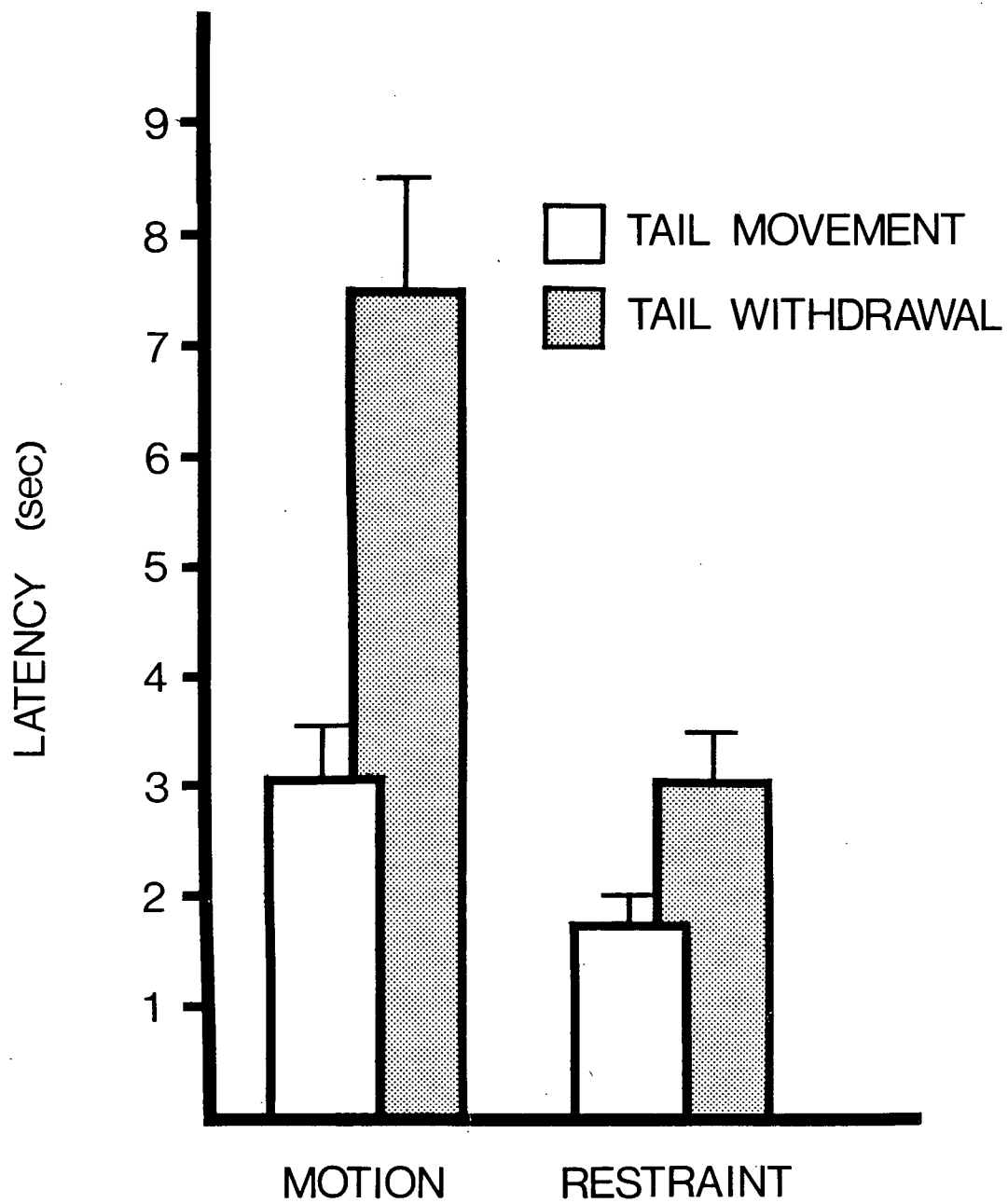
A brief period of swinging motion or vertical oscillation, such as that utilized by Staubli & Huston (1979), produces an effect commonly observed in the animal laboratory. Animals undergoing this treatment appear calmed and react much less violently to an injection or other acute noxious treatment than do animals not subjected to abnormal motion.

This seemingly reduced reactivity to noxious stimuli following a brief period of abnormal motion has led to the fortuitous finding of a possible endogenous pain modulation system that is triggered by vestibular stimulation. Gray (unpublished data, 1979) enclosed laboratory rats in cylindrical restraining tubes and exposed the rats to either 25 sec of manually generated back and forth swinging motion (180° oscillations in a 1.5 m diameter vertical arc, longitudinal axis of rat parallel to the plane of rotation, approximately 15 cycles per session), or an equivalent period of comparable restraint only. Immediately after the motion or restraint, a standard hot-water test for analgesia (Grotto & Sulman, 1967; Sewell & Spencer, 1976) was administered. During the test, the tail of the rat was immersed in hot (55°C) water and the latencies to the first movement of the tail and latency to complete withdrawal of the tail from the water were recorded. As shown in Figure 1, rats that had been exposed to abnormal motion had significantly longer latencies to both first movement and tail withdrawal ($t=2.74$, $df=10$, $p<.05$; $t=4.15$, $df=10$, $p<.05$, respectively).

It would seem from these data that there exists a quantifiable decrement in the responsiveness of rats to a noxious challenge following abnormal motion in space. The exact nature of this antinociceptive effect of abnormal motion is unknown and one of the primary purposes of the present thesis was to further explore the nature of this antinociceptive effect of abnormal motion.

The antinociceptive response was chosen for further

FIGURE 1. Mean tail movement and tail withdrawal latencies for rats exposed to brief periods of motion or restraint. Lines on bars indicate standard error of the mean.



intensive study for a number of reasons. First, the study of an antinociceptive response to abnormal motion may provide information relating to endogenous pain control mechanisms. Endogenous pain control mechanisms, inferred by control of pain by non-pharmacological analgesic agents, have been thought to exist for some time (see Melzack, 1973; Melzack & Dennis, 1978). However, little information concerning the underlying neurochemical mediation was available until the recent discovery of endogenous opiate peptides in the central nervous system (for reviews, see Barchas, Akil, Elliot, Holman, & Watson, 1978; Goldstein, 1978; Kosterlitz & Hughes, 1978; Terenius, 1978). These opiate peptides are presumed to be released in response to some stimuli and act at stereospecific receptor sites (Snyder, 1975; Snyder & Pert, 1975) in much the same fashion as the morphine molecule (Snyder, 1977). In addition to this endogenous opiate model of endogenous pain modulation, it appears that a non-opiate form of endogenous pain modulation may also exist (e.g. Bodnar, Kelly, Brutus, Greenman, & Glusman, 1980; Bodnar, Kelly, Steiner, & Glusman, 1978; Spiaggia, Bodnar, Kelly, & Glusman, 1979). If these mechanisms and the stimuli that activate them could be elucidated, the antinociceptive effect of abnormal vestibular stimulation could conceivably have some application as a non-pharmacological means of pain control.

Second, an investigation of the physiological mechanisms underlying the easily quantifiable antinociceptive effect of abnormal vestibular stimulation may provide information relating to the mechanisms underlying the other behavioural effects of abnormal motion. It is possible that abnormal vestibular

activity activates a single physiological mechanism that may then be manifest in a variety of behavioural changes. On the other hand, it is also possible that abnormal vestibular stimulation activates a number of different mechanisms, each responsible for a particular behavioural effect.

Third, the use of an easily quantified, previously validated behavioural measure allows a relatively precise evaluation of the antinociceptive effects of various types and durations of motion. Hence, the effects and effectiveness of various types and durations of motion may be easily investigated.

The experiments described in the present thesis are presented in the following sequence. In Section I, the existence of an antinociceptive response to abnormal motion was confirmed, and parametric data concerning the type and duration of motion effective in inducing antinociception and the duration and magnitude of the antinociceptive response are presented. The main purpose of the experiments in this section therefore, was to explore the characteristics of the antinociceptive effect and the properties of the stimulus that are effective in inducing the effect.

Section II includes a series of experiments that were directed at determining the role of the vestibular system in the antinociceptive effect of motion. It is possible that stimuli effective in inducing antinociception have little or no effect on vestibular function. The first experiment in this section investigated this possibility by examining the effects of motion in animals whose vestibular apparatus had been rendered non-

functional. Additional experiments involving both lesion and electrical stimulation techniques attempted to investigate the role of central vestibular components in the antinociceptive effect of abnormal motion.

Section III was devoted to an investigation of the possible physiological mechanisms of motion-induced antinociception and used a variety of pharmacological and surgical manipulations. Other behavioural effects of vestibular stimulation in animals were examined in Section IV. Motion sickness and its physiological basis were investigated in the first two experiments of this section, and a third experiment was directed at quantifying a possible anxiolytic or calming effect of vestibular stimulation.

SECTION I - The Antinociceptive Effects of Abnormal Motion

The experiments described in Section I were directed at confirming the the existence of an antinociceptive effect of abnormal motion and exploring some of the parameters governing the effect. Specifically, Experiment 1 confirmed the existence of the antinociceptive effect and examined the duration of this effect, whereas Experiment 2 examined the antinociceptive effects of various types of motion. Experiments 3 and 4 explored two important issues related to the phenomenon: the degree of vestibular dysfunction produced by the abnormal motion and the generality of the antinociceptive effect. The final experiment in this section, Experiment 5, examined the duration of the motion stimulus necessary to elicit an antinociceptive effect and the duration of the antinociceptive response elicited by a complex form of motion.

In these and subsequent studies, the rat hot-water tail immersion test (tail flick test, tail withdrawal test) was utilized as an assay for the presence of an antinociceptive effect (Grotto & Sulman, 1967; Sewell & Spencer, 1976). This and other tests utilizing exposure of the rat's tail to a thermal stimulus (i.e., radiant heat, D'Amour & Smith, 1941) have been widely used as measures of analgesia (Glick, 1976). The tail flick or withdrawal response was chosen as the dependent measure for a variety of reasons. The tail flick response is mediated spinally (Hayes, Bennet, Newlon, & Mayer, 1978), and hence does not require the integrity of supra-spinal structures for its appearance (Hayes, Price, Bennet, Wilcox, & Mayer, 1978). The tail withdrawal test also accurately reflects

and predicts the relative potency of various analgesic agents in humans (e.g., Sewell & Spencer, 1976). The tail withdrawal response has other advantages in that it is a straightforward and easily scored behavioural response and the exposure to the pain-producing stimulus is terminated by the subject, thus ensuring that excessive pain is not produced. The use of hot-water as the pain-producing stimulus has advantages in that the temperature of the stimulus may be easily controlled and the thermal stimulus applied uniformly, in contrast to radiant heat techniques that require blackening of the skin to insure uniform stimulus intensity.

Experiment 1

Experiment 1 was an attempt to replicate and further explore the nature of the antinociceptive effect found by Gray (unpublished data, 1979) using swinging as means of inducing antinociception. Repeated tail withdrawal tests were conducted following cessation of the motion stimulus in order to determine the duration of the effect. In addition, the effectiveness of two different motion durations in producing antinociception was evaluated.

METHOD

Subjects

Serving as subjects in the present experiment were 30 naive male hooded (Long-Evans) rats (obtained from Canadian Breeding Farms and Laboratories, St. Constant, Que.) weighing approximately 350 gm. The rats were housed in groups of six in standard hanging wire cages (24 X 64 X 18 cm) under a reversed

12 hr light/dark (lights off at 0800) lighting cycle. All subjects remained in the colony room for a minimum of 14 days prior to participation in the experiment. Food and water were freely available and the colony temperature was nominally maintained at 21° C.

Apparatus

A cardboard tube, 21.5 cm long and 7.5 cm in diameter served as the restraining device. Two removable ventilated plastic caps at each end of the tube prevented the rats from escaping. The dimensions of the restraining tube were such that the rats were not unduly constrained yet could not easily reverse direction within the tube. A constant temperature circulating water bath (Blue M, Magni-Whirl constant temperature bath) was used to provide a constant (52° C) thermal stimulus.

Procedure

Rats were randomly assigned to one of three conditions (n = 10); a restraint-only control group, or to one of two different motion duration conditions. The motion was a manually-produced semicircular oscillation of the restraining tube produced with the longitudinal axis of the rat aligned parallel to the plane of rotation. Oscillation was through a vertical 180 arc at an approximate rate of 50 traverses of the arc (i.e. swings, back and forth) per min. The 10 rats in one experimental group were exposed to 30 swings, whereas the rats in the other experimental group were exposed to 200 swings. Rats in the restraint condition were placed in the restraining tubes for a period of time equivalent to that required to complete 200 swings in the motion condition (approximately 4 min). All rats were tested in

squads of three rats each with one rat from each of the three conditions in each squad.

Immediately following the termination of the appropriate motion or restraint treatment, the rear cap of the restraining tube was removed and the rat's tail was allowed to hang free from the tube. The tail was then lowered to a depth of 8 cm into the hot (52° C) water. At the time of immersion into the hot water, an electronic stopwatch was started. The stopwatch was stopped when the rat had completely removed its tail from the hot water and the latency to do so was then recorded. The rat and restraining tube were then placed into a wire mesh holding cage that had dimensions such that replacing the rear cap was not necessary to prevent escape from the tube.

Another analgesia test was conducted 180 sec following the termination of the motion or restraint treatment. A final analgesia test was conducted 300 sec following the termination of the treatment. The experimental design was thus a 3 X 3 repeated measures with the three treatment conditions and the 3 treatment-test intervals.

All testing was conducted in the late afternoon (approximately 1600 hr) under normal room illumination and temperature. Latency to first movement of the tail was not recorded in the present study or in subsequent studies although it had been recorded in the Gray (unpublished data, 1979) study described earlier. In the previous study, tail movement latency was found to correlate highly ($\rho = +.729$, $p < .05$, Spearman rank order correlation) with tail withdrawal latency, and because tail withdrawal was felt to be a less ambiguous behavioural

measure, the movement-latency measure was excluded from subsequent investigations.

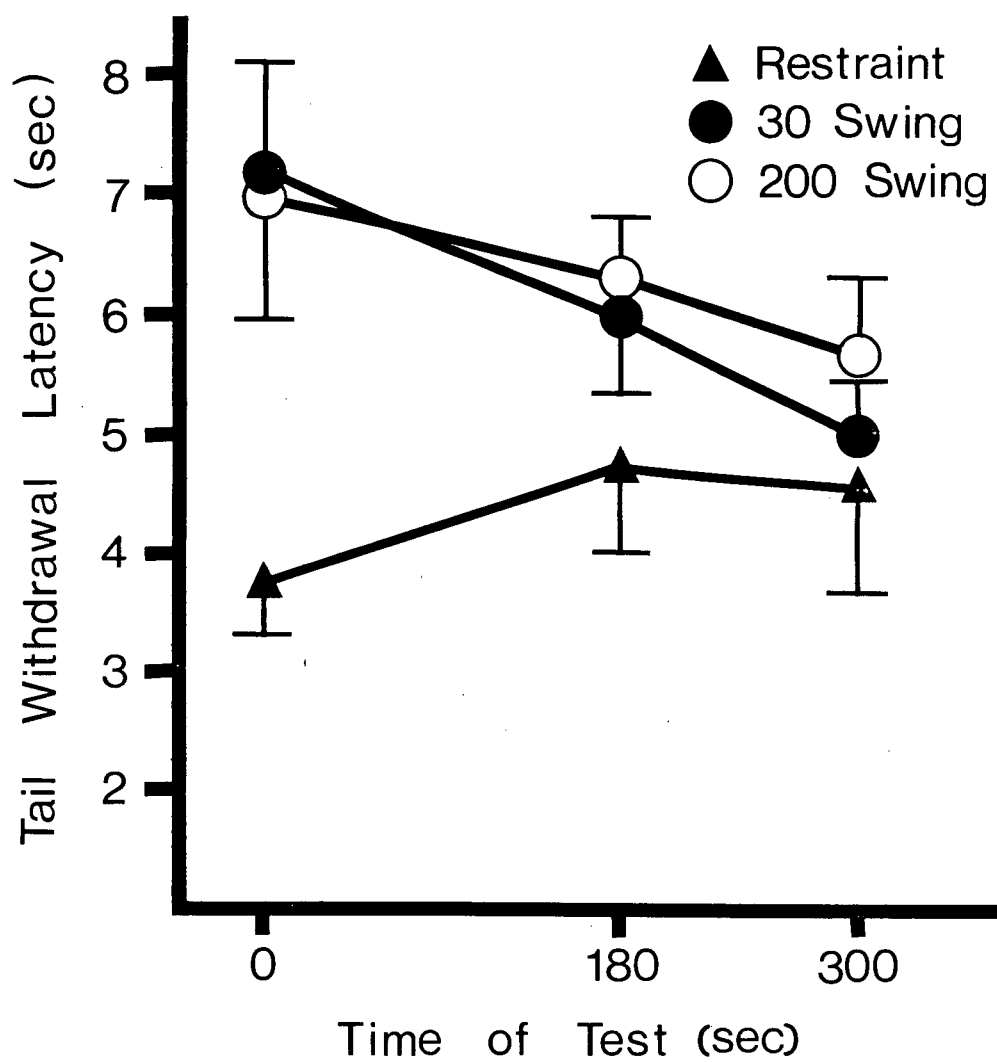
RESULTS AND DISCUSSION

As shown in Figure 2, exposure of rats to either the 30- or 200- swing condition resulted in a significant ($F=7.57$, $df=2/27$, $p<.05$) increase in tail withdrawal latencies. Post hoc tests (Tukey) indicated no significant differences between the effects of 30 or 200 swings ($p>.05$). Although the effect of repeated tests was not significant ($F=2.35$, $df=2/54$, $p>.05$), a significant interaction between treatment and repeated tests ($F=3.02$, $df=27/54$, $p<.05$) suggested that the antinociceptive effect of motion declined with time. Post hoc analysis indicated a significant effect of motion at the 0- sec and 180- sec test times ($p<.05$) but no significant differences were found between restraint and the two motion conditions at 300 sec.

These results confirm the existence of the antinociceptive effect of exposure to swinging motion that had been previously noted in our laboratory (Gray, unpublished data). A stimulus consisting of 200 swings was no more effective than one of 30 swings in producing the increase in tail withdrawal latencies. The effect also appears to decay in a relatively short period of time as tail withdrawal latencies did not differ among groups in the 300 sec test. This would suggest that whatever physiological mechanism underlies this effect, it is activated to some maximum in a short period of time and declines rapidly following removal of the provocative stimulus.

It appears then, that there is a large reliable decrement in the rats reaction to a noxious stimulus following exposure to

FIGURE 2. Mean tail withdrawal latencies for rats exposed to restraint or one of two different motion conditions in Experiment 1. Vertical lines indicate standard errors.



at least one form of abnormal motion. It is not clear however, exactly what attributes of the motion were important in eliciting this antinociceptive response.

Experiment 2

It is difficult to identify exactly which features are important in eliciting the antinociceptive response to abnormal motion when swinging is used as the stimulus. Not only is the swinging motion difficult to control in terms of degree and duration, it also confounds vertical and horizontal linear acceleration with angular acceleration components. These types of motion are thought to be detected (in mammals, at least) by two relatively independent components of the peripheral vestibular apparatus (Goldstein, 1974; Johnson & Jongkees, 1974; Reason & Brand, 1975). One component, the labyrinthine canals, are primarily responsible for detecting angular accelerations in three approximately orthogonal planes. Within each of three narrow fluid-filled semi-circular canals lies a 'plug' of gelatinous material, the cupula. Angular accelerations in the appropriate plane cause motion of the fluid relative to the walls of the canals, and this relative movement of the fluid causes a displacement of the cupula proportional to the degree of acceleration. Displacement of the cupula causes deformation of the hairs of receptor cells that are embedded in the base of the cupula. This deformation of the hairs causes either inhibition or excitation of firing activity in the receptor cells proportionate to the amount of hair cell deformation.

The second component of the peripheral vestibular organs is

the otolithic mechanism, thought to be primarily sensitive to linear and gravitational acceleration. A dense fibrous matrix containing calcium crystals overlies the receptor cell areas (the maculae) of both the utricle and saccule. These receptor areas are situated so that the saccular otolith is primarily vertical in orientation and the utricular otolith is horizontal. Accelerations in a plane parallel to the orientation of an otolith causes deformation of hair cells embedded in the overlying matrix. This hair cell deformation causes excitation or inhibition of receptor cell activity in a manner similar to that described above.

Given that the swinging motion is composed of both linear and angular acceleration components, it is possible that one of these components may be more important than the other in eliciting the antinociceptive effect of abnormal motion. Different types of motion do appear to be differentially effective in eliciting various behavioural effects. For example, vertical oscillation was found to be much more effective than horizontal oscillation in soothing infants (Pederson & Ter Vrugt, 1973; Ter Vrugt & Pederson, 1973), and complex coriolis-type motion is much more effective than simple rotation in inducing motion sickness (Reason & Brand, 1975).

Accordingly, Experiment 2 was designed to investigate the antinociceptive effects of three different types of motion, rotation in a horizontal plane, vertical acceleration, or a combination of both.

Because there have been reports of circadian variations in pain perception in rats (Frederickson, Weshe, & Richter, 1978;

Rosenfeld & Rice, 1979), time of testing was included as an additional factor in the present experiment. Time of testing was investigated primarily to determine a suitable time of day (i.e., AM versus PM) for subsequent experimentation. Experiment 2 was not intended to be a systematic exploration of circadian variation.

METHOD

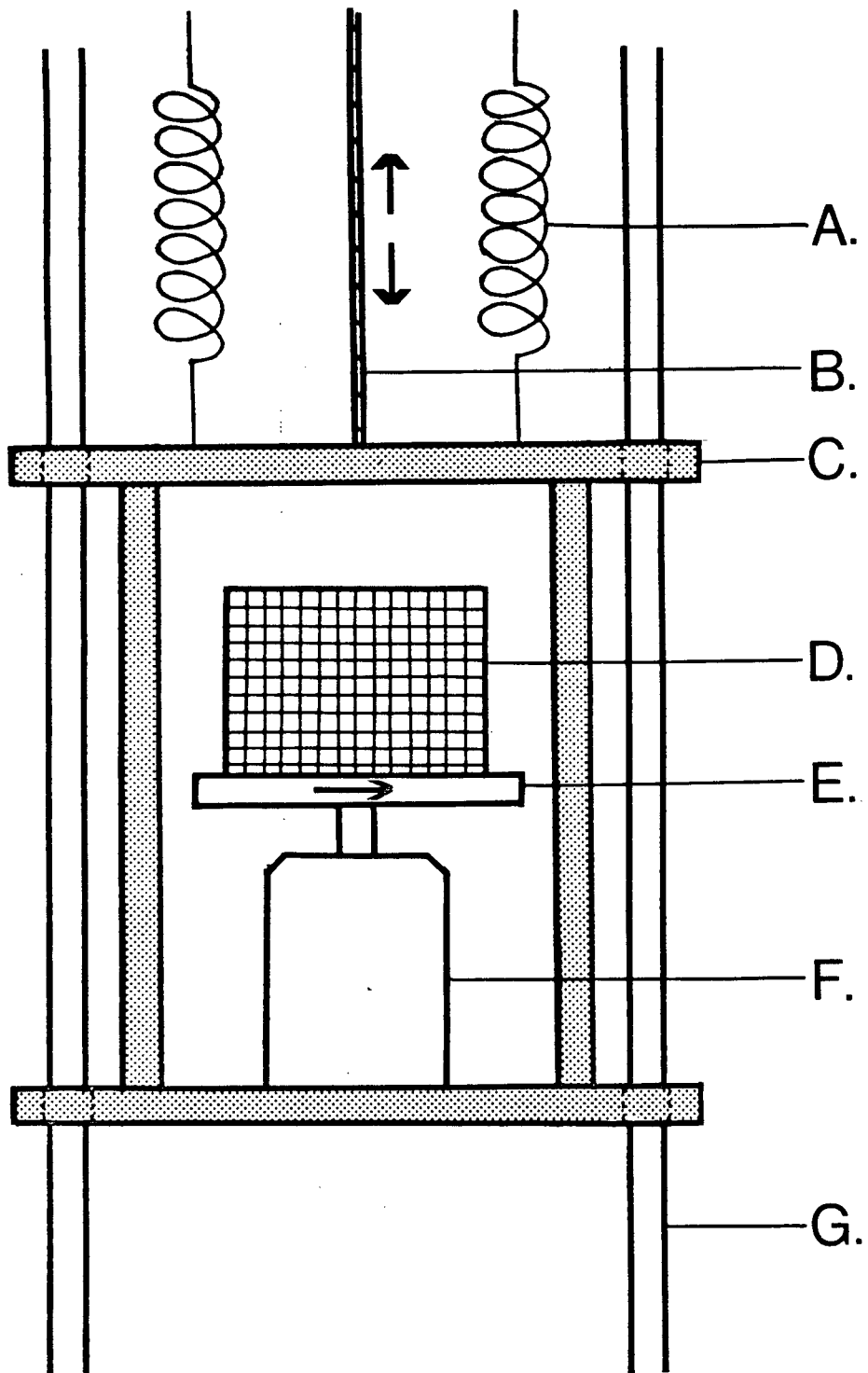
Subjects

Serving as subjects in the present experiment were 48 naive male hooded rats weighing approximately 350 gm. The subjects were purchased, housed, and maintained as in Experiment 1.

Apparatus

The apparatus used to administer the abnormal motion treatments in the present experiment was a horizontal turntable mounted in a spring-suspended frame that was free to move on vertical guide rails. A schematic representation of the device is shown in Figure 3. The rotational speed of the electric turntable motor could be adjusted with a transformer and the vertical oscillation rate and amplitude were controlled manually. A wire mesh cage, mounted on the turntable, provided a carrier device for the restraining tubes described in Experiment 1. The wire mesh cage allowed two restraining tubes to be mounted side-by-side on the turntable and an additional four restraining tubes could be stacked in the mesh cage if necessary. The slightly off-centre placement of the tubes resulted in each rat's head being placed approximately 11 cm away from the centre of rotation. In horizontal rotation at 30 RPM, this placement would result in a force of approximately

FIGURE 3. Schematic representation of the motion device used in Experiment 2: (A) spring suspension, (B) vertical oscillation cable, (C) frame, (D) wire mesh cage, (E) horizontal turntable, (F) variable speed electric motor, (G) vertical guide rails.



0.14 G exerted at the rat's head. This device is similar to that described by Brizze and co-workers (Brizze, Ord, & Mehler, 1980; Ord & Brizze, 1980; Roy & Brizze, 1979) and the motion parameters used in the present experiment were chosen to coincide with those used by Brizze et al., within the limitations of the present apparatus. The horizontal rotation speed was 30 RPM and the vertical oscillation rate was approximately 50 cycles per min with an amplitude of approximately 25 cm. The analgesia testing apparatus was identical to that described in Experiment 1.

Procedure

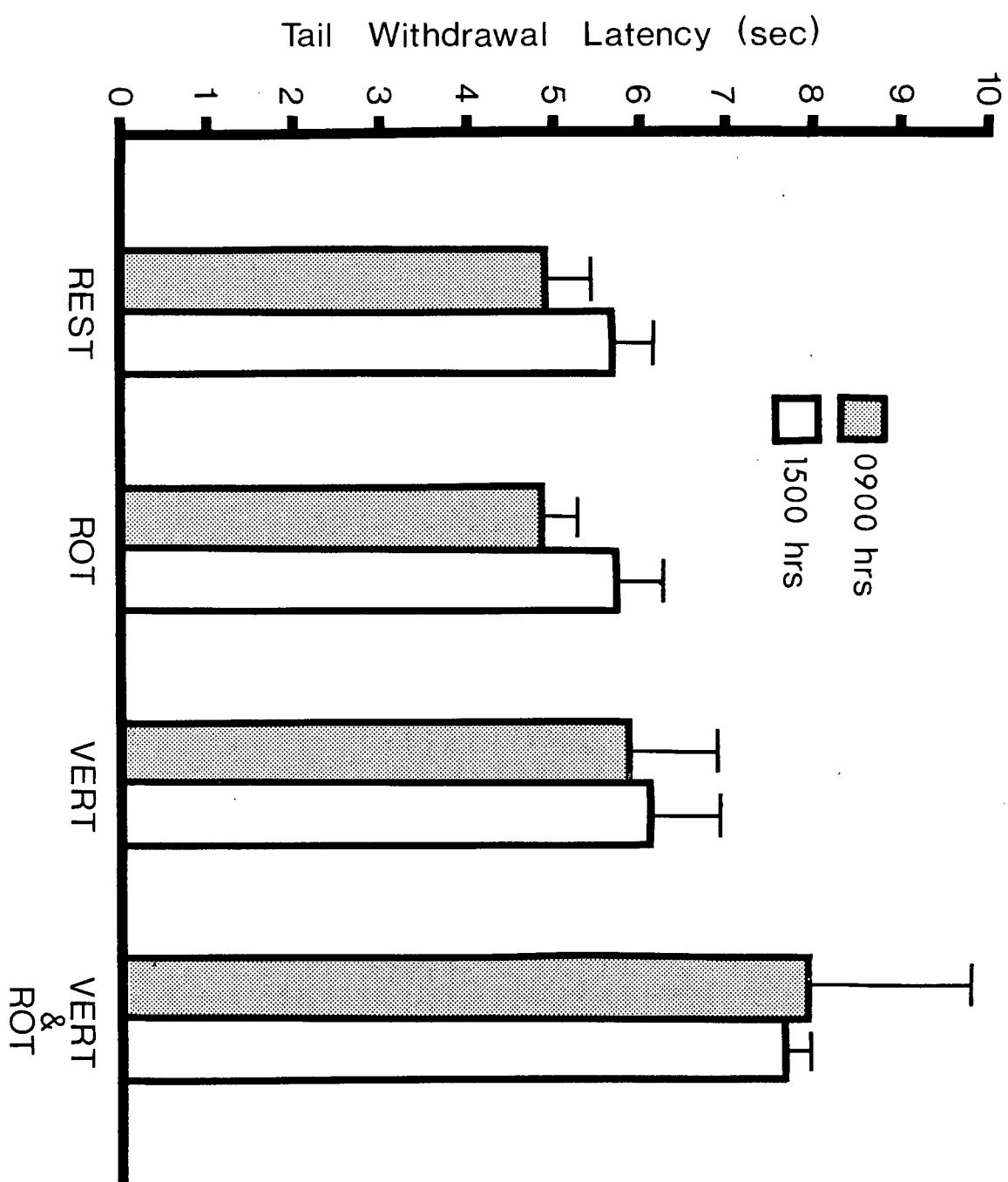
On each of 2 days prior to the initiation of testing, all animals were acclimated to the restraining tubes for a 5 min period at approximately 1200 hr. On the day of testing, 12 animals were randomly assigned to each of four motion conditions: 1) restraint only, 2) horizontal rotation (30 RPM), 3) vertical oscillation (50 cycles per min), or 4) horizontal rotation combined with vertical oscillation. Six rats from each group were tested beginning at 0900 hr and the remaining six were tested in the afternoon beginning at 1400 hr. The experimental design was thus a 2 X 4 factorial.

All rats were tested sequentially in squads of four animals each, composed of one rat from each of the four treatment conditions. Immediately following 5 min of exposure to either restraint or to one of the three motion conditions, a hot-water tail withdrawal test was administered as described previously.

RESULTS AND DISCUSSION

The results of Experiment 2 are depicted in Figure 4.

FIGURE 4. Mean tail withdrawal latencies for rats in Experiment 2. Rats were tested in one of four motion conditions: restraint (REST), horizontal rotation (ROT), vertical oscillation (VERT), or vertical oscillation in combination with horizontal rotation (VERT + ROT).



Analysis of variance indicated a significant overall increase in tail withdrawal latencies following exposure to abnormal motion ($F=3.51$, $df=3/39$, $p<.05$). Post hoc analysis (Tukey) indicated that only horizontal rotation in combination with vertical oscillation was effective in significantly elevating tail withdrawal latencies ($p<.05$) and no significant differences were found when restraint, horizontal rotation, and vertical oscillation were compared ($p>.05$). As shown in Figure 4, horizontal rotation or vertical oscillation alone produced no significant change. No significant main effect of time of day was found ($F=.28$, $df=1/39$, $p>.05$) nor was the interaction term of the analysis significant ($F=.19$, $df=3/39$, $p>.05$). There did however, seem to be a trend towards greater uniformity in tail withdrawal scores in the afternoon test session. Thus most testing in subsequent experiments was conducted in the afternoon in an effort to reduce variance.

It would seem from these results that an antinociceptive effect may be elicited by types of motion other than the swinging motion used in Experiment 1. The present results further suggest that the antinociceptive effect is best elicited by relatively complex forms of motion such as the swinging motion used previously and the horizontal rotation in combination with vertical oscillation utilized in the present study. Relatively simple forms of motion such as horizontal rotation or vertical oscillation do not appear to elicit any appreciable degree of antinociception, at least not at the stimulus intensities and durations used here. It would seem then, that different types of motion are differentially

effective in producing an antinociceptive effect. Conclusions regarding angular and linear acceleration components must be advanced cautiously however, due to the limited range of motions used and the somewhat imprecise control of the intensity of acceleration in the present experiment.

Although no formal comparison can be made, it should be noted that the degree of analgesia (measured by tail withdrawal latency) produced by the complex motion treatment in the present experiment (approximately 35% over control values) was not as great as the degree of analgesia produced by the much shorter duration swinging motion used in Experiment 1 (approximately 86% over control values).

One possible criticism concerning the use of abnormal motion to elicit antinociception may be that the apparent antinociception produced by abnormal motion may reflect nothing more than an artifact of vestibular stimulation. That is, it is possible that 'dizziness' or 'vertigo' produced by abnormal vestibular stimulation (Reason & Brand, 1975) interferes in some fashion with the rats ability to withdraw its tail from the noxious stimulus. Experiment 3 was designed to test this hypothesis.

Experiment 3

If dizziness or vertigo is responsible in some manner for inhibiting the rats ability to withdraw its tail from the hot-water used in the analgesia test, either through some form of motor disruption or a distraction effect, one would expect the efficacy of a particular motion treatment in inducing analgesia

to be correlated with the degree of dizziness or vertigo produced by that motion treatment. The purpose of Experiment 3 was to compare the four motion treatments used in Experiment 2 in terms of the degree of general vestibular dysfunction induced by each.

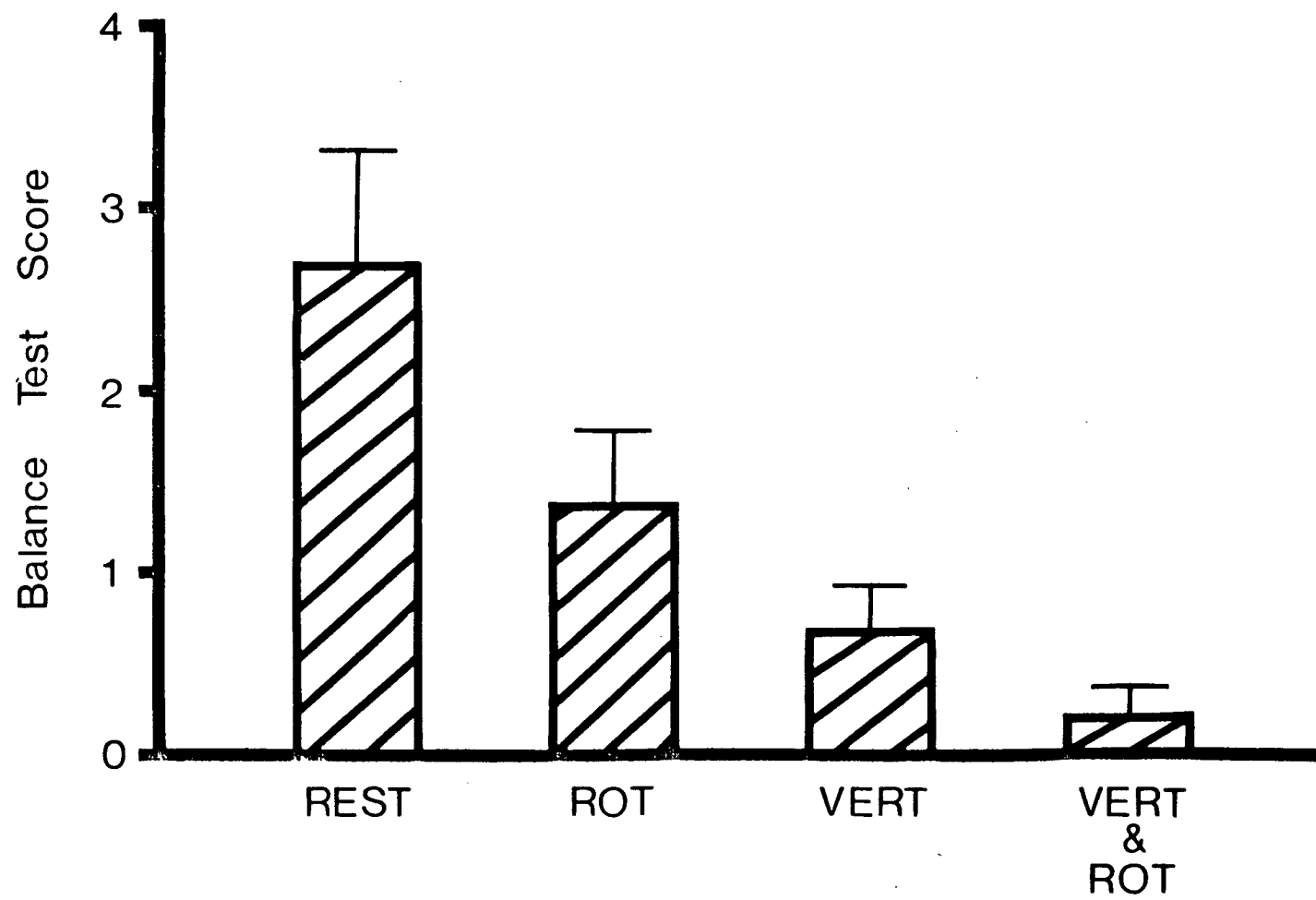
METHOD

The day following the completion of Experiment 2, six rats were selected at random from each of the four motion groups used in Experiment 2 and subjected to the same motion treatment they had previously received. Immediately following the termination of the 5 min treatment period, each rat underwent a balance beam test. The balance beam test was a slightly modified version of the test for vestibular dysfunction described by Modianos and Pfaff (1976). The rat was placed lengthwise in the centre of a 2 cm X 61 cm suspended beam. During a 10-sec test, the behaviour of the rat was scored as follows: 4 - if the rat walked steadily to one end of the beam, 3 - if the rat moved to one end of the beam but appeared unsteady, 2 - if the rat did not move along the beam but appeared stable, 1 - if the rat did not move along the beam and appeared unstable, and 0 - if the rat fell from the beam. Scores attained by normal rats in our laboratory generally range from 2 to 4.

RESULTS AND DISCUSSION

As illustrated in Figure 5, balance scores were significantly decreased by pretest exposure to abnormal motion ($F=7.48$, $df=3/20$, $p<.05$). Although Figure 5 suggests that this effect was greatest in the combined horizontal rotation and vertical oscillation condition, the three motion treatments did

FIGURE 5. Mean balance beam scores for rats tested in one of four motion conditions in Experiment 3: restraint (REST), horizontal rotation (ROT), vertical oscillation (VERT), or vertical oscillation combined with horizontal rotation (VERT & ROT).



not differ significantly ($p > .05$). Balance scores in the vertical oscillation and combined condition were, however, significantly less than those in the restraint condition ($p < .05$). It would seem from the results of Experiment 3 that exposure to abnormal motion does induce dizziness or some type of vestibular dysfunction in the rat, at least as inferred by the rats ability to maintain its balance on a narrow beam. The degree of deficit in balancing ability produced by the various motion treatments also appears to roughly correspond with the ability of these treatments to induce analgesia (compare Figures 4 and 5). The horizontal rotation combined with vertical oscillation produced the greatest degree of analgesia in Experiment 2 and produced the greatest degree of disruption in the balancing task in the present experiment.

Although there does appear to be a relationship between the ability of an abnormal motion treatment to induce analgesia and its ability to produce vestibular dysfunction, it is not clear if this relationship is causal in nature. If dizziness and analgesia are both effects of abnormal vestibular stimulation, one might expect that treatments effective in producing one effect would also be effective in eliciting the other. For example, although dizziness, nausea, vomiting, and drowsiness are all effects of abnormal vestibular stimulation, there may be no causal relationship between them. On the basis of the results of the present experiment however, it is difficult to resolve the problem and this issue is treated at length elsewhere in this thesis (see Section II, Experiments 7 and 8).

Experiment 4

If abnormal motion does produce an antinociceptive effect, then this effect should also be apparent when the rats reaction to a noxious stimulus is measured using a different behavioural technique. The technique used in the present experiment was a modification of the hot plate paw-lick jump-escape test for analgesia (e.g. Amir & Amit, 1978; Ankier, 1974; Bardo & Hughes, 1979; Glick, 1976). When rats are placed on a hot surface (approximately 50-55° C), they exhibit at least two characteristic behaviours in temporal sequence. After some time on the hot surface, the rat will begin to lick and manipulate the ventral surface of the paws that have been in contact with the surface. The latency to the first paw lick is the usual measure (Amir & Amit, 1978). Eventually the rat will jump from the floor of the hot-plate apparatus and the latency to the first jump-escape response typically constitutes the second measure. The purpose of the present experiment then, was to demonstrate the generality of the antinociceptive effect of abnormal motion using a different test of antinociception, the hot plate paw-lick jump-escape test.

METHOD

Subjects

Serving as subjects in the present experiment were 20 naive male hooded rats weighing approximately 350 gm. The subjects were purchased, housed, and maintained as previously described.

Apparatus

The hot plate apparatus consisted of an open-topped Plexiglas box (15 X 19.5 X 41 cm). The bottom of the box was

constructed of thin sheet metal and all seams were sealed with silicone sealant. In use, the Plexiglas box rested on two wooden supports in a constant temperature (55° C) water bath (Blue M) with the metal floor at a depth of 1 cm in the water bath. The use of a constant temperature water bath as a heat source rather than the usual electric hot-plate ensured even heat distribution over the entire floor. The metal floor of the apparatus was cleaned and dried after each use.

Procedure

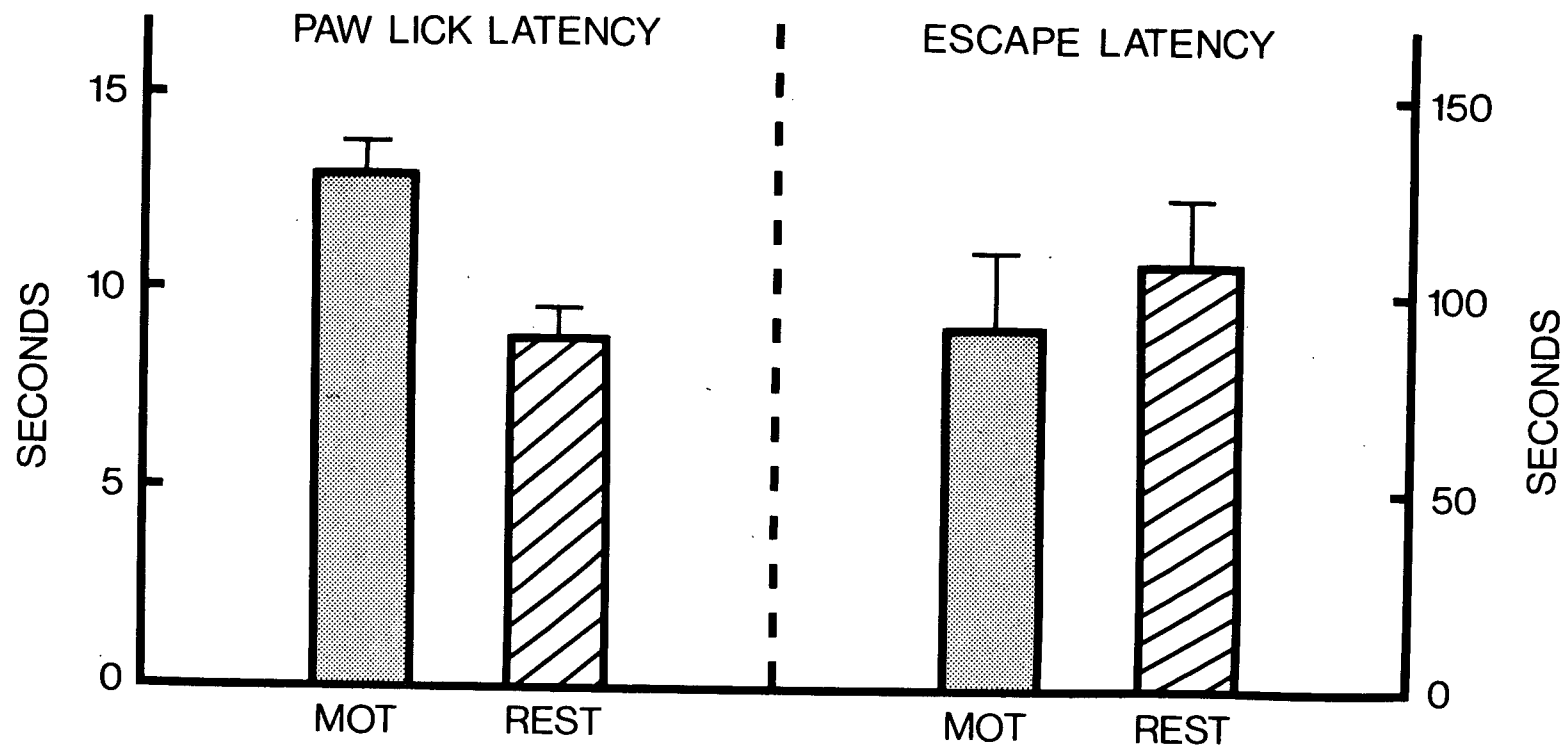
On each of the 2 days prior to testing, all subjects were acclimated to the restraining tubes for 5 min and to the non-functional hot plate apparatus for another 5 min. On the day of testing, subjects were randomly assigned to either the motion or restraint conditions. The abnormal motion treatment was identical to the combined horizontal rotation and vertical oscillation treatments used in Experiments 2 and 3. Rats in the restraint condition were merely placed in the restraining tubes for the 5 min period. Immediately following the expiration of the 5 min treatment period, the rat was withdrawn from the restraining tube and placed in the now functional hot plate apparatus. Latency to the first paw-lick response was recorded on one timer, and latency to the first jump-escape response that completely cleared the floor of the apparatus was recorded on the second timer. The rats were removed from the apparatus upon completion of the jump-escape response or when 200 sec had expired without a successful jump-escape response. This maximum was imposed to prevent possible tissue damage from sustained exposure to the thermal stimulus.

RESULTS AND DISCUSSION

The paw-lick and jump-escape latencies are illustrated in Figure 6. There was a significant difference between motion and restraint conditions in the latency to paw-lick ($t=3.66$, $df=16$, $p<.05$) but differences in the jump-escape measure were not significant ($t=.73$, $df=16$, $p>.05$). If one considers only the paw-lick response, it is clear that exposure to abnormal motion produces an analgesic effect. The failure to find an antinociceptive effect in the jump-escape measure is somewhat more difficult to interpret. It may be that this measure is merely less sensitive than the paw-lick response in assessing the presence or absence of antinociception, or the two responses may well reflect different underlying mechanisms. Amit and Amir (1978) for example, suggest that the paw-lick response reflects the sensory components of pain perception, whereas the jump-escape response reflects the affective component of pain perception. If this is true, one could perhaps argue that the antinociceptive activity of abnormal motion exerts its effects primarily on the sensory components of nociception.

It is also possible that the lack of difference in the jump-escape measure may be explained by an attenuation of the analgesic effect of abnormal motion with time. Paw-lick latencies were about 10 sec, whereas jump-escape latencies were about 100 sec. It is possible that the antinociceptive effect of abnormal motion detected by the paw-lick response could have declined over the subsequent 90 sec. Accordingly, Experiment 5 was designed to provide information concerning the duration of the antinociceptive effect of the combined horizontal rotation

FIGURE 6. Results of analgesia testing in Experiment 4. MOT refers to the abnormal motion treatment while REST refers to the restraint control treatment.



and vertical oscillation motion stimulus used in this and previous experiments.

Experiment 5

Experiment 5 was designed to assess the duration of the antinociceptive effects produced by different periods of exposure to combined horizontal rotation and vertical oscillation.

METHOD

Subjects

The subjects were 64 male hooded rats, weighing approximately 350 gm, obtained and maintained as described previously.

Procedure

On each of the three days prior to testing, all animals were acclimated to the restraining tubes for a 5 min period. On the day of testing, eight animals were randomly assigned to each of four motion durations, 5 sec, 30 sec, 300 sec, or 900 sec, and to each of four equivalent duration restraint conditions.

Immediately following the expiration of the motion or restraint treatment, the usual hot-water tail withdrawal test for analgesia was conducted (0 min test). A series of subsequent tests were conducted 1 min, 3 min, 10 min, and 30 min following termination of the treatment condition. All rats remained in the restraining tubes throughout the analgesia testing in order to eliminate possible undue effects attributable to repeated handling. The design of the experiment then, was a 2 X 4 X 5 repeated measures.

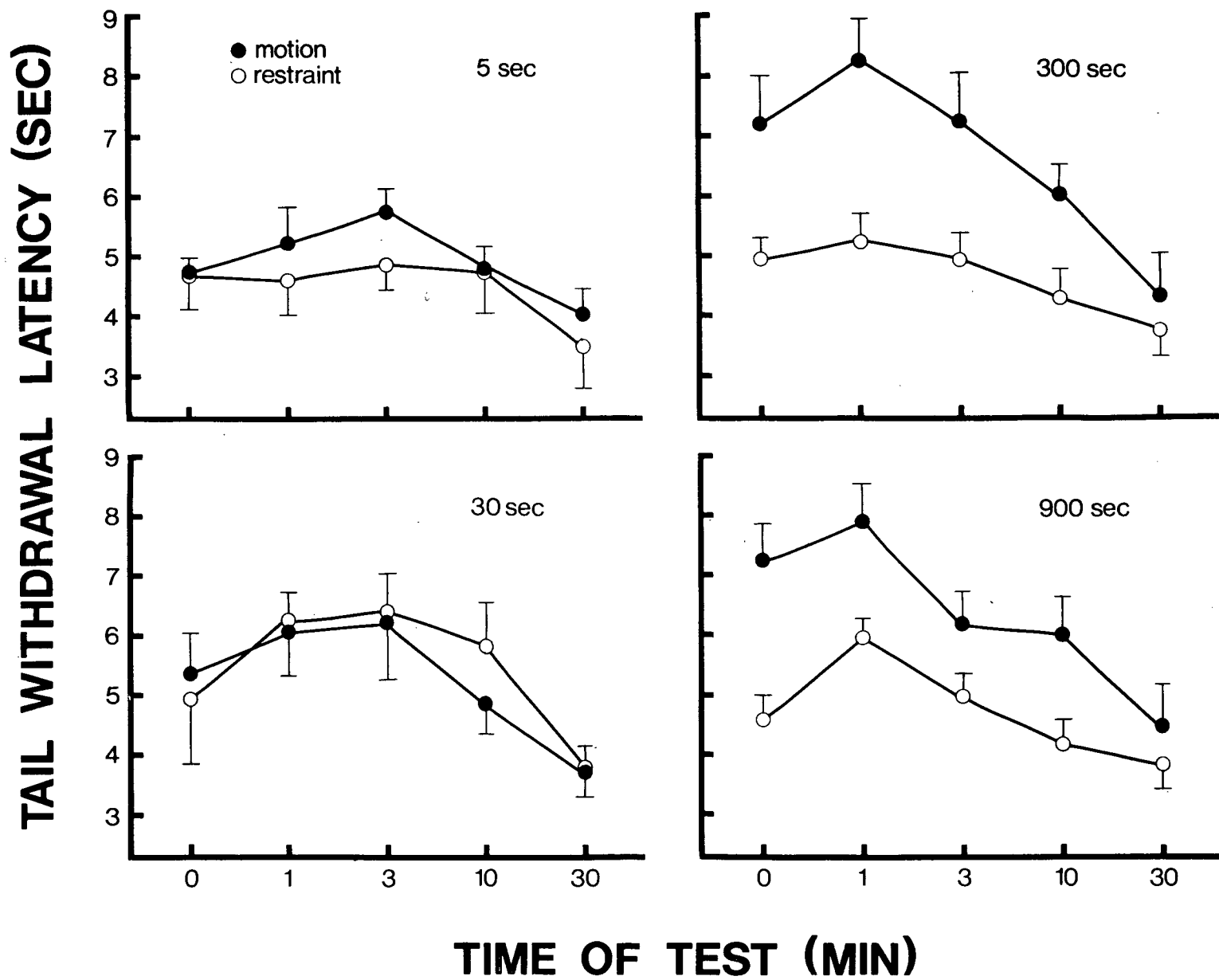
Rats were tested in pairs, each pair consisting of one rat from one of the four motion conditions and the other from the equivalent duration restraint only condition. The restraint only condition of the pair was begun approximately 30 sec following initiation of the motion condition so that analgesia testing could be conducted at the appropriate intervals without conflict. Testing was completed over sessions on four consecutive afternoons with one quarter of the rats from each treatment condition ($n = 16$) tested on each of the 4 days.

RESULTS

The results of Experiment 5 again confirm the existence of an antinociceptive effect of abnormal motion (see Figure 7). Analysis of variance indicated a significant analgesic effect of motion ($F=10.50$, $df=1/56$, $p<.05$). The effect of different motion durations did not reach significance ($F=2.12$, $df=3/56$, $p>.05$) in the overall analysis, but the motion treatment by duration of motion interaction was significant ($F=2.98$, $df=3/56$, $p<.05$). Post-hoc analysis (Tukey) indicated that tail withdrawal latencies in the four restraint groups and the 5 and 30 sec motion exposure groups were not significantly different ($p>.05$). Analysis of main effects (Kepple, 1973) indicated that the analgesic effect of abnormal motion was significant in the 300 and 900 sec motion duration conditions ($F=10.97$, $df=1/56$, $p<.05$; $F=7.90$, $df=1/56$, $p<.05$, respectively) but not in the 5 and 30 sec groups (see Figure 7).

The overall analysis of variance also indicated a significant overall decline in tail withdrawal latencies over repeated tests ($F=36.53$, $df=4/224$, $p<.05$) and a significant

FIGURE 7. Mean tail withdrawal latencies for rats exposed to 5-, 30-, 300-, or 900-sec periods of the abnormal motion treatment used in Experiment 5. Time of test refers to the times at which repeated analgesia tests were administered after termination of the motion or restraint treatment.



duration of exposure by repeated tests interaction ($F=2.04$, $df=12/224$, $p<.05$). Neither the motion condition by repeated tests interaction nor the three-way interaction term reached significance. A priori comparisons (t-test) of the motion and restraint conditions at the various test intervals indicated that motion produced a significant elevation in tail withdrawal latencies ($p<.05$) at the 0, 1, and 10 min test intervals in the 900 sec motion duration condition ($t=3.88$, $df=14$; $t=2.68$, $df=14$; $t=2.55$, $df=14$; respectively). In the 300 sec motion duration condition, motion produced a significant elevation in tail withdrawal latencies ($p<.05$) in the 0, 1, 3, and 10 min motion conditions ($t=2.53$, $df=14$; $t=3.82$, $df=14$; $t=2.27$, $df=14$; $t=2.50$, $df=14$). No significant changes in tail withdrawal latencies were found at any test interval in the 5 and 30 sec motion duration conditions.

DISCUSSION

Experiment 5 not only provides additional confirmation of an antinociceptive effect resulting from exposure to abnormal motion conditions in rats but also provides additional information concerning the exposure time necessary to elicit the phenomenon and the duration of the analgesia once elicited. The present results suggest that the antinociceptive effect of abnormal motion does not appear instantaneously upon initiation of the abnormal motion regimen but requires between 30 and 300 sec to develop with the type of motion used here. It also appears that the analgesia elicited by this motion reaches some asymptotic level and does not increase significantly with further exposure (300 to 900 sec). A similar asymptotic level

of analgesia was also found in Experiment 1, in which a swinging motion was the provocative stimulus. It is not known however, if the transition from a state of no analgesia to full blown analgesia with increasing motion exposure duration is a smooth gradual function or represents an abrupt transition. This question could possibly be answered with the use of more testing intervals between the 30- and 300-sec analgesia test intervals used here. The fact that a 5- or 30-sec exposure to abnormal motion fails to elicit analgesia suggests that the analgesia elicited by longer exposure durations is not produced by 'fear' or 'surprise' elements of the abnormal motion. If these factors were operating in the antinociceptive effect seen here, one would expect their effect to be maximal near the beginning of the exposure period.

It also appears that the antinociceptive effect decays gradually with time from termination of the abnormal motion, at least in repeated tests. This decay in the strength of the antinociceptive effect is almost certainly not an artifact of the repeated testing procedure. Control rats exposed only to restraint for periods of up to 45 min demonstrated remarkably stable tail withdrawal latencies over time and repeated tests. If repeated testing were a factor in the decay of the antinociceptive effect, a similar decline in tail withdrawal latencies should have been shown in the control animals exposed to restraint only.

General Discussion - Section I

The preceding five experiments demonstrated the existence of an antinociceptive effect of abnormal motion in rats. The antinociceptive effect was robust, producing increases of 35 to 100% in two different assays of analgesia. It also seems that once exposure to an abnormal motion environment is initiated, the exposure must continue for some period of time before full expression of the antinociceptive effect is achieved. This lag in the onset of the behavioural effect following onset of the motion stimulus is similar to the development of other behavioural effects of abnormal motion. Motion sickness, for example, does not generally appear immediately following onset of the motion stimulus but signs and symptoms develop progressively as stimulus exposure proceeds (Reason & Graybiel, 1970).

In addition, it appears that there is an asymptotic degree of analgesia that may be elicited by the particular motion stimuli of the present experiments. Percentage comparisons of the swinging motion and the combined horizontal rotation and vertical oscillation motion to their respective controls (swinging - 85% greater than controls, rotation and oscillation - 35% greater than controls), suggests that this asymptotic level of analgesia may differ depending on the type of motion used to elicit the antinociceptive effect.

The degree of the antinociceptive effect appears to depend on the form of the motion stimulus used. In the preceding experiments, complex motions (i.e., swinging or rotation and oscillation) were more effective than relatively less complex

forms of motion (ie. rotation or vertical oscillation). If the antinociceptive effect is dependent on abnormal vestibular stimulation, it is not unreasonable to suggest that complex abnormal motions such as swinging or horizontal rotation combined with vertical oscillation would have more impact on more components of the vestibular system and hence produce greater overall vestibular activity than would relatively simple forms of vestibular stimulation. Other effects of abnormal vestibular stimulation such as motion sickness are also more easily elicited by relatively complex forms of abnormal motion (Reason & Brand, 1975).

Although there is a decrement in the responsiveness of rats to noxious or painful stimuli following a period of abnormal motion, there are a number of issues that may have a bearing on the generality and usefulness of this effect. Such issues as the validity of the use of restraint as the appropriate control condition, the possibility of unnecessary error introduced by the technique used to measure latencies, and the generalizability of the phenomenon are discussed in the following paragraphs.

It is possible that the magnitude of the antinociceptive effect described here is somehow affected by the use of an inappropriate control condition. That is, the use of restraint as the control condition may have perhaps masked or exaggerated the effects of abnormal motion by either increasing or decreasing the baseline analgesia measures. For example, Amir and Amit (1978) have shown that a significant amount of analgesia can be induced by completely immobilizing rats for

periods of time. This immobilization-induced analgesia may also explain the antinociceptive effects of exposing rats to radial accelerations of 7G (Hayes, Bennet, Newlon, & Mayer, 1978). It must be remembered that the restraining system used here in no way 'immobilized' the rat but did restrict the range of movements available to the animal. Studies in our laboratory indicated that tail withdrawal latencies did not differ between non-restrained rats and rats subjected to 5 min of restraint ($X = 4.05$ sec, $s.d. = 1.45$; $X = 4.30$ sec, $s.d. = 1.81$, respectively). Because latencies did not change noticeably with increasing periods of restraint (up to 45 min), the results of Experiment 5 also suggest that the restraint condition itself has little effect on tail-withdrawal latencies.

It is also possible that the present studies could be criticized with respect to the technique used to measure tail withdrawal latencies, the primary measure of the antinociceptive effect of abnormal motion. Although it is perhaps true that human observers operating electronic stopwatches are susceptible to observer biases, reaction time deficits, and other subtle forms of data acquisition errors, these factors did not appear to present difficulties in the present experiments. A paid observer was used to record tail withdrawal latencies in many of the experiments and the reliability of the human measurement technique was examined by two different methods. First, an inter-observer reliability coefficient was calculated between two independent observers and resulted in a correlation of .995 (Pearson product-moment). Second, latency measures obtained with the use of an electronic device (Skelton & Gray,

unpublished manuscript, 1980) were compared to latencies obtained by a human observer using the stopwatch method. A correlation of .975 (Pearson product-moment) resulted from this comparison. The electronic device was not used in subsequent tests because it was susceptible to an occasional failure, which resulted in a loss of data.

The final issue concerns the generalizability of the antinociceptive effect and the potential usefulness of abnormal motion as a means of non-pharmacological pain control in humans. The exclusive use of male rats in the preceding studies may tend to restrict the generality of the antinociceptive effect somewhat. Although female rats have been found in our laboratory to exhibit motion-induced analgesia identical that displayed by male rats, the generality of this phenomenon across species has not yet been established. It seems likely however, that this generality exists as other behavioural effects of abnormal motion (e.g., motion sickness, drowsiness) demonstrate wide generality across species. Dogs, cats, monkeys, and other animals all demonstrate motion sickness and drowsiness upon exposure to appropriate forms of abnormal motion (Brizze, Ord, & Mehler, 1980; Money, 1970; Suri, Crampton, & Daunton, 1979).

The relatively short duration of analgesia following abnormal motion in rats would seem, at first glance, to restrict the usefulness of the technique for pain control in humans. It appears however, that the duration of analgesia produced by nonpharmacological methods in rats does not accurately predict the duration of analgesia produced by the same methods in humans. Transcutaneous electric shock for example, may produce

long-lasting and even permanent relief from pain in human patients suffering from chronic pain (Melzack & Dennis, 1978), whereas the same technique produces relatively short periods of analgesia in the rat (Hayes, Bennet, Newlon, & Mayer, 1978). This same disparity between experimental results in animals and clinical efficacy in humans may well exist for analgesia produced by abnormal motion. If this were true, abnormal motion would seem to offer some advantages over other forms of nonpharmacological pain control such as transcutaneous electrical stimulation, acupuncture, and electrical stimulation. It is easy to administer, not painful for the patient, has no risk of infection or tissue damage, and requires no surgical preparation of the patient. As yet however, there has been no empirical test of antinociceptive responses to abnormal motion in humans.

SECTION II - Vestibular Mediation of the Antinociceptive Phenomenon

It has been assumed in the preceding discussions that the vestibular system is the primary mediator of the antinociceptive effects of abnormal motion. Although this assumption may have some intuitive validity based on the primary sensory role of the vestibular system in detecting motion (e.g., Brodal, Pompeiano, & Walberg; Goldstein, 1974), it is also possible that other sensory mechanisms such as the visual and kinesthetic senses play an important role in the neural mediation of the antinociceptive effect of abnormal motion. The experiments discussed below in Section II were explicitly designed to test the hypothesis that the vestibular system is an essential component of the neural mediation of the antinociceptive effect of abnormal motion and to further explore the role of the vestibular system in this effect.

Previous investigations of the role of the vestibular system in mediating other behavioural effects of abnormal motion, although few, have suggested that an intact vestibular system is essential for the appearance of such effects as motion sickness and drowsiness. Labyrinthine defective human subjects, for example, are insensitive to the illness-inducing and soporific properties of abnormal motion (Graybiel, 1965; Johnson & Jongkees, 1974). Dogs with lesions of various portions of the vestibular system, including peripheral and central components, also appear immune to the illness-inducing properties of abnormal motion (Money, 1970; Money & Friedberg, 1964). Moreover, rats with lesions of the peripheral vestibular

apparatus do not develop aversions to a novel fluid paired with exposure to abnormal motion (Haroutunian, Riccio, & Gans, 1976).

Section II of the present thesis, consists of three experiments directed at exploring the role of the vestibular system in mediating the antinociceptive effect of abnormal motion. Experiment 6 investigated the effect of lesioning the peripheral receptor organs, whereas Experiments 7 and 8 used discrete lesion and electrical stimulation techniques respectively, to explore the role of some central nervous system components of the vestibular system.

Experiment 6

The purpose of Experiment 6 was to investigate the possible effects of a dysfunctional vestibular system on the antinociceptive effects of abnormal motion. This was accomplished by destroying portions of the peripheral receptor organs, thus disrupting input from the receptor organs to the central vestibular system. If an intact vestibular system is necessary for the expression of the antinociceptive effect of abnormal motion, then disruption of vestibular input should eliminate or attenuate the antinociceptive phenomenon.

METHOD

Subjects and Surgery

The subjects were 30 male hooded rats weighing approximately 300 gm at the time of surgery. Subjects were purchased, housed, and maintained as described previously.

The general surgical procedure involved a transauricular approach to the peripheral vestibular receptor organs through

the oval window, followed by a radio-frequency produced lesion in the inner ear. These lesions effectively eliminate the ability of the inner ear vestibular structures to respond to accelerative stimuli in a normal manner. This general procedure is identical to the procedure used by Potegal, Abraham, Gilman, and Copak (1975) and Haroutunian, Riccio, and Gans (1976) to produce deafferentation of the vestibular system.

All rats were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg, i.p.) and assigned to one of three lesion groups: a vestibular-damaged group ($n = 12$), an operated-control group ($n = 12$), or an anesthetized-control group ($n = 12$).

In the vestibular damaged group, a small cut was made anterior to the tragus to allow full visualization of the auditory meatus and the tympanic membrane. The auditory meatus was held open with a pair of fine forceps and, with the aid of a 25-power surgical microscope (Zeiss), the tympanic membrane was punctured and peeled away with a 23 ga standard bevel hypodermic needle (Becton-Dickinson, disposable). The malleus and incus were then gently pried from their positions and the footplate of the stapes visualized. The stapes footplate was then gently pried from its position on the oval window. Great care was taken not to injure the pterygopalatine artery which lies directly above the footplate and through the 'stirrup' portion of the stapes. If this artery was damaged, profuse bleeding ensued and the surgical procedure was terminated. A stainless steel insulated electrode (size '00' insect pin) was then inserted in the oval window to a depth of approximately 2 mm and the radio frequency current passed through the electrode and an

anal ground electrode. Radio frequency current was generated by a Grass RF-4 lesion generator and current parameters were as indicated 20 mA for a 20-sec period. The electrode was then removed and the procedure was repeated on the contralateral side. The entire procedure required approximately 20 min per subject for completion. Surgical procedures were identical for the operated control group except that the procedure was terminated when the stapes footplate had been visualized and moved slightly.

As both the operated control group and the vestibular damaged group were made deaf in the course of the surgical procedure, an additional group of rats was included to control for the possible confounding effects of deafness. This additional group, the anesthetized control group, was anesthetized with sodium pentobarbital and allowed to recover from the anesthetic with no further surgical intervention.

Following surgery, all animals were housed in groups consisting of six animals from the same surgical conditions. Two animals from the vestibular lesion group and one from the operated control group died in the interval between surgery and testing, reducing group sizes accordingly. Food and water were freely available and additional food pellets were placed daily on the floors of all cages. A 14-day recovery period was allowed between surgery and behavioural testing.

Procedure

On each of three days prior to testing, all rats were individually habituated to the restraining tubes for a 5-min period. On the test day, five rats from each surgical group

were randomly assigned to the motion condition, and the remaining five were assigned to the restraint-only condition. The motion used in the present experiment was the swinging motion described in Experiment 1. Two rats from each surgical condition were tested simultaneously, one rat in the motion condition and the other in the restraint condition. Immediately following the termination of the motion or restraint treatment, a hot-water tail withdrawal analgesia test was administered (Test 1) using the same apparatus and procedures described earlier.

On the following day, a second analgesia test (Test 2) was conducted. In Test 2, rats that had previously served in the motion condition were tested in the restraint condition, whereas rats that had served in the restraint condition in Test 1 were tested in the motion condition. Each rat then, was tested in both the motion and restraint conditions. The experimental design was thus a 3 X 2 repeated measures design, counterbalanced for test order.

An additional 18 animals that had previously served in various pilot experiments, also underwent surgery in order to determine the effectiveness of the surgical procedures in producing vestibular dysfunction. Six rats served in each of the three surgical conditions described above. Following the 14-day recovery period, all rats were tested in a battery of three tests designed to evaluate vestibular dysfunction (Modianos & Pfaff, 1976). The first test was the balance beam test for vestibular dysfunction that had also been used in Experiment 3. Following the beam test, each rat was placed on a

flat table top and rated on two 3-point scales for head and body position during a 10 sec observation period. Head position was scored as 0- if the head was predominantly held above horizontal, 1- if the head was held horizontal, and 2- if the head was usually held below horizontal. Body position was scored as 0- if the body was held so that the ventral surface was in continuous contact with the tabletop, 1- if the ventral surface was usually or partially elevated from the tabletop, and 2- if the ventral surface was always elevated. Normal rats in our laboratory typically score from 2 to 4 in the beam test and 1 to 2 in the head and body position tests.

RESULTS AND DISCUSSION

As shown in Figure 8, rats with defective vestibular systems do not show the elevation of tail withdrawal latencies shown by rats in both the operated control and anesthetized control groups after exposure to abnormal motion. Analysis of variance indicated a significant effect of motion ($F=22.15$, $df=1/30$, $p<.05$), a significant effect of surgical condition ($F=8.37$, $df=2/30$, $p<.05$) and a significant motion by surgery interaction ($F=9.22$, $df=2/30$, $p<.05$). Post-hoc analyses (Tukey) indicated that tail withdrawal latencies for vestibular damaged rats did not differ in the motion and restraint conditions ($p>.05$), whereas rats in both the operated and anesthetized control groups displayed significantly higher tail withdrawal latencies as a result of exposure to abnormal motion ($p<.05$).

The effectiveness of the various surgical treatments in producing vestibular dysfunction is illustrated in Figure 9. In both the balance beam and head position test, animals in the

FIGURE 8. Mean tail withdrawal latencies for the peripheral vestibular apparatus lesion (VESTIB LESION), the operated control (OPER CONTROL), and the anesthetized control (ANES CONTROL) groups of Experiment 6 after exposure to motion or restraint.

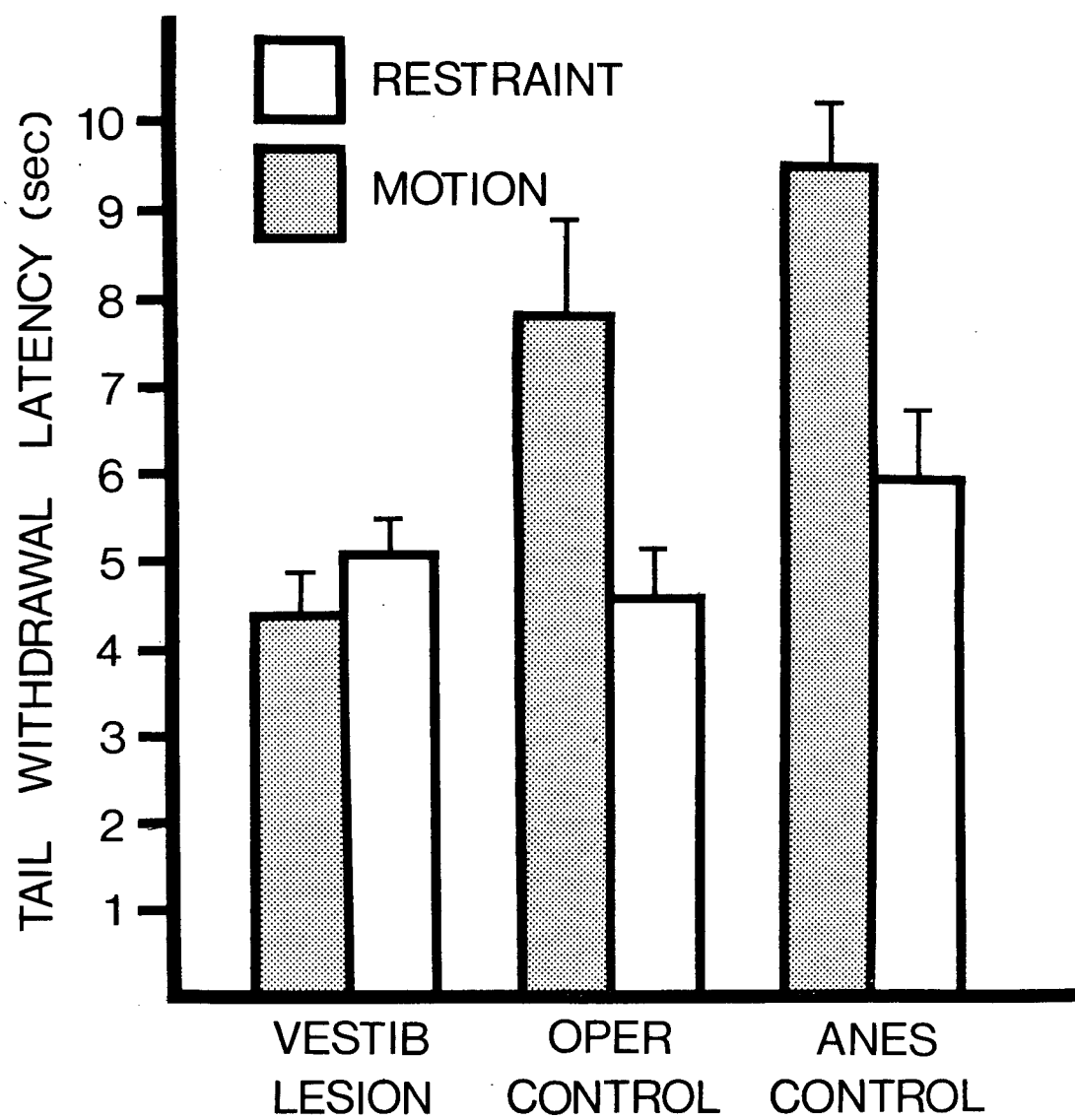
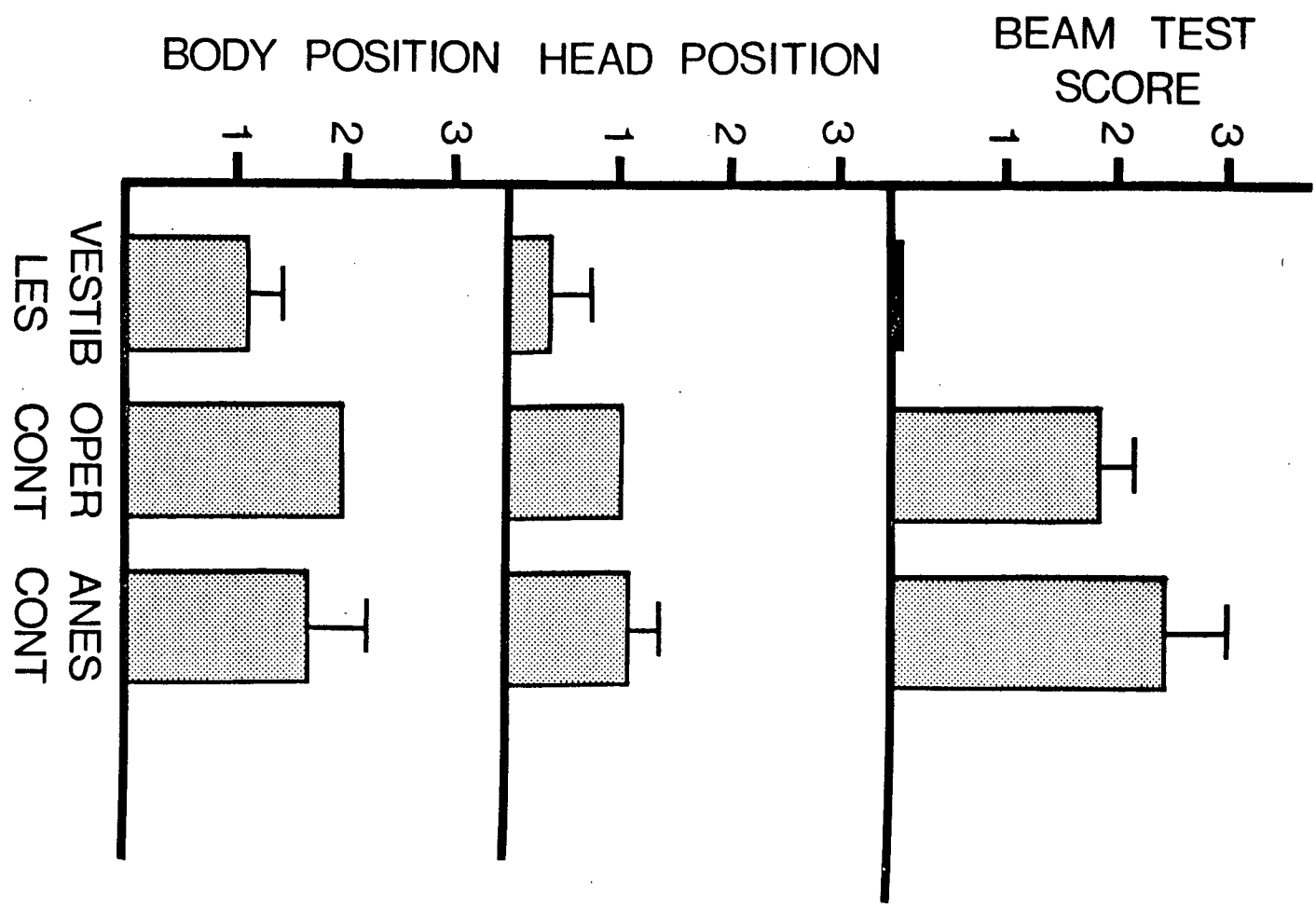


FIGURE 9. Results of vestibular dysfunction tests in Experiment 6. Rats in the peripheral vestibular apparatus lesion (VESTIB LESION), operated control (OPER CONTROL), and anesthetized control (ANES CONTROL) groups were tested in a balance beam test and were also scored on head position and body position measures.



vestibular-damaged condition showed significant performance deficits when compared to the anesthetized and operated control groups ($F=23.82$, $df=2/15$, $p<.05$ and $F=4.20$, $df=2/15$, $p<.05$, respectively). In the body position test, a significant main effect was found ($F=7.31$, $df=2/15$, $p<.05$) but post-hoc tests (Tukey) revealed that the vestibular damaged rats did not differ from the anesthetized control rats ($p>.05$). In no case did operated control and anesthetized control rats differ significantly.

These results then, provide strong support for the assumption that the vestibular system is of primary importance in mediating the antinociceptive effect of abnormal motion. When the vestibular system was rendered non-functional by destruction of the peripheral receptor organs, the antinociceptive effect of abnormal motion did not appear. This finding is consistent with that of a number of other studies that indicate a primary role for the vestibular system in the behavioural effects of abnormal motion (Graybiel, 1965; Haroutunian, Riccio, & Gans, 1976; Money, 1970) but is the first evidence that the vestibular system is essential for the antinociceptive effect of abnormal motion.

Experiment 7

It is clear from the results of Experiment 6 that the vestibular system is necessary for the antinociceptive effect of abnormal motion. The peripheral receptor lesions used in Experiment 6 disrupted all receptor input to the central vestibular nuclei, the primary processing and relay nuclei of

the vestibular system (Baloh & Honrubia, 1979; Brodal, Pompeiano, & Walberg, 1962). Although an intact vestibular receptor seemed critical for the antinociceptive effect, the role of the central nervous system vestibular structures remained unknown. Within the brainstem there are four central vestibular nuclei that receive topographic projections from the peripheral labyrinthine and otolithic receptor mechanisms (Gacek, 1975). In addition, there are direct and indirect projections from the peripheral receptors and nuclei to cerebellar nuclei (Gacek, 1975). It is unknown whether any of these central structures are of primary importance in mediating the antinociceptive effect of abnormal motion. Accordingly, the present experiment was designed to explore the possible role of some of these central vestibular mechanisms in the mediation of the antinociceptive effect.

METHOD

Subjects and Surgery

Serving as subjects in the present experiment were 40 male hooded rats, weighing approximately 300 gm at the time of surgery. Subjects were housed, purchased, and maintained as described in previous experiments. Ten rats were randomly assigned to each of four lesion groups. Three of these groups received bilateral lesions of the medial vestibular nucleus (MVN), the lateral vestibular nucleus (LVN), and cerebellum dorsal to the lateral and medial vestibular nucleus (CER), whereas, the fourth group acted as a sham lesion control group (SHAM). Of the four vestibular nuclei, only the lateral and medial vestibular nuclei were chosen for investigation because

they are relatively large and accessible in the rat.

All rats were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg, i.p.) and mounted in a stereotaxic head-holder. The scalp was incised and retracted and two small holes were drilled in the skull dorsal to the location of the intended lesion. Stereotaxic lesion coordinates were modified from those of Modianos and Pfaff (1976) and were as follows: MVN, 4.0 mm posterior to lambda, \pm 0.8 mm lateral to midline, 5.6 mm ventral to the dura; LVN, -3.8 mm post., 1.8 mm lat., 5.6 mm ventral; CER, same post. and lat. measurements as MVN (n = 5) and LVN (n = 5), 4.0 mm ventral; SHAM, same post. and lat. measurements as MVN (n = 5) and LVN (n = 5), 5.0 mm ventral. All anterior-posterior measurements were posterior to lambda with the skull level from bregma to lambda. A stainless steel electrode (size '00' insect pin, insulated with varathane except .5 mm at the tip) was then lowered to the appropriate depth and anodal direct current was passed between the electrode and an anal cathode. Current parameters were as follows: MVN lesions, .3 mA for 15 sec; LVN, .4 mA for 15 sec; CER, .3 mA for 15 sec; Sham lesioned rats underwent a similar procedure except that the electrode was lowered to a point just dorsal to the MVN (n = 5) or LVN (n = 5) and no current was passed. One rat from each of the MVN, LVN, and SHAM lesion groups died following surgery but prior to behavioural testing.

Procedure

On each of 3 days prior to testing, rats were individually adapted to the restraining tubes for a 5 min period. On the first day of testing, half of the rats in each lesion group were

assigned to the motion condition, whereas, the remaining rats in each group served in the restraint condition. Rats in the motion condition were subjected to the swinging motion used previously (30 swings). Immediately following the termination of the motion or restraint period, the standard hot-water tail withdrawal test for analgesia was administered. Immediately following the tail movement test, the balance beam test for vestibular dysfunction was administered. On the second day of testing, the same procedure was repeated except that the rats that had been subjected to abnormal motion on the first day of testing now served in the restraint condition and vice versa. Balance beam tests were again administered on Day 2. The experimental design was thus similar to that of Experiment 6. Tail flick latencies and balance scores were combined across subgroups in the cerebellar and sham lesion groups, thus providing a 4 X 2 repeated measures design with the four lesion conditions and the two analgesia tests as the levels of the two factors.

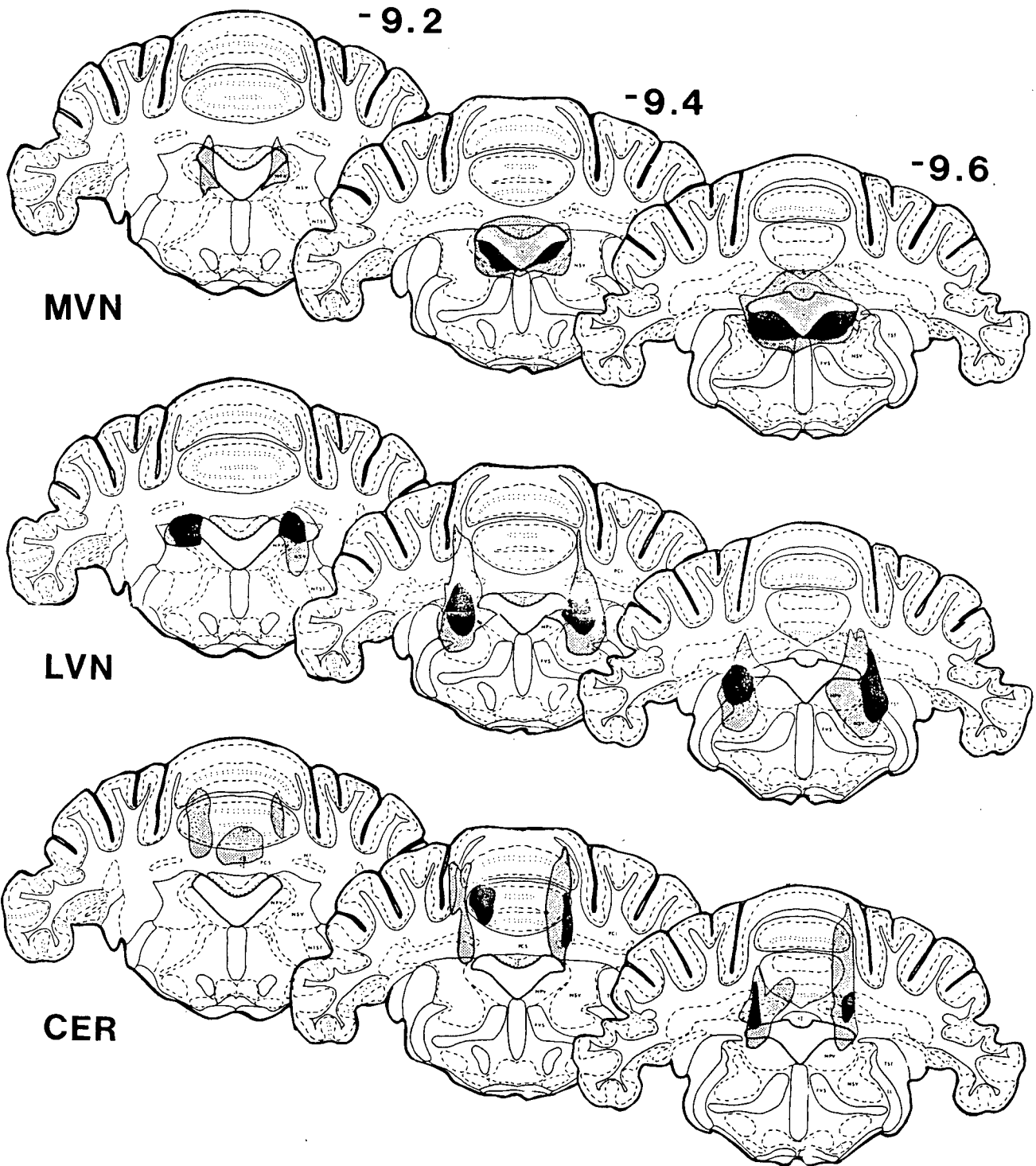
Following behavioural testing, all rats were killed in a carbon dioxide chamber and perfused intra-cardially with a .9% saline solution followed by a 10% Formalin solution. The brains were then removed and serial coronal frozen sections (30 μ m) were taken and mounted on slides to permit examination of lesion size and location.

RESULTS AND DISCUSSION

Histological results

Figure 10 illustrates the results of histological analysis and depicts both maximal and typical lesions in the LVN, MVN,

FIGURE 10. Schematic representation of lesion size and location in the medial vestibular (MVN), lateral vestibular (LVN), and cerebellar (CER) lesion groups of Experiment 10. Shaded areas indicate maximal composite extent of lesion damage while black areas indicate a typical lesion. Sections were taken from Pellegrino and Cushman (1967) and the numbers refer to the posterior distance of the section from bregma (in mm).



and CER lesion groups. All animals showed at least some damage to the intended structures but overall, the lesions were not bilaterally consistent. LVN lesions tended to include portions of the MVN and other adjacent structures such as the superior cerebellar peduncle and spinal tract of the trigeminal nerve. MVN lesions, although inconsistent, were generally restricted to the MVN with little damage to adjacent structures. CER lesions usually included damage to the nucleus interpositus and cerebellar cortex. Little or no gross damage was apparent in the sham lesioned control group (not shown in Figure 10).

Analgesia tests

Mean tail withdrawal latencies for all lesion and control groups are shown in Figure 11. Analysis of variance indicated only a significant antinociceptive effect of abnormal motion versus restraint ($F=24.13$, $df=1/33$, $p<.05$). Although the mean antinociceptive measures shown in Figure 11 are perhaps suggestive of a blocking effect of the LVN and CER lesions, the analysis of variance indicated no significant differences among lesion conditions ($F=.39$, $df=3/33$, $p>.05$) and no significant interaction between lesion type and motion or restraint ($F=1.18$, $df=3/33$, $p>.05$).

Balance tests

As shown in Figure 12, only LVN lesions resulted in profound vestibular dysfunction as measured by the balance beam test. Analysis of variance indicated a significant ($F=22.93$, $df=3/33$, $p<.05$) effect of type of lesion, but there was no significant effect of exposure to abnormal motion on subsequent

FIGURE 11. Results of Experiment 7, depicting the effects of abnormal motion on tail withdrawal latencies in the medial vestibular (MVN), lateral vestibular (LVN), cerebellar (CER), and sham (SHAM) lesion groups.

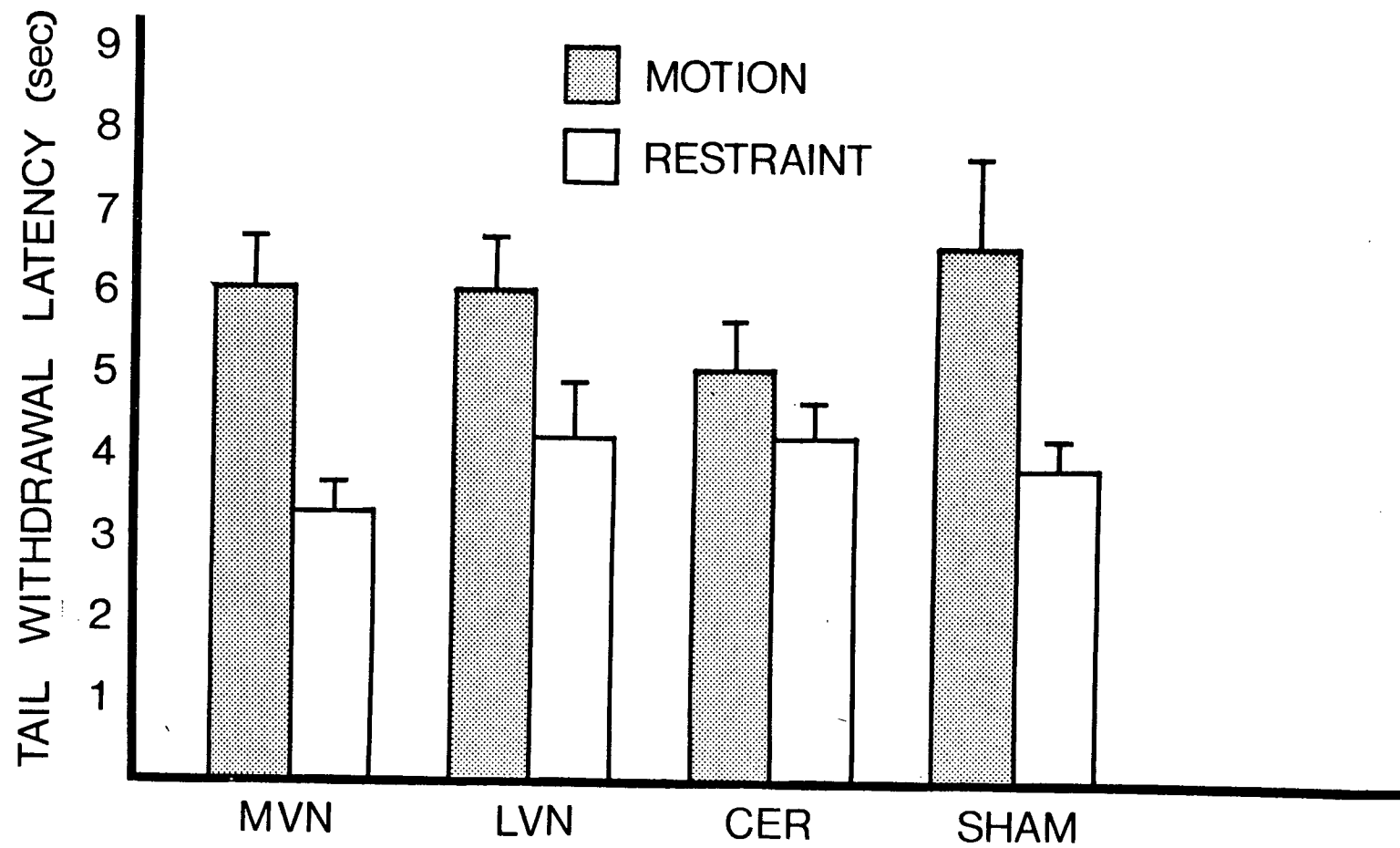
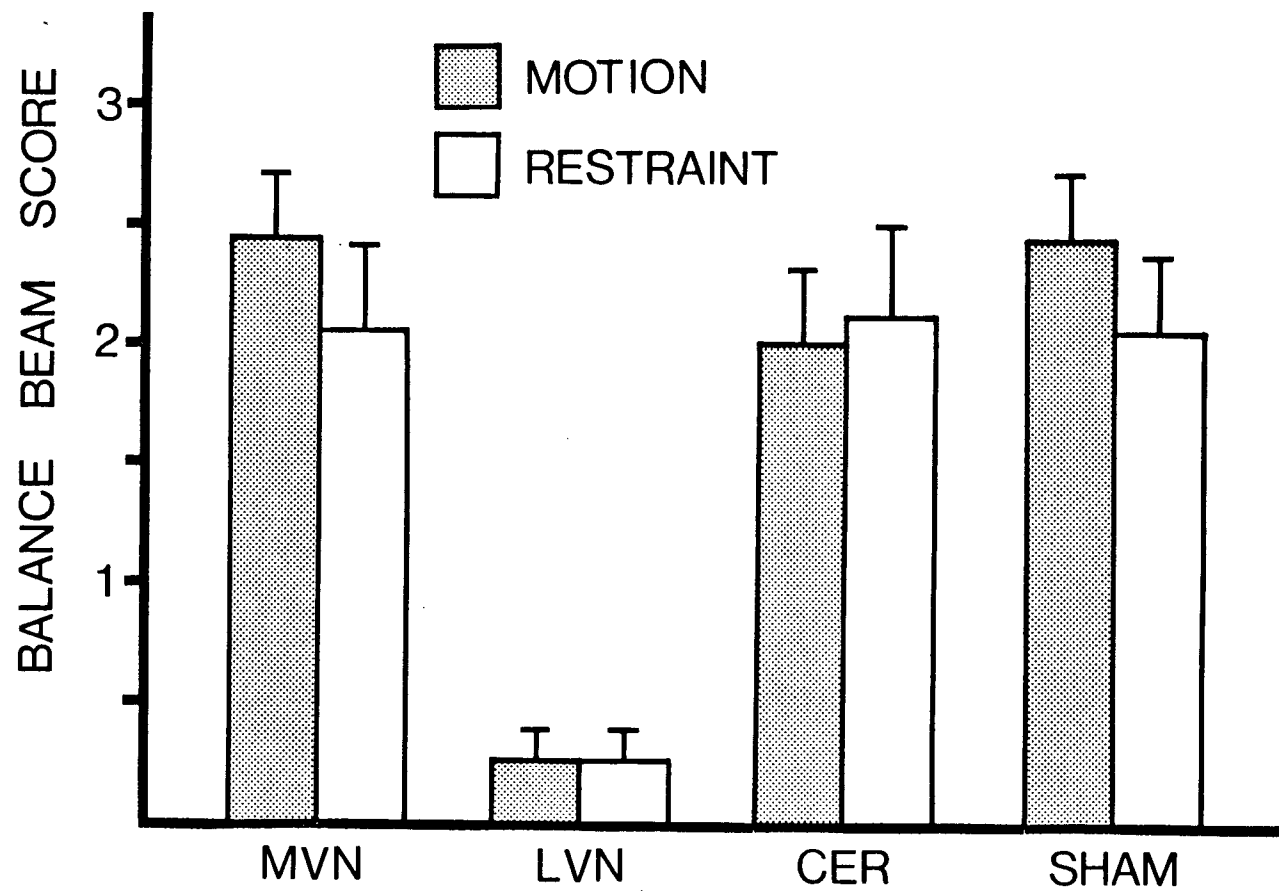


FIGURE 12. Effects of motion and restraint on balance beam scores in the medial vestibular (MVN), lateral vestibular (LVN), cerebellar (CER), and sham (SHAM) lesion groups of Experiment 7.



ability to perform in the balance beam task ($F=.45$, $df=1/33$, $p>.05$). In addition, there was no significant interaction between type of lesion and motion condition ($F=.32$, $df=3/33$, $p>.05$).

Perhaps the most important conclusion to be reached from these data concerns the fact that performance on the balance beam does not appear to be disrupted by exposure to abnormal motion. Neither the MVN or SHAM lesion groups, both of which demonstrated a clear antinociceptive response in the tail withdrawal test, appeared to suffer any performance deficit in the subsequent beam test. This would suggest that 'dizziness' is not a factor in the antinociceptive effect produced by the swinging motion. The balance beam test, although subsequent to the analgesia test, was administered well within the duration of the antinociceptive response established in Experiment 1 with an identical motion stimulus.

The failure of MVN lesions to produce a deficit in the balance beam test is somewhat puzzling. Soon after surgery, these rats were exhibiting symptoms similar both to those produced by LVN lesions in the present experiment and the peripheral vestibular apparatus lesions of Experiment 6. By the time of testing however, these MVN lesioned rats were able to perform in the balance beam test as well as the sham and cerebellar lesioned rats, none of whom showed any sign of vestibular dysfunction following surgery. It seems then, that there is a rapid recovery of function following MVN lesions. This rapid recovery of function following MVN lesions has also been noted by Modianos and Pfaff (1976) in a study of vestibular

interactions in female rat sexual behaviour. In this study, MVN lesions were found to produce severe dysfunction soon after surgery but this dysfunction was followed by a rapid recovery to near normal levels of performance within 2 weeks. Given the 2 week delay between surgery and testing used in the present experiment, this rapid recovery may well explain the apparently normal performance of the MVN lesioned animals in the balance task. Animals with LVN lesions in the Modianos and Pfaff (1976) study demonstrated vestibular dysfunction for much longer periods of time with a much slower recovery of function, also consistent with the results of the present experiment.

From these data, it is impossible to delineate a relationship between the antinociceptive effect of abnormal motion and certain central neural structures that are presumably responsible for integrating and processing information concerning the provocative stimulus. It remains possible that such a relationship exists and the failure to uncover the relationships here is merely a function of the techniques used in the investigation or the limited number of structures investigated. Lesion techniques suffer from a variety of difficulties including ion deposition, inconsistent lesion size and location, glial formation around the lesion site, etc. (see Isaacson, 1976), and hence may not be sufficiently refined or sensitive. The following experiment attempted to explore this possible brain-behaviour relationship using a different technique, electrical brain stimulation.

Experiment 8

Experiment 8 attempted to again investigate the possible involvement of some components of the central vestibular system in the neural mediation of the antinociceptive effect of abnormal vestibular stimulation. If any of these components of the central vestibular system are involved in the direct mediation of antinociception, the direct electrical stimulation of these components might elicit an antinociceptive effect. In the present experiment, electrodes were implanted in the lateral vestibular nucleus (LVN), medial vestibular nucleus, and cerebellum. Antinociception was assessed using the tail withdrawal test following a period of electrical stimulation.

METHOD

Subjects and Surgery

Serving as subjects in the present experiment were 30 male hooded rats, weighing approximately 350 gms at the time of surgery. Following surgery, all rats were individually housed in standard hanging wire mesh cages, under a reversed 12 hr light/dark cycle. Food and water were freely available at all times.

All rats were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg, i.p.) and mounted in a stereotaxic headholder. Small stainless steel screws were secured in holes drilled in the skull to provide an anchor for the acrylic cement (Flash Dental Acrylic) used to affix the electrode. Once burr holes had been placed in the skull in the appropriate locations, a unilateral bipolar electrode was lowered to the appropriate location within the brain. Electrodes were constructed of .6 mm

diameter insulated nichrome wire twisted together to form a spiral-wound pair of wires. The electrode tips were scraped clean of insulation for approximately .2 mm at the tips and the tips separated by approximately .5 mm. These bipolar electrodes were implanted in three locations within the central vestibular system: the lateral vestibular nucleus, the medial vestibular nucleus, or the cerebellum dorsal to the lateral and medial vestibular nucleus. All coordinates were based on a level skull and were identical to those described in Experiment 7. Once the electrode was in place, acrylic cement was used to secure the electrode and to build up a smooth cap on the skull containing the terminal connectors for the electrode. A 30 day recovery period was allowed to elapse between surgery and behavioural testing.

Procedure

Analgesia testing was conducted over two consecutive days. Each rat received brain stimulation followed by the hot-water tail withdrawal test one day and on the other, an equivalent period of no stimulation was followed by the tail withdrawal test. Each of the three implant groups (LVN, MVN, and CER) was divided in two; half of the group received brain stimulation the first day and a no-stimulation test on the second, whereas the remainder of the group received a no-stimulation test the first day and brain stimulation the second day. The design was thus a 3 X 2 repeated measure design, counterbalanced for test order.

In the stimulation condition, rats were connected by lightweight leads to a 60 Hz sine-wave stimulator. Stimulation parameters were controlled by a solid-state timing device that

produced a stimulation pattern of 10 sec on followed by 10 sec off. This cycle was repeated for the duration of the 5 min stimulation period. Current intensity was adjusted for each rat immediately preceding the 5 min stimulation period so that the stimulation produced a noticeable behavioural effect. Stimulation intensity was limited to a maximum of 150 ua to prevent possible damage at the electrode tip. The behavioural effects observed typically consisted of head turning and a dramatic loss of balance. Immediately following the last 10 sec stimulation period, the rat was placed in a restraining tube and the hot-water tail withdrawal test for antinociception was conducted. Rats in the no-stimulation condition were connected to the stimulator leads but no brain stimulation was delivered.

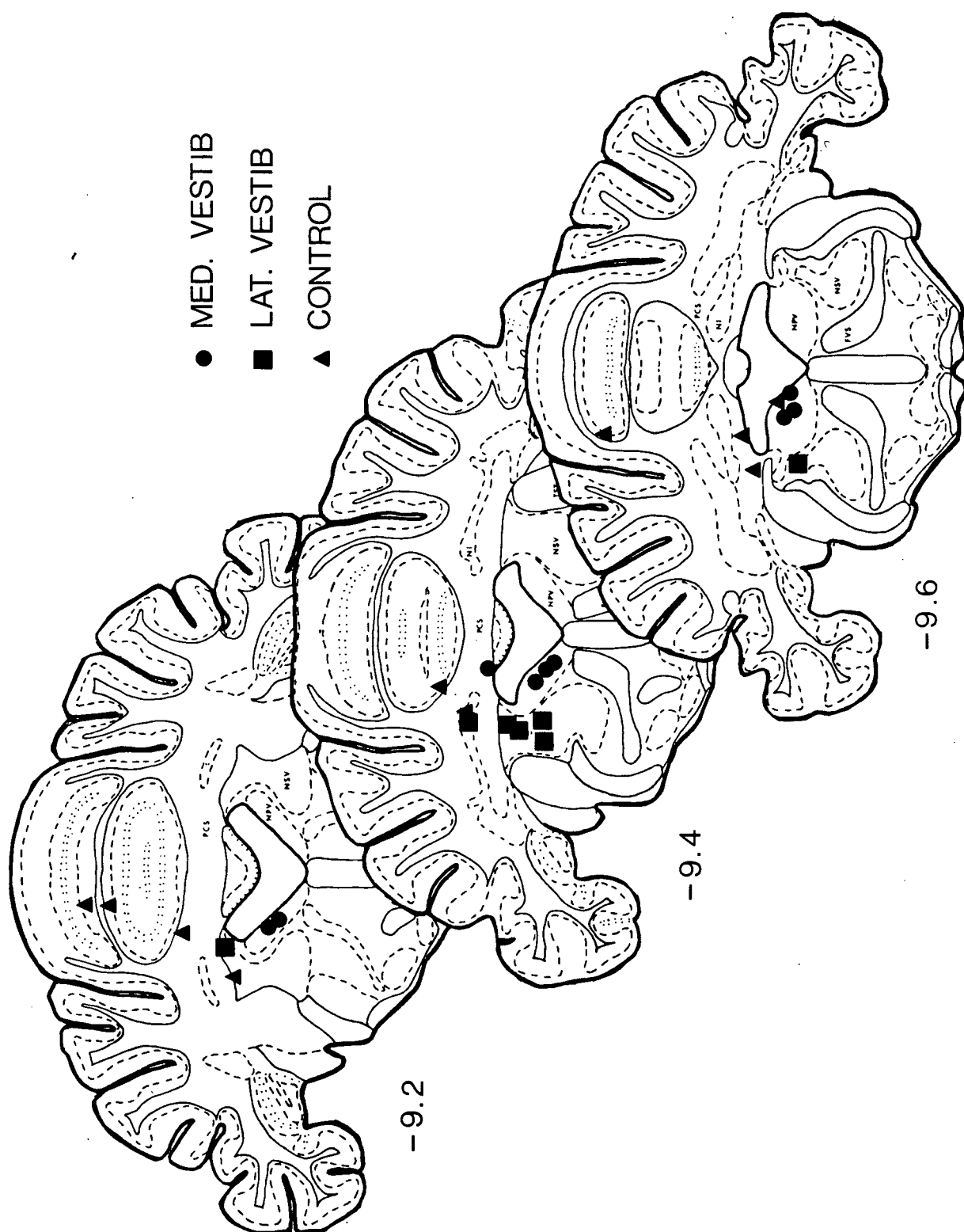
Following behavioural testing, the rats were killed in a carbon dioxide chamber and perfused intra-cardially with a .9% saline solution followed by a 10% Formalin solution. The brains were removed and serial frozen coronal sections were taken at a thickness of 30 um. Brain sections were mounted on slides and projected through a projection microscope to permit examination of electrode locations.

RESULTS

Histological results

Two animals were lost from the LVN implant group following surgery and prior to testing due to a failure of the electrode cap assembly. Electrode placements for the remaining animals are shown in Figure 13. Three animals in the MVN group had electrodes outside the MVN and hence were deleted from the analysis. Similarly, two animals were deleted from the LVN

FIGURE 13. Locations of stimulating electrodes in the medial vestibular (MVN), lateral vestibular (LVN), and control implant groups of Experiment 8.



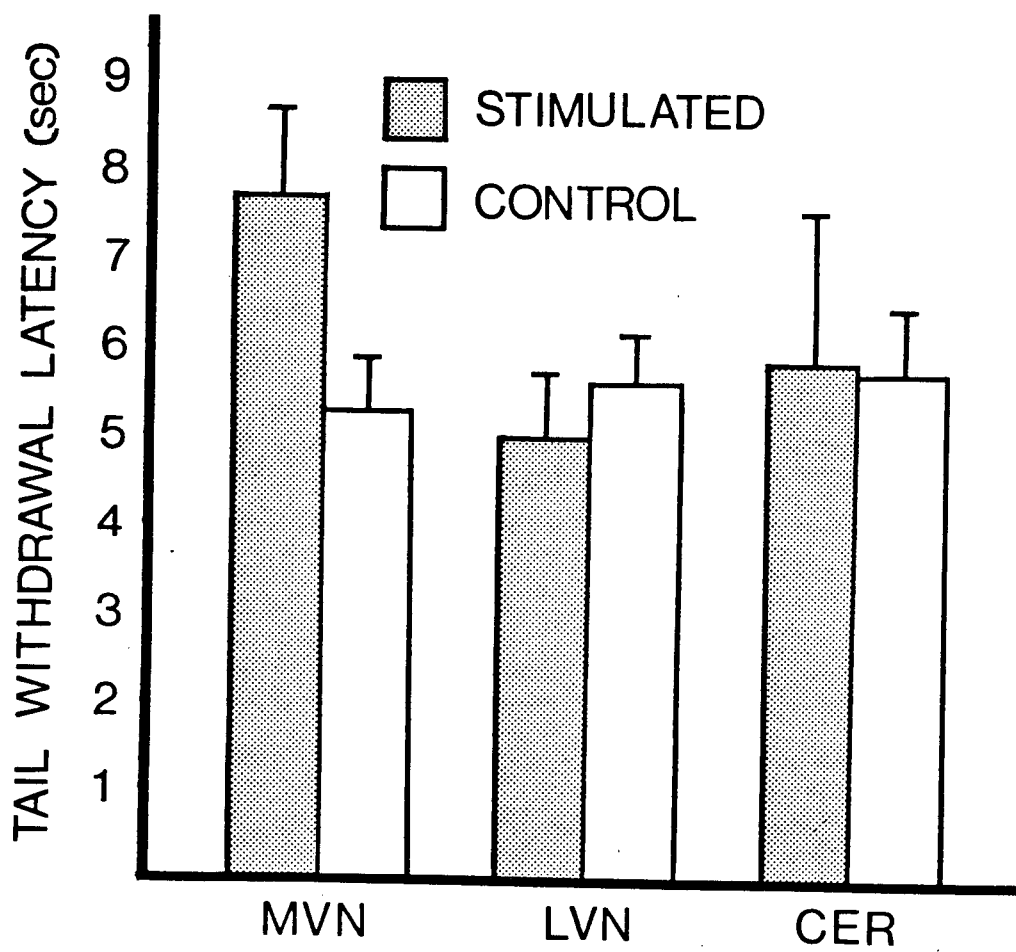
group and one from the cerebellar implant group.

Analgesia tests

As shown in Figure 14, electrical stimulation of the LVN, MVN, or cerebellum did not produce any obvious changes in tail withdrawal latencies. Analysis of variance indicated no significant effect of electrical stimulation with any electrode placement ($F=.46$, $df=2/19$, $p>.05$; $F=.33$, $df=1/19$, $p>.05$). It was clear from informal observation that all subjects included in the analysis exhibited behaviours consistent with stimulation of the vestibular system (Modianos & Pfaff, 1977). The most frequent result of stimulation was a tilting of the body and the head in the MVN and LVN placements. Cerebellar placements produced a variety of effects that were less consistent than the LVN and MVN behaviours such as tilting to the right or left, falling forward, or no effect. Electrode placements outside the intended stimulation sites generally produced either no effect or behavioural effects qualitatively different than those produced by LVN or MVN stimulation. These stimulus bound effects included chewing and licking directed at the floor of the cage or body appendages, in vacuo chewing and facial movements, and in one case, backwards walking and rapid respiration. Stimulation in these sites also did not produce a noticeable antinociceptive effect in the present experiment.

The results of the present experiment using electrical stimulation failed to find a clear relationship between central vestibular components and the antinociceptive effect of abnormal motion. These data, considered with the results of Experiment 7, which involved the lesion technique, would suggest that if

FIGURE 14. Effects of electrical stimulation in the medial vestibular nucleus (MVN), lateral vestibular nucleus (LVN), or cerebellum (CER) on tail withdrawal latencies in Experiment 8.



this relationship exists, it is not a simple one. It would seem that the antinociceptive response is not obviously mediated by any one component of the central vestibular system. It is possible then, that the antinociceptive effect is mediated by the interaction of the various components and selectively eliminating or activating one component cannot reveal the nature of the interaction.

It is also possible that other factors in the present experiment could have obscured the presence of an existing one-to-one correspondence between antinociception and a particular vestibular component. First, the small group sizes that remained for statistical analysis following histological analysis may have decreased the power of the analysis sufficiently that an antinociceptive effect was not detected. Second, the non-physiological nature of the electrical stimulation itself may also have masked the involvement of particular components. That is, it is unlikely that the pattern and intensity of electrical stimulation used here activates vestibular components in a manner that exactly resembles activation produced by the normal innervation of these components.

A third possible criticism applies to the limited number of stimulation sites chosen for investigation. While the LVN, MVN, and cerebellum are the largest and perhaps major components of the rat vestibular system, there are other components such as the descending and superior vestibular nuclei (Gacek, 1975) that were not investigated here.

The possibility that dizziness resulting from vestibular

stimulation is the primary explanation for the antinociceptive effect is also addressed here. The electrical stimulation used in the present study produced behavioural effects (loss of balance, head tilt, etc.) consistent with dizziness. This stimulation-induced 'dizziness' however, produced no detectable analgesic action in the tail-withdrawal test. It would seem that although dizziness may certainly result from abnormal vestibular function, its role as a causal factor in the antinociception phenomenon is far from a simple relationship.

General Discussion - Section II

The experiments contained in this section attempted to explore the role of the vestibular system in an antinociceptive effect of abnormal motion. The results of Experiment 6 indicate that the vestibular system is indeed an important and necessary component for the genesis of the antinociceptive phenomenon. When input from the vestibular receptor organs was removed by destruction of the peripheral mechanisms, the antinociceptive effect of abnormal motion failed to occur.

It is clear that the vestibular system is an integral part of the antinociceptive response mechanism yet further attempts to delineate the relative contributions of some central nervous system components to this effect were unsuccessful. Although it seems reasonable to suggest that the vestibular system must be involved in mediating this effect at a somewhat higher level than the receptor level, no clear-cut relationships were found to exist between the central vestibular structures investigated and the antinociceptive effect. This lack of an obvious relationship between the antinociceptive effect of vestibular stimulation and central components of the vestibular system could be the result of a number of factors.

First, it is possible that the lesion and electrical stimulation techniques used here are not sufficiently refined or sensitive to allow delineation of the involvement of the various components examined. The electrolytic lesion technique suffers from a variety of problems including difficulty in controlling the size and location of the lesion produced, ion deposition, etc. (Isaacson, 1976), and the electrical stimulation technique

used here did not exactly mimic physiological activity in the structures stimulated.

Second, the failure to find an obvious relationship between the antinociceptive effect and a particular structure could imply that no one specific structure is directly responsible for the antinociceptive phenomenon. That is, the central vestibular system may not be involved through a specific mechanism limited to a particular portion of the vestibular system but through a much more general mechanism involving more components. It is also possible that the complexity and flexibility of the central vestibular system itself renders a straightforward lesion or stimulation approach to the study of the involvement of various components extremely difficult. The rapid recovery of function found following MVN lesions is a case in point. If the MVN were involved in the antinociceptive effect, the rapid compensation for its destruction by other mechanisms could well obscure this relationship.

The experiments described here also provide a great deal of useful information concerning the nature of the antinociceptive response itself. It could perhaps be argued that the apparent antinociceptive effect of abnormal motion reflects nothing more than a direct inhibitory effect on the spinal tail withdrawal reflex used here as a behavioural measure of antinociception. There are a number of vestibulo-spinal projections and these projections may well affect spinal reflex behaviours (Gacek, 1975). Modianos and Pfaff (1976a, 1976b) for example, have shown that lesions of brainstem and cerebellar vestibular nuclei result in an inhibition of the spinal lordosis reflex in female

rats and that stimulation of these same structures results in facilitation of this same reflex.

In contrast, the present series of experiments found that lesions and electrical stimulation of the same structures had no effect on performance of the tail withdrawal reflex when compared to non-lesioned control animals (Experiments 7 and 8). It should also be noted that if vestibular stimulation were directly related to tail withdrawal performance in the same manner as that described for the lordosis reflex (Modianos & Pfaff, 1977), one would predict vestibular stimulation to facilitate rather than inhibit performance of the tail withdrawal reflex as seen here. The antinociceptive effect of abnormal motion then, most probably does not involve a direct vestibulo-spinal inhibitory effect.

The issue of dizziness as a result of vestibular stimulation, discussed earlier as a possible causal factor in the antinociceptive effect, is also addressed by the experiments presented in this section. The experiments presented here provide at least three arguments against the 'dizziness' hypothesis. First, lesions that produce deficits in the balance beam task do not necessarily block the appearance of an antinociceptive effect of motion nor do they appear to produce any analgesic effect themselves. If dizziness produced antinociception in some simple fashion, one would expect animals that were dizzy to show altered baseline tail withdrawal measures relative to non-dizzy controls. Second, motion treatments such as swinging, are capable of producing a significant antinociceptive effect while not producing any other

behavioural evidence of vestibular dysfunction. The swinging motion used in Experiment 7 for example, produced an analgesic effect while not affecting performance on a subsequent balance beam test. Third, Experiment 8 demonstrated that it is possible to produce behavioural evidence of vestibular dysfunction (i.e. inability to remain upright) that may be analogous to dizziness without producing an antinociceptive response.

The foregoing experiments, although not conclusive, suggest that 'dizziness' is certainly not related in any simple fashion to the antinociceptive effect of abnormal motion. It is, of course, possible that a relationship does exist but it seems that this relationship is not easily delineated.

In summary then, the experiments presented here demonstrate that the vestibular system is a necessary component of the physiological mechanism of the antinociceptive effect of abnormal motion. The following series of experiments attempted to investigate the physiological mechanisms by which abnormal vestibular stimulation may exert an effect on nociception.

SECTION III - Mechanisms of Motion-Induced Analgesia

The purpose of the experiments in Section III was to determine whether the physiological mechanisms involved in mediating the antinociceptive effect of abnormal motion are the same as those that have recently been proposed to account for other forms of nonpharmacological pain modulation.

Although a variety of nonpharmacological treatments have been reported (e.g., Melzack, 1973) to induce analgesia (e.g., acupuncture, trans-cutaneous electric shock, massage, intense broad spectrum noise, electrical brain stimulation, and hypnosis), the physiological mechanisms underlying these effects has been difficult to assess. However, two recent findings have stimulated interest in this problem. The first was the discovery of endogenous opiate-like peptides within the central nervous system, and the second was the discovery of the stress-induced analgesia phenomenon.

The stress-induced analgesia phenomenon involves the presence of analgesia following exposure of the subject to severe physiological stressors such as footshock (Buckett, 1979; Chesher & Chan, 1977; Hayes, Bennet, Newlon, & Mayer, 1978), immersion in cold water (Bodnar, Kelly, Spiaggia, & Glusman, 1978), 2-deoxy-D-glucose injections (Bodnar, Kelly, & Glusman, 1979), insulin injections (Bodnar, Kelly, Mansour, & Glusman, 1979), exposure to high gravity environments (Hayes, Bennet, Newlon, & Mayer, 1978), or food deprivation (McGivern, Berka, Berntson, Walker, & Sandman, 1979). Exposure to such physiological stressors produces a large antinociceptive effect in a variety of tests for analgesia such as radiant-heat tail-

flick tests (Chance & Rosecrans, 1979), flinch-jump tests (Bodnar, Kelly, Spiaggia, & Glusman, 1978), hot-plate tests (Amir & Amit, 1978), and operant shock threshold tests (Bodnar, Kelly, Brutus, Mansour, & Glusman, 1978). The antinociceptive effects of these treatments have been variously found to exist for periods of 5 (e.g. Buckett, 1979) to 120 min (Bodnar, Kelly, & Glusman, 1978) following termination of the stressor.

Mechanisms of Stress-Induced Analgesia

Much of the research directed at the physiological mechanisms of stress-induced analgesia involves the possible role of endogenous opiate peptides (endorphins) in endogenous pain modulation. The endorphin hypothesis of pain modulation arises from an extremely large body of literature demonstrating that there are stereospecific receptors for opiates in the central nervous system (Snyder, 1975; Snyder & Pert, 1975) and that there are a number of endogenous opiate-like peptides that bind to these receptors (Kosterlitz & Hughes, 1978; Leong Way, 1979; Terenius, 1978). There are three endorphin molecules that are commonly thought to have a possible role in endogenous pain modulation (Adler, 1980; Basbaum & Fields, 1978; Bishop, 1980; Kosterlitz, 1979). The first of these is B-endorphin. B-endorphin is restricted in the central nervous system to the basal hypothalamus and pituitary and is derived from B-Lipoprotein, a precursor common to B-endorphin and α -melanocyte stimulating hormone (Li, 1979; Rossier & Bloom, 1979). The remaining two endogenous opiate peptides are Met-enkephalin and Leu-enkephalin. These molecules are smaller in size than B-endorphin and are much more widely distributed throughout the

nervous system (Kuhar & Uhl, 1979). Met- and Leu-enkephalin are generally found to coexist within the same sites in both the CNS and periphery (Kuhar & Uhl, 1979). Although there are differences in duration of action, structure, and localization of these three peptides (Basbaum & Fields, 1978; Bishop, 1980; Kosterlitz, 1979), in the present context they are considered together as a general class of neuromodulators, the endorphins, unless distinctions are necessary.

Consistent with the proposed role of opiate-like peptides in endogenous pain modulation (Basbaum & Fields, 1978; Bishop, 1980; Kosterlitz, 1979; Liebeskind, 1978; Terenius, 1979), the endorphins have been shown to have definite pain modulating properties in a variety of species. B-endorphin, when administered intravenously (Tseng, Loh, & Li, 1977), intracranially (Rossier & Bloom, 1979), or intrathecally (Yaksh & Henry, 1978) is capable of producing analgesia similar to that produced by morphine. The enkephalins, Met- and Leu-enkephalin, are also capable of producing analgesia upon intra-cranial administration (Miller & Cuatrecasas, 1979) although the analgesia produced is of much shorter duration than that produced by intracranial B-endorphin. Although there is some doubt as to whether the endorphins are capable of penetrating the blood-brain barrier when administered intravenously (Rapoport, Klee, Pettigrew, & Ohno, 1980), it is clear that they are capable of analgesia in at least some cases of exogenous administration (Kastin, Jemison, & Coy, 1979; Tseng, Loh, & Li, 1977). Other evidence of a role of endorphins in pain modulation is somewhat less direct in nature. Brain areas that

produce analgesia when stimulated electrically (Mayer, Wolfe, Akil, Carder, & Liebeskind, 1971; Soper, 1976) tend to be the same areas in which endorphins are concentrated (Basbaum & Fields, 1978; Kuhar & Uhl, 1979)). Naloxone, a relatively pure opiate antagonist, is able to at least partially reverse or block the analgesic effects of brain stimulation in these areas (Akil, Mayer, & Liebeskind, 1976). Patients in severe chronic pain have been shown to have decreased levels of endorphins in cerebro-spinal fluid (von Knorring, Almay, Johansson, & Terenius, 1978) and females of the several species have been shown to have highly elevated plasma levels of endorphins at parturition (Csontos, Rust, Holtt, Mahr, Kromer, & Teschemacher, 1979; Gintzler, 1980; Torda, 1978). In addition, severe physiological stress has also been shown to increase central nervous system endorphin activity and to produce a significant degree of analgesia in subsequent tests (Akil, Madden, Patrick, & Barchas, 1976; Chance, White, Krynock, & Rosecrans, 1978).

The possible mechanism for stress-induced analgesia seems clear: stress induces a release of endorphins and this increased activity in endogenous opiate peptide systems produces analgesia in a manner similar to the analgesia produced by exogenous opiate administration.

In order to validate the endorphin model of stress-induced analgesia, at least two commonly accepted criteria must be met (Sawynok, Pinsky, & LaBella, 1979). The stress-induced analgesia effect should be reversed or blocked with the use of a specific opiate antagonist, and it should display cross-tolerance with morphine. Both of these criteria must be met in

order to infer that the stress-induced analgesia effect is operating through an opiate mechanism. The use of an antagonist drug, which presumably occupies the receptor sites (Snyder, 1975; Snyder & Pert, 1975), establishes action on an opiate receptor and the cross-tolerance establishes the common mechanism of action of stress-induced and opiate analgesia.

The SIA phenomenon does not consistently meet either of these criteria. Chesher and Chan (1977) and Buckett (1979) have shown that analgesia induced by footshock is both reversible by naloxone and shows cross-tolerance with morphine. Bodnar, Kelly, and Glusman (1979) have shown that 2-deoxy-D-glucose analgesia shows cross-tolerance with morphine but is little affected by naloxone administration. Other studies have demonstrated analgesic effects that are neither affected by naloxone administration nor show cross-tolerance with morphine (e.g. Chance & Rosecrans, 1979a, 1979b).

This inability to implicate endogenous opiate peptides in all forms of SIA has led to the formulation of a dual mechanism hypothesis. This hypothesis (e.g. Bodnar, Kelly, & Glusman, 1979; Bodnar, Zimmerman, Nilaver, Mansour, Thomas, Kelly, & Glusman, 1980; Spiaggia, Bodnar, Kelly, & Glusman, 1979) suggests that there are two forms of endogenous pain modulation systems activated by stress, one an opiate mechanism and the other a non-opiate mechanism. These mechanisms may be activated either independently, or together and would thus explain the inconsistent findings. For example, if naloxone is ineffective in reversing or blocking a stress-induced analgesic effect, one might infer that the analgesic mechanism operating is non-opiate

in nature.

Although this hypothesis may explain the analgesic actions of different stressors, it also has some implications for the use of the term 'stress' in a general sense as a unitary phenomenon in inducing analgesia. Commonly accepted definitions usually define stress in terms of physiological variables (Leschner, 1978; Selye, 1956). That is, a stressor is any event that produces a supra-normal activation of the pituitary-adrenal axis and adrenal medullary system (e.g. Leschner, 1978; Mason, 1968). The presence and magnitude of this physiological response is thought to reflect the presence and magnitude of the 'stress' on the organism (e.g. see Burchfield, Woods, & Elich, 1980; Pfister, 1979). It is clear from the data discussed above that although the environmental events used to induce analgesia are stressors by the present definition, there is no consistent activation of a single pain modulation system by these stressors. In fact, there are stressors such as exposure to ether and horizontal oscillation that do not produce any analgesic effect at all (Hayes, Bennet, Newlon, & Mayer, 1978). In terms of the mechanisms of stress-induced analgesia then, it appears that stress may activate both an opiate and non-opiate pain modulation system, one or the other of these systems, or neither system at all.

The purpose of Section III was to evaluate the antinociceptive effect of abnormal motion in terms of the mechanisms proposed for the stress-induced analgesia phenomenon. Although as discussed above, stress may not be sufficient for the appearance of an antinociceptive response or the activation

of a particular pain modulating mechanism, it does appear necessary for the appearance of a stress-induced analgesic effect. For the antinociceptive effect of abnormal motion to be viewed within the stress-induced analgesia paradigm, it would seem necessary to show a 'stressor' effect of abnormal vestibular stimulation.

In humans, it seems clear that abnormal vestibular stimulation produces an activation of the pituitary-adrenal axis and other physiological effects consistent with the definition of stress. Humans subjected to abnormal vestibular stimulation show elevated plasma adrenal steroid levels, increased urinary steroid metabolite levels, and increased prolactin and growth hormone secretion (Eversman, Gottsman, Uhlich, Ulbrecht, von Werder, & Scriba, 1978; Reason & Brand, 1975). In animals, increased levels of plasma vasopressin and adrenal steroids have been found in the cat during motion induced illness (Fox, Kiel, Daunton, Thomson, Dictor, & Chee, 1980).

The experiments described below were designed to evaluate the antinociceptive effect of abnormal motion in terms of the mechanisms proposed for SIA. Particular attention then, was directed at attempting to discriminate the possible involvement of opiate or non-opiate mechanisms of the motion-induced analgesic effect. This possibility was tested in terms of the two criteria discussed above: reversal by an opiate antagonist and the development of cross-tolerance with morphine.

Experiment 9

The purpose of Experiment 9 was to investigate a possible

mechanism of the antinociceptive effect of abnormal motion. If this effect is mediated by endogenous opiates, then the antinociceptive effect should be blocked or attenuated if the rat is pre-treated with an opiate antagonist drug prior to exposure to abnormal motion. Opiate antagonists are thought to occupy the opiate receptor sites on the neuron and exert varying degrees of opiate-like actions themselves (Snyder, 1975; Snyder & Pert, 1975). Some opiate antagonists, such as naloxone and naltrexone, are relatively 'pure' antagonists in that they block opiate action at the receptor level but exert few if any opiate-like actions themselves (Snyder, 1975; Snyder & Mathysse, 1975; Snyder & Pert, 1975).

Accordingly, rats were pre-treated with varying doses of an opiate antagonist prior to exposure to the abnormal motion treatment and subsequently tested in the hot-water tail withdrawal test for antinociception.

METHOD

Subjects

Serving as subjects in the present experiment were 60 male hooded rats. The rats weighed between 300 and 400 gm and were group housed in hanging wire cages under a reversed 12 hr light/dark cycle. Food and water were freely available.

Procedure

Five groups of 12 rats each were injected with one of four different doses (.125 mg/kg, .25 mg/kg, .50 mg/kg, 1.0 mg/kg) of naloxone hydrochloride (Endo Laboratories) or the vehicle only. The naloxone hydrochloride was dissolved in sterile saline solution (.9% w/v) such that all groups received an equivalent

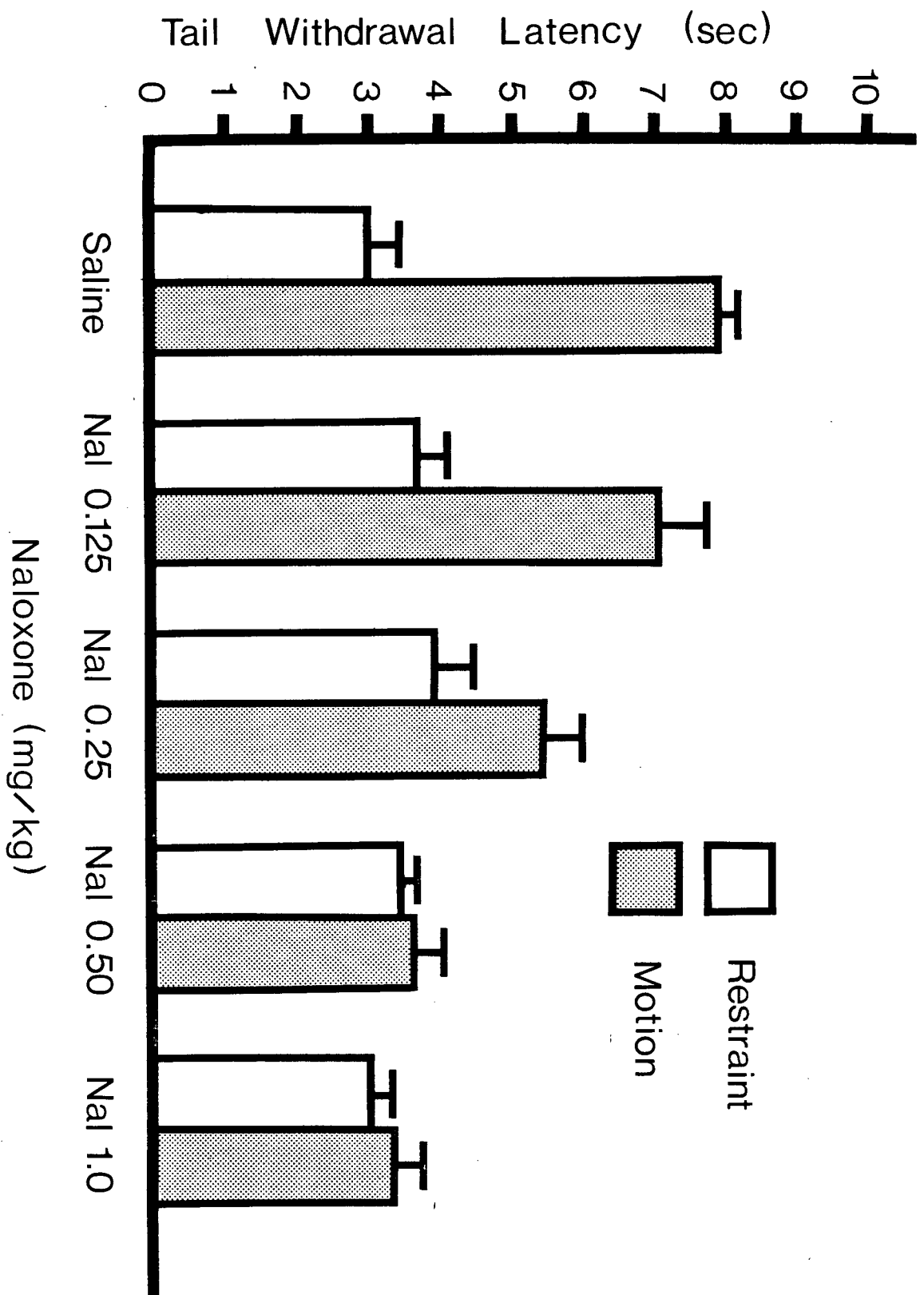
injection volume (1 ml/kg). All drug and vehicle treatments were administered (i.p.) 15 min prior to testing.

Six rats from each of the naloxone or vehicle groups were subjected to the swinging motion (30 swings) described previously and the remaining six received restraint only. The experimental design was thus a 2 X 5 factorial with motion or restraint and naloxone dose as the two factors. Each rat was placed in a restraining tube and underwent the motion treatment or an equivalent period of restraint 15 min after the drug injection. Immediately following the motion or restraint treatment, a hot-water tail withdrawal test of analgesia was conducted. Rats were individually tested and the order of testing was counterbalanced across groups.

RESULTS

As may be seen in Figure 15, naloxone hydrochloride at doses of .5 and 1.0 mg/kg appeared to block the antinociceptive effect of motion shown in the vehicle injected controls and in those animals treated with .125 mg/kg naloxone. Analysis of variance indicated a significant effect of motion ($F=84.73$, $df=1/50$, $p<.05$), a significant dose effect ($F=19.75$, $df=4/50$, $p<.05$), and a significant motion by dose interaction ($F=16.68$, $df=4/50$, $p<.05$). Post-hoc analysis (Tukey) indicated that of the five naloxone and vehicle groups, only the .5 and 1.0 mg/kg groups did not differ significantly with respect to tail withdrawal latencies in the swing and restraint conditions, thus confirming the blocking action of naloxone in these groups. In the restraint condition, tail withdrawal latencies did not differ significantly among the vehicle and naloxone-injected

FIGURE 15. Effects of various doses on naloxone hydrochloride on the motion-induced analgesia phenomenon in Experiment 9.



groups.

DISCUSSION

The present results indicate that pretreatment with the opiate antagonist naloxone hydrochloride produces a dose-dependent blockade or reversal of the antinociceptive effect of abnormal motion. At doses of .5 and 1.0 mg/kg, this reversal was total and the antinociceptive effect of abnormal motion was completely blocked. This reversal of the antinociceptive effect is consistent with the involvement of an endogenous opiate mechanism in the production and maintenance of this antinociceptive effect.

This evidence does not conclusively implicate an endogenous opiate pain modulation system. Naloxone, in addition to its opiate antagonist action, appears to have other pharmacological effects (Sawynok, Pinsky, & LaBella, 1979). It is possible that the blocking or reversing effect of naloxone on the antinociceptive effect of abnormal motion is due to an action of naloxone other than its action on the opiate receptor. It is for this reason that Sawynok, Pinsky, and LaBella (1979) have suggested that naloxone reversal is a necessary but not a sufficient criterion for implicating an opiate mechanism. Other authors however, appear to disagree (e.g. Fanselow, 1979; Fanselow & Bolles, 1979).

One means of differentiating between an opiate and non-opiate mechanism would be to demonstrate a dissociation between the effects of naloxone on antinociceptive effects produced by two different stressors: cold-water swimming-induced antinociception, a putative non-opiate stress-induced analgesia

(Bodnar, Kelly, Steiner, & Glusman, 1978) and abnormal motion-induced antinociception, a putative opiate analgesia mechanism.

Experiment 10

Experiment 10 was an attempt to dissociate the effects of naloxone on two forms of stress-induced analgesia: one produced by abnormal motion and the other produced by cold-water swimming. Analgesia produced by cold-water swimming has been suggested to be mediated by a non-opiate mechanism and is relatively unaffected by naloxone treatment (Bodnar et al., 1980; Spiaggia et al., 1979). If the antinociceptive effects of abnormal motion and cold-water swimming were differentially affected by naloxone, one could argue that the inhibitory effects of naloxone on analgesia produced by abnormal motion is due to a factor other than some nonspecific effect of naloxone (Sawynok, Pinsky, & LaBella, 1979).

METHOD

Subjects

Serving as subjects in the present experiment were 60 male hooded rats, weighing approximately 300 gm at testing. served as subjects in the present experiment. All subjects were housed in groups and were purchased and maintained as described previously.

Procedure

On each of 3 days prior to testing, all subjects were acclimated to the restraining tubes for a 5 min period. On the fourth day, 20 rats were randomly assigned to one of three conditions: motion, restraint, or cold-water swim. Ten animals

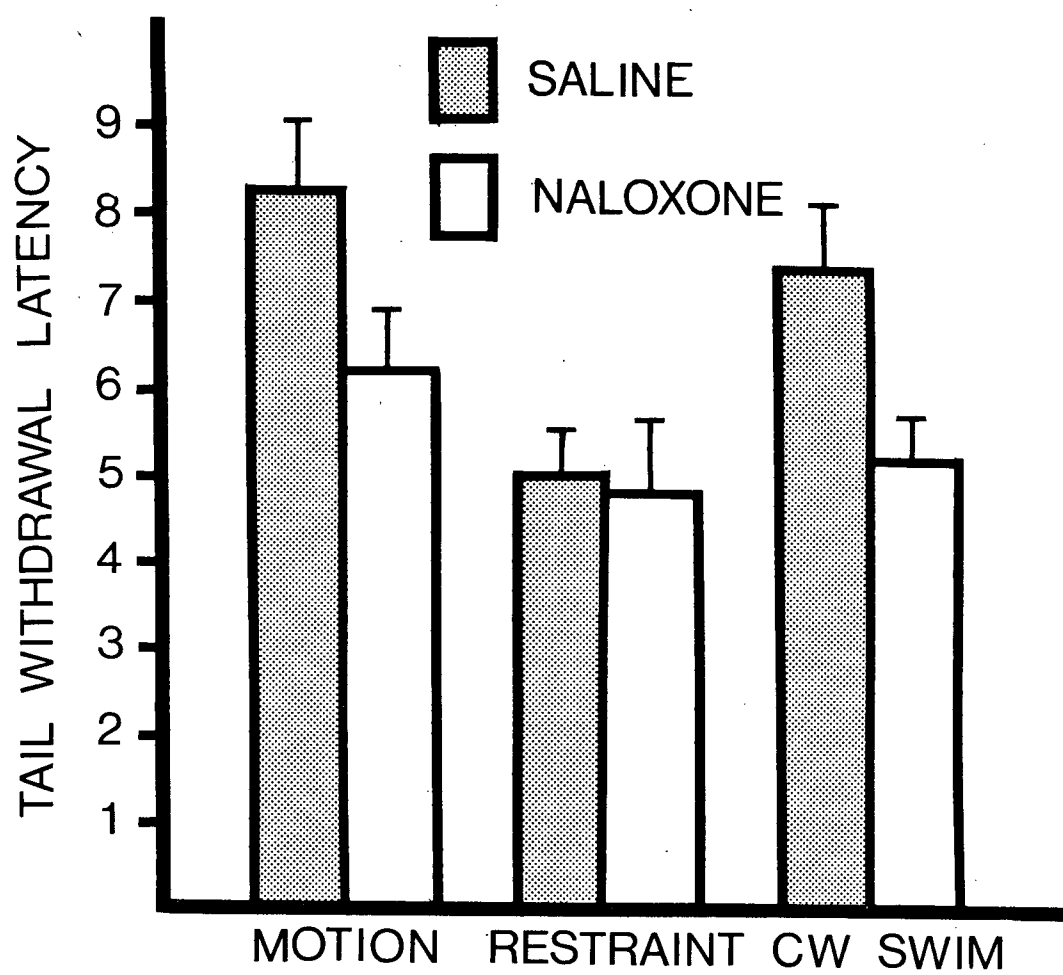
from each group received an injection (i.p.) of naloxone hydrochloride (5 mg/kg) and the remaining 10 animals received injections of the sterile saline vehicle. This high dose of naloxone was chosen in an effort to extend the dose response relationship of Experiment 9 and to ensure the antinociceptive effect of motion would be totally blocked. The design of the experiment was thus a 2 X 3 factorial.

The appropriate treatment was administered 15 min following the naloxone or vehicle injection. In the motion condition, each rat was subjected to the swinging motion used previously (30 swings). In the restraint condition, each rat was placed in the restraining tube for an amount of time equivalent to that required to administer the motion treatment (approximately 30 sec). In the cold-water swim condition, the rats were placed in a 36.5 cm deep, 34 cm diam tank containing 22 cm of constantly circulating cold water (12° C). The animals remained in the water for 2.5 min (Bodnar, Kelly, Thomas, & Glusman, 1980) and were then removed and placed in a restraining tube for an additional 2.5 min. Immediately following the administration of these treatments, the hot-water tail withdrawal test for analgesia was conducted and tail withdrawal latencies recorded. In addition, balance beam tests were administered to the rats in the motion and restraint groups to determine the possible effects of naloxone on vestibular functioning.

RESULTS AND DISCUSSION

The results of Experiment 10 are shown in Figure 16. As shown by the figure, naloxone appeared to block the antinociceptive effects of both abnormal motion and cold-water

FIGURE 16. Results of Experiment 10 illustrating differential effects of naloxone (5 mg/kg) on tail withdrawal latencies in motion, restraint, and cold-water swim (CW SWIM) treatments.



swimming. A priori comparisons (t-test) indicated a significant effect of naloxone in the motion ($t=2.45$, $df=17$, $p<.05$) and cold-water swim ($t=2.45$, $df=18$, $p<.05$) conditions, but not in the restraint condition ($t=.35$, $df=18$, $p>.05$). Subsequent analysis of variance indicated a significant effect of naloxone ($F=6.6$, $df=1/54$, $p<.05$), a significant effect of type of treatment ($F=5.76$, $df=2/54$, $p<.05$), but the interaction term was not significant ($F=.99$, $df=2/54$, $p>.05$). Post hoc comparisons (Tukey) indicated that in the naloxone-injected groups, restraint, cold-water swim, and motion group scores did not differ ($p>.05$). In the saline-injected groups, the motion and cold-water swim groups did not differ from each other but both had significantly greater tail withdrawal latencies than those of the restraint group ($P<.05$).

These results confirm that naloxone hydrochloride is capable of reversing or blocking the antinociceptive effect of abnormal motion. Naloxone also appeared to inhibit the development of analgesia when rats were exposed to forced swimming in cold-water. This is particularly surprising because Bodnar, Kelly, Spiaggia, Ehrenberg, and Glusman (1978) had failed to observe any substantial effects of naloxone on cold-water swim-induced analgesia even at doses as high as 20 mg/kg. It is possible however, that procedural differences could account for this apparent discrepancy. Bodnar et al. used cold-water at 2° C and the rats were unable to touch the bottom of the swim tank. In the present study, the water was somewhat warmer (12° C) and the rats were able to touch the bottom of the swim tank and leap briefly out of the water along the smooth

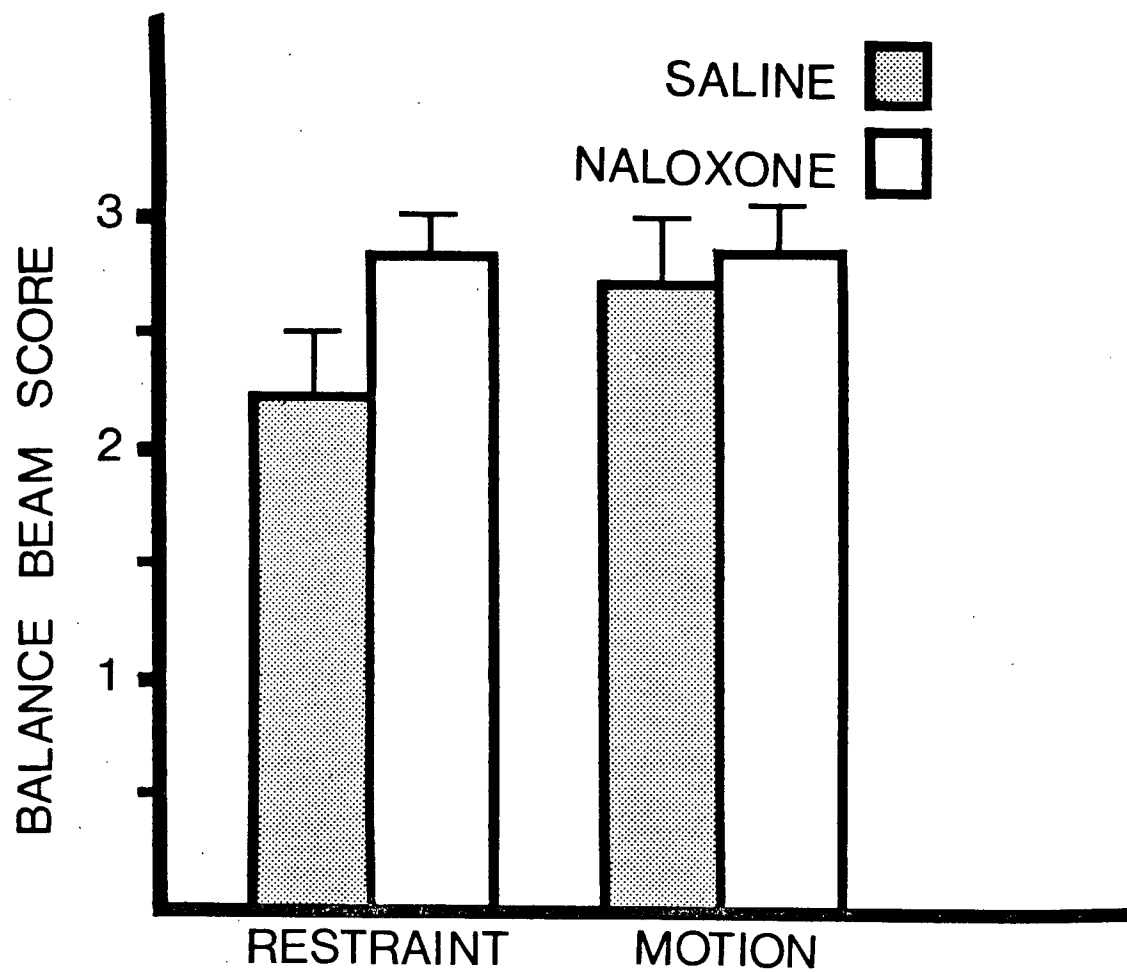
sides of the tank. Lewis, Cannon, and Liebeskind (1980) and Jackson, Maier, and Coon (1979) have shown that the reversibility of footshock-induced analgesia by naloxone varies with the manner in which the shock is administered and whether the shock is escapable or inescapable. A similar situation may have existed in the present experiment and may thus explain the failure to dissociate an opiate or non-opiate mechanism in terms of the effects of naloxone in two different forms of stress-induced analgesia.

Balance scores

Analysis of the balance beam scores (see Figure 17) indicated no effect of either motion ($F=1.21$, $df=1/36$, $p>.05$) or naloxone administration ($F=3.94$, $df=1/36$, $p>.05$). Clearly the 'dizziness' or possible vestibular dysfunctions induced by swinging or the possible elimination of dizziness by naloxone do not explain either the antinociceptive effect or its reversal by naloxone.

The present experiment then, has confirmed the naloxone sensitivity of the antinociceptive effect of abnormal motion. While this is a necessary condition, it is not sufficient for implicating an endogenous opiate mechanism (Sawynok, Pinsky, & LaBella, 1979). Because the naloxone also appeared to decrease tail withdrawal latencies in the CWS group, it was not possible to differentiate possible opiate from non-opiate mechanisms for motion-induced antinociception. In order to determine whether or not motion-induced antinociception was mediated by an opiate mechanism, it was necessary to demonstrate the development of cross-tolerance between the antinociceptive effects of morphine

FIGURE 17. Mean balance beam scores for rats receiving saline or naloxone in the restraint or motion treatment conditions of Experiment 10.



and motion. This issue was addressed in Experiment 11.

Experiment 11

Experiment 11 investigated the possible development of cross-tolerance between the antinociceptive effect of abnormal motion and the antinociceptive effect of morphine. Tolerance refers to the decline in effectiveness of a particular treatment with repeated administration (Julien, 1975; Leavitt, 1974). For example the analgesic efficacy of a particular dose of morphine declines over repeated administration of the drug. Cross-tolerance between two or more treatments indicates that once tolerance has developed to a particular treatment, then tolerance will also exist for a novel treatment. If cross-tolerance does develop between two treatments, this would imply that each treatment exerts its effect through a similar mechanism (Bodnar, Kelly, Steiner, & Glusman, 1978; Chance & Rosecrans, 1979; Pert & Maxey, 1975; Sawynok, Pinsky, & LaBella, 1979). For example, in an organism made tolerant to morphine, demerol will produce less analgesia than usual. One can infer then, that both of these drugs exert their individual effects through an identical action of the opiate receptor.

This technique for determining the nature of a tolerance mechanism may also be applied to analgesia induced by non-pharmacological means. If cross-tolerance develops between the treatment in question and a treatment for which the mechanisms are identified, then it may be inferred that the non-pharmacological treatment is exerting its effect through the same mechanisms as the known treatment. In the case of the

antinociceptive effect of abnormal motion, if the antinociceptive effect is mediated through an endogenous opiate mechanism, then cross-tolerance should develop between abnormal motion and exogenous opiate administration. The purpose of the present experiment then, was to examine the possible development of cross-tolerance between abnormal motion and morphine administration.

METHOD

Subjects

Serving as subjects in the present experiment were 40 naive male hooded rats, weighing approximately 350 gm. Subjects were housed in groups and were purchased and otherwise maintained as described previously.

Procedure

The experiment consisted of two consecutive phases: first, a chronic phase during which the development of tolerance to abnormal motion and morphine was assessed, and second, an acute test phase during which possible cross-tolerance between the treatments was assessed.

Chronic phase. Ten animals were randomly assigned to each of the four treatment conditions: abnormal motion, restraint, morphine, or morphine vehicle. The abnormal motion used was the swinging motion (30 swings) used previously. The restraint treatment consisted of placing the rat in the restraining tube for a period of time equivalent to the duration of the swinging motion. Immediately following the motion or restraint treatment, a hot-water tail withdrawal test for analgesia was conducted. Morphine sulfate (7.5 mg/kg) was dissolved in

sterile saline (.9% w/v) in a concentration of 7.5 mg/ml and administered (i.p.) 15 min prior to analgesia testing in the hot-water tail withdrawal test. In the vehicle condition, a body weight dose of the saline vehicle was administered 15 min prior to analgesia testing.

Each treatment was administered at 24 hr intervals for 6 days. The repeated testing in the morphine and abnormal motion groups allowed the development of tolerance over time to be examined. The inclusion of the restraint and vehicle conditions allowed the elimination of non-specific factors that may have affected the analgesia measures obtained and also allowed the presence and magnitude of the analgesia produced by each of these treatments to be assessed. The development of tolerance was demonstrated by comparing scores obtained in each treatment condition on Day 1 to the respective scores on Day 6 using a priori comparisons (t-test for dependent measures).

Acute test phase. On the day following the chronic treatment phase, the acute cross-tolerance test phase was begun. All 40 animals in the four chronic treatments were tested for antinociception in a no-treatment baseline condition, the abnormal motion condition, and the morphine condition. The no-treatment baseline test was included to ensure that there were no residual effects of the previous chronic treatments or that the tail withdrawal reflex had in any way been altered. In the acute motion test, all animals were individually subjected to the swinging motion used in the chronic phase of the experiment. Tail withdrawal latencies were taken immediately following the cessation of motion. Two hours following the acute motion test,

the rats were injected with 7.5 mg/kg morphine sulfate dissolved in sterile saline. Another tail withdrawal test was conducted 15 min following the injection.

A priori comparisons between the experimental groups and the appropriate control groups were conducted for each of the baseline, motion, and morphine conditions in the acute phase. These comparisons were used to evaluate the possible development of cross-tolerance. If for example, cross-tolerance was found to exist between morphine and abnormal motion, the chronic morphine group should show significantly less antinociception than the chronic vehicle-injected animals.

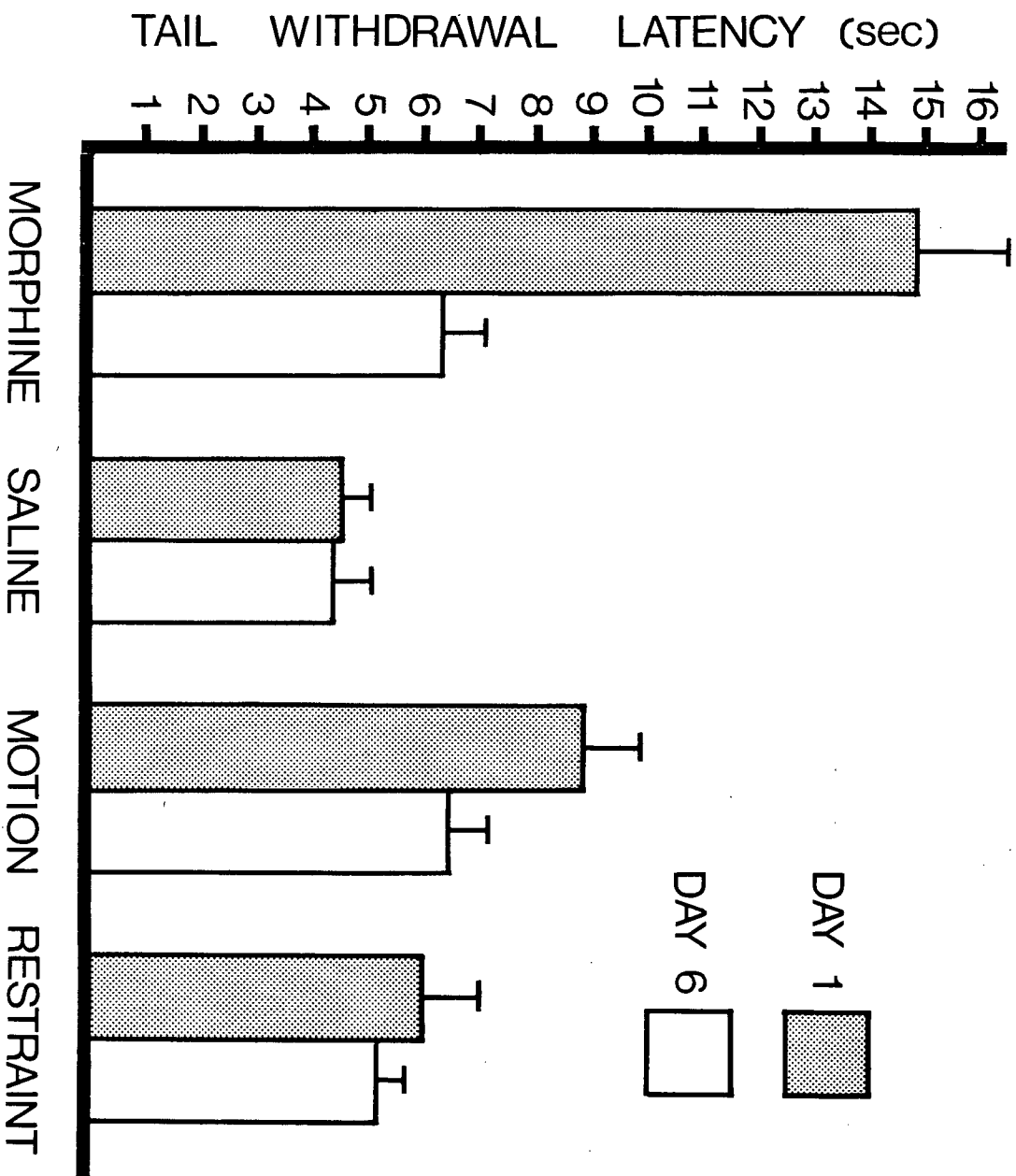
RESULTS

Chronic administration phase

It is clear from Figure 18 that there was a decrease in tail withdrawal latencies as a function of repeated administration of morphine and motion. A priori comparisons (t-tests for dependent measures) of Day 1 and 6 scores indicated that this decrease was significant in the repeated morphine condition ($t=3.77$, $df=8$, $p<.05$) but the change in tail withdrawal latencies failed to reach significance in the repeated motion exposure condition ($t=1.72$, $df=9$, $p>.05$). Neither the saline nor restraint conditions demonstrated any significant change in tail withdrawal latencies from Day 1 to Day 6. The failure to find significant tolerance development in the motion condition raises some questions concerning the capability of the antinociceptive effect of abnormal motion to develop tolerance following repeated administration.

Analysis of variance indicated a significant effect of

FIGURE 18. Mean tail withdrawal latencies for rats receiving daily administration of morphine, saline, motion, or restraint in the chronic phase of Experiment 11. The figure illustrates tail withdrawal latencies on the first (DAY 1) and last (DAY 6) days of the chronic administration phase.



treatment ($F=25.6$, $df=3/35$, $p<.05$), a significant effect of repeated administration ($F=17.03$, $df=3/35$, $p<.05$), and a significant interaction between these factors ($F=8.57$, $df=3/35$, $p<.05$). Post-hoc analysis (Tukey) indicated that both the morphine and motion treatments produced significant analgesia when compared to the saline and restraint conditions, respectively ($p<.05$). The data for one animal in the restraint condition were deleted from this analysis in accordance with procedures described by Li (1969) for outlying data points.

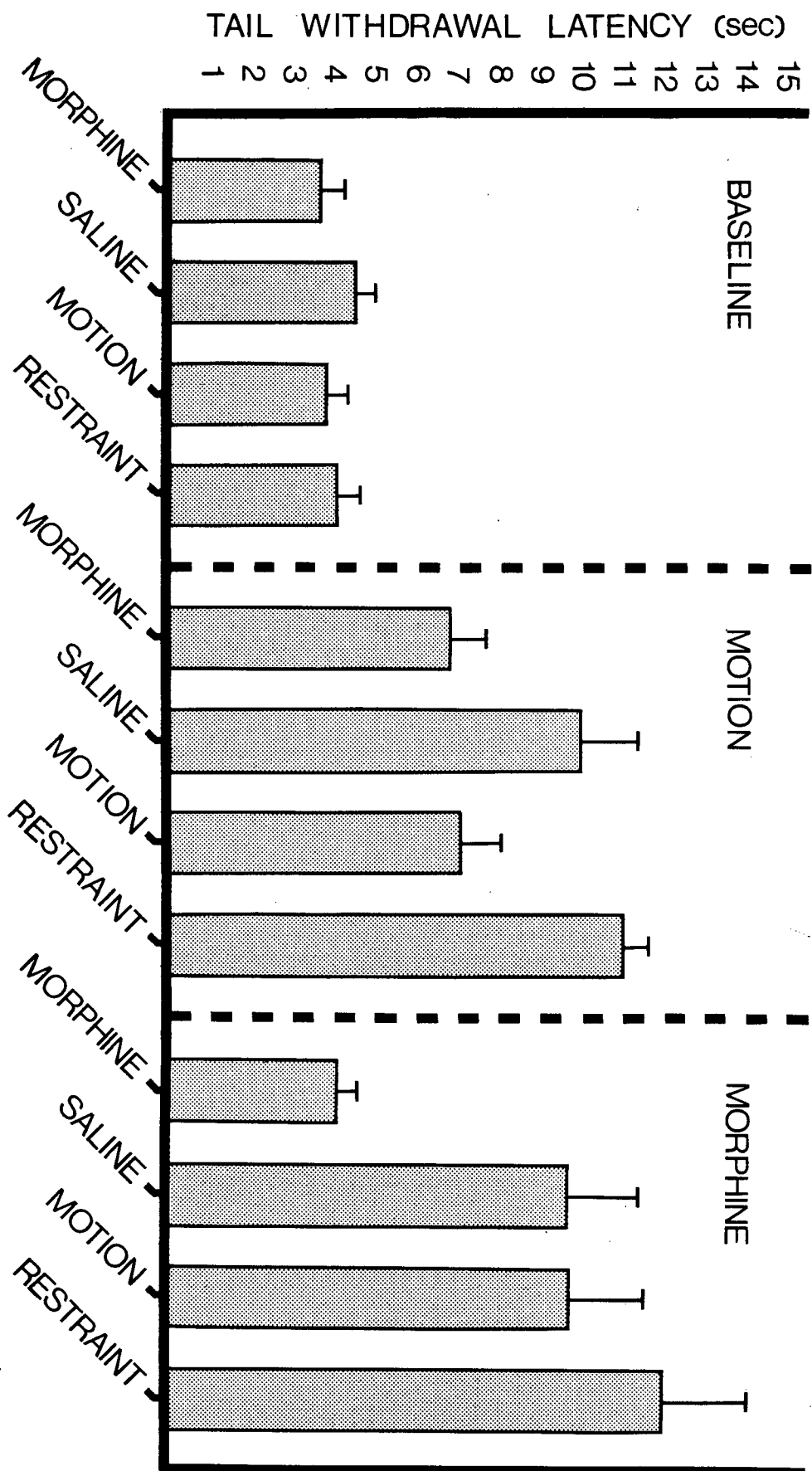
Acute test phase

The results of the three tests in the acute test phase are illustrated in Figure 19. A priori comparisons (t-test for independent measures) were used in all three tests to compare the experimental groups to their respective controls.

Baseline test. When rats in the four treatment conditions were tested in the no-treatment baseline test, no differences were found between the motion and morphine groups when compared to their respective control groups (motion versus restraint, $t=.51$, $df=18$, $p>.05$; morphine versus saline, $t=-1.24$, $df=17$, $p>.05$).

Motion test. In the acute motion test, both the motion and morphine groups were found to exhibit tail withdrawal latencies that were significantly lower than those shown by the appropriate control groups (motion versus restraint, $t=3.79$, $df=18$, $p<.05$; morphine versus saline, $t=2.12$, $df=17$, $p<.05$). In contrast to the results of the chronic phase of the present experiment, the acute motion test indicated that repeated exposure to motion did produce tolerance to the antinociceptive

FIGURE 19. Results of the acute test phase of Experiment 11. The figure illustrates a no-treatment baseline test and the effects of abnormal motion and morphine (7.5 mg/kg) in rats that had been chronically exposed to morphine, saline, motion, or restraint.



effects of abnormal motion. Prior repeated exposure to morphine also attenuated the antinociceptive effect when this group was exposed to abnormal motion for the first time.

Morphine test. In the acute morphine test, the morphine treatment group displayed significantly lower tail withdrawal latencies than did animals that were exposed to morphine for the first time ($t=2.97$, $df=17$, $p<.05$). Prior repeated exposure to motion however, did not result in significant cross-tolerance to morphine as the latencies in the motion group were not significantly different from those exhibited by the restraint group when both groups were exposed to morphine ($t=.86$, $df=18$, $p>.05$).

DISCUSSION

The results of the chronic and acute testing phases of the present experiment indicate that tolerance can develop to the antinociceptive effects of morphine and abnormal motion, the degree of antinociception produced by each of these treatments declined with repeated daily treatments. This effect was not due to repetition of the tail withdrawal test as neither the restraint nor the saline groups showed any change in tail withdrawal latencies over repeated administration of the test in the chronic phase. Moreover, the fact that tail withdrawal latencies were almost identical across the treatment groups in the no-treatment baseline test in the acute phase further demonstrated that the apparent tolerance effect was not due to a direct effect on the integrity of the tail withdrawal reflex.

Results of the acute testing phase of the present experiment seem to implicate an endogenous opiate mechanism in

the mediation of the antinociceptive effect of abnormal motion. Rats that had been made tolerant to the analgesic effects of morphine showed reduced antinociception in response to motion in a subsequent test when compared to groups of animals chronically exposed to either restraint or saline injections. The tail withdrawal scores were virtually identical in the chronic morphine and chronic motion groups. This cross tolerance would suggest that the antinociceptive effects of abnormal motion and the antinociceptive effects of morphine are mediated by similar mechanisms (Buckett, 1979; Sawynok, Pinsky, & LaBella, 1979). The fact that an opiate receptor mechanism is involved in the analgesic effect of morphine (Snyder & Pert, 1975) further indicates that the abnormal motion effect must also involve an opiate receptor mechanism and hence an endogenous opiate system that is activated upon exposure to the abnormal motion.

Although cross-tolerance does appear to exist between chronic morphine and acute testing with motion, cross-tolerance does not appear to exist between chronic motion preexposure and acute testing with morphine. One could argue that if there were a common mechanism of action, then cross-tolerance should exist regardless of which treatment was chronically administered (see Sawynok, Pinsky, & LaBella, 1979). This reciprocal or symmetrical cross-tolerance phenomenon however, would seem to assume that each treatment activates the underlying mechanism to the same extent. In fact, asymmetric cross-tolerance is not an unusual finding (e.g., Brown, Amit, Smith, & Rockman, 1979; Pert & Maxey, 1975). For example, consider the situation where two different doses of the same drug are used for both the chronic

and acute testing phase. If a high dose of the drug were used chronically and tolerance develops, one would expect no analgesic effect upon administration of the low dose of the same drug. If on the other hand, the low dose were used to develop tolerance, the high dose would likely still produce a behavioural effect upon acute testing. It would be unparsimonious to argue that the same drug is affecting two different mechanisms at the two doses, yet the data would suggest asymmetrical cross-tolerance. Reciprocal cross-tolerance then, would seem to be an unnecessary criterion for establishing common mechanisms between drugs. A similar situation may have existed in the present experiment and would explain the lack of reciprocal cross-tolerance between morphine and abnormal motion.

The present experiment then, by demonstrating cross-tolerance between morphine administration and abnormal motion, has provided additional evidence that an endogenous opiate mechanism plays a role in the antinociception induced by abnormal motion. This finding and those of Experiments 9 and 10 demonstrating that the antinociceptive effect can be blocked with the use of a relatively pure opiate antagonist, fulfil the criteria discussed earlier for implicating an endogenous opiate mechanism in motion-induced antinociception. The motion-induced analgesia phenomenon is perhaps unusual in that the mechanism appears relatively straightforward: motion induces a release of endogenous opiate peptides and these peptides then exert a pain modulating effect. Although the evidence for an endogenous opiate mechanism is strong, which opiate peptides are involved

and the locus and release mechanisms of these peptides is unknown. A preliminary investigation of this question was undertaken in Experiment 12.

Experiment 12

B-endorphin, Met-enkephalin, and Leu-enkephalin are distributed differentially throughout various gland and organ systems in the body (Basbaum & Fields, 1978; Bishop, 1980; Miller & Cuatrecasas, 1979; Rossier & Bloom, 1979). B-endorphin for example, is primarily restricted to the pituitary and basal hypothalamus. Met- and Leu-enkephalin, on the other hand, are located in the adrenal cortices and the adrenal medulla (Schultzberg, Lundberg, Hokfelt, Terenius, Brandt, Elde, & Goldstein, 1978; Yang, Hexum, & Costa, 1980) as well as being distributed in some CNS sites (Kuhar & Uhl, 1979).

It seems reasonable to suggest that if the endorphins are involved in analgesia induced by stress, they would be stored in and released from systems that are responsive to stress. Such systems include the CNS itself and hormonal systems such as the hypothalamic-pituitary-adrenal axis and the adrenal medullary system (Mason, 1968; Selye, 1956). The present experiment focussed on the possible involvement of the hypothalamic-pituitary axis and the adrenal medullary system in the mediation of the antinociceptive effect of abnormal motion. Both of these hormonal systems have been shown to be extremely responsive to physiological stressors and the pituitary-adrenal axis has been previously implicated in some forms of stress-induced analgesia.

The hypothalamic-pituitary-adrenal axis responds to stress

in the following manner (Leschner, 1978; Levine, 1972; Selye, 1956). Application of a stressor causes a release of corticotropin releasing factor (CRF) from the basal hypothalamus which passes through the hypophyseal portal system to the anterior pituitary. From the pituitary, adrenocorticotrophic hormone (ACTH) is released into the circulation and then stimulates the production and release of steroid hormones from the adrenal cortices (e.g., corticosterone, cortisol). These secretory products exert a negative feedback influence on CRF release in the hypothalamus and in the absence of an ongoing stressor, would cause ACTH secretion from the pituitary to cease. These hormonal events are, of course, not the only hormonal events to occur upon application of a stressor. In addition to activation of the pituitary-adrenal axis, thyroid activity is stimulated, prolactin is released from the pituitary, and various other hormonal events occur (Leshner, 1978).

Not only do B-endorphin and ACTH share the same precursor molecule (Adler, 1980; Li, 1979; Rossier & Bloom, 1979) but they are also located together in the pituitary (Goldstein & Cox, 1977). It also appears that B-endorphin and ACTH are secreted simultaneously by the pituitary (Guillemin, Vargo, Rossier, Minick, Ling, Rivier, Vale, & Bloom, 1977). A situation accompanied by ACTH secretion then, may well be accompanied by an increase in B-endorphin secretion from the pituitary.

Pituitary B-endorphin has been implicated by a number of authors in a variety of non-pharmacological pain modulation effects. Bodnar and his co-workers (Bodnar, Glusman, Brutus,

Spiaggia, & Kelly, 1979; Bodnar, Kelly, Mansour, & Glusman, 1979) have shown that hypophysectomy, or removal of the pituitary, greatly decreases the analgesia produced by cold-water swimming or 2-deoxy-d-Glucose in animals. Amir and Amit (1978) have further demonstrated that hypophysectomy greatly attenuates the analgesia produced by immobilization in rats. Treatment with dexamethasone, a synthetic glucocorticoid, attenuates the analgesia produced by acupuncture (Cheng, Pomeranz, & Yu, 1979). Dexamethasone is thought to produce this effect by mimicking adrenal steroid negative feedback action on the hypothalamus and thus decreasing ACTH (and presumably B-endorphin) secretion.

The other stress-sensitive hormonal mechanism considered here is the adrenal medullary system. This system responds to stress by secreting epinephrine (adrenaline) and norepinephrine (noradrenaline) into the circulatory system. These catecholamines have a variety of autonomic effects including changes in blood pressure, heart rate, respiration, and glucose mobilization. Although endorphins (Met- and Leu-enkephalin) have been found within neurosecretory cells in the adrenal medulla (Yang, Hexum, & Costa, 1980), they have yet to be implicated in pain modulation. It is also possible that the adrenal medullary hormones are involved in stress-induced analgesia in another manner. Dworkin, Filewich, Miller and Craigmyle (1979) have recently demonstrated that analgesia may be produced by activation of the carotid reflex by treatment with a sympathomimetic drug. A similar antinociceptive effect may be produced if catecholamines released by the adrenal

medulla elicit the carotid reflex in a similar fashion.

One way of testing these hypotheses would be to assess the degree of motion-induced antinociception following removal of the adrenal gland. Removal of the adrenal gland eliminates the feedback inhibition of ACTH secretion and hence produces greatly increased secretion of ACTH (Martini, Motta, & Muller, 1964). If Guillemin et al. (1977) are correct, increased ACTH secretion should be accompanied by greatly increased pituitary B-endorphin secretion. This increase in B-endorphin concentrations could have at least two direct results. One possible result would be an antinociceptive effect of adrenalectomy alone as a by-product of increased ACTH secretion. As this effect could mask the effect of abnormal motion, adrenalectomized animals not subjected to abnormal motion were included in the present experiment. The second result might be the development of tolerance to the analgesic effects of B-endorphin secreted by the pituitary. Tolerance does develop to the effects of exogenously administered B-endorphin (Adler, 1980; Huidobro-Toro & Leong Way, 1978; Kosterlitz, 1979) and this tolerance effect would attenuate any antinociceptive effect of abnormal motion in adrenalectomized animals. Adrenalectomy would also remove any contribution of adrenal medullary hormones (catecholamines or enkephalins) and hence should also attenuate the antinociceptive effect of abnormal motion if these substances are involved. Adrenalectomy also has the advantage of a minimal debilitating effect on the animal (providing a saline solution is available), at least when compared to the effects of hypophysectomy. The present experiment then,

investigated the possible effects of adrenalectomy on the antinociceptive effects of abnormal motion.

METHOD

Subjects and surgery

Forty male hooded rats weighing approximately 350 gm served as subjects in the present experiment. Subjects were purchased and maintained in groups as described previously.

On the day of surgery, all subjects were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg, i.p.) and randomly assigned to either the adrenalectomy (ADREX, n = 20) or sham-adrenalectomy (SHAM, n = 20) surgical groups. Adrenalectomies were accomplished using a bilateral lumbar approach. The kidney was gently extracted from the body cavity and the adrenal gland visualized and removed. The kidney was then replaced and the abdominal wall and skin incisions were closed with silk sutures. Sham-adrenalectomies were accomplished following the same procedure except the adrenal was merely visualized. Following surgery, all adrenalectomized animals were allowed continuous access to .9% saline solution. Following behavioural testing, the animals were sacrificed in a carbon dioxide chamber and autopsies were conducted to verify removal of the adrenal glands.

Procedure

Three weeks following surgery, a time when ACTH secretion is thought to be maximal (Martini et al., 1964), the adrenalectomized and sham-adrenalectomized rats were randomly assigned to either a motion or restraint test condition. The experimental design was thus a 2 X 2 factorial. On each of 3

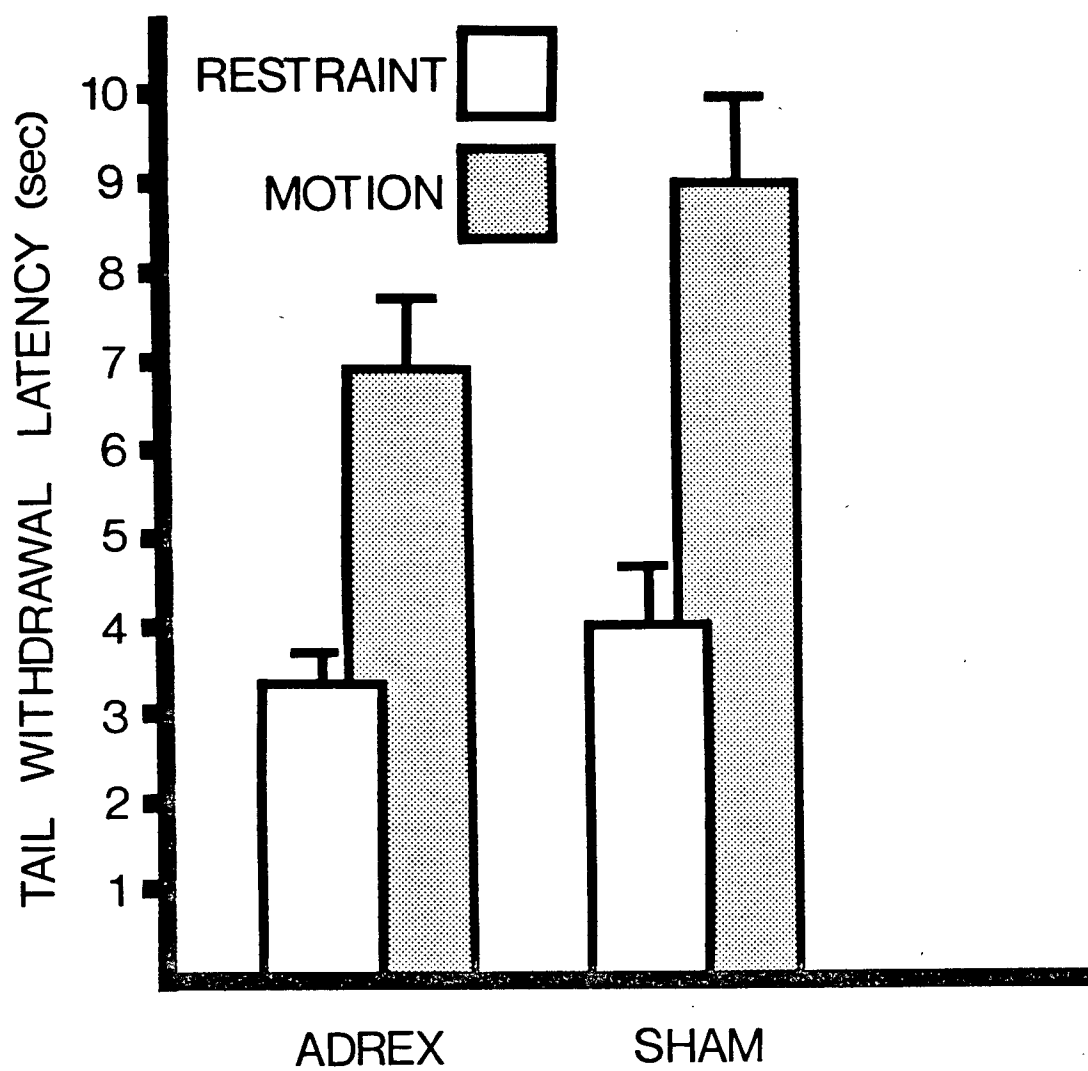
days prior to testing, all rats were acclimated to the restraining tubes for a period of 5 min. On the day of testing, each ADREX or SHAM rat underwent the appropriate motion or restraint treatment. The motion used was the swinging motion (30 swings) described previously, whereas the restraint condition involved a period of restraint equivalent to the motion treatment duration. Immediately following motion or restraint, the hot-water tail withdrawal test for analgesia was administered and the tail withdrawal latencies recorded.

RESULTS AND DISCUSSION

The results of Experiment 12 are shown in Figure 20. It is apparent from this figure that adrenalectomy had little effect on either baseline tail withdrawal latencies or on the expression of the antinociceptive effect of abnormal motion. Analysis of variance confirmed that although there was a significant effect of motion on tail withdrawal latencies ($F=32.69$, $df=1/27$, $p<.05$), there was neither a significant effect of adrenalectomy ($F=3.12$, $df=1/27$, $p>.05$), nor a significant interaction ($F=1.52$, $df=1/27$, $p>.05$). Subsequent autopsies confirmed that the adrenalectomies had been complete.

These results, although not conclusive (due to the problems associated with accepting the null hypothesis), would suggest that there is little involvement of the pituitary-adrenal axis in the mechanisms of the abnormal motion-induced antinociceptive phenomenon. Adrenalectomized rats showed normal tail withdrawal latencies in the restraint condition and, like the sham-adrenalectomized animals, demonstrated elevated tail withdrawal latencies as a result of exposure to abnormal motion. Although

FIGURE 20. The effects of abnormal motion on tail withdrawal latencies in rats that had been adrenalectomized (ADREX) or sham-adrenalectomized (SHAM) in Experiment 12.



some authors (see Gray & Gorzalka, 1980) have suggested that there are changes in sensory thresholds following adrenalectomy, such changes were not evident in the present experiment. Other authors (e.g., Grevert, Baisman, & Goldstein, 1978) have confirmed that adrenalectomy has little effect on antinociceptive mechanisms.

It would seem then, that there is no simple or obvious relationship between the adrenal-pituitary axis or the adrenal medullary system and the antinociceptive effects of abnormal motion. The opiate mechanism responsible for the antinociceptive effects of abnormal motion appears to be located in the central nervous system rather than in the pituitary or adrenal glands. The reader must be cautioned however, that this conclusion is, to a large extent, based on a negative result.

General Discussion - Section III

The experiments described in this section indicate that the antinociceptive effect of abnormal motion relies on an endogenous pain modulation system that is opiate in nature. The opiate nature of this mechanism was established by applying two criteria that are necessary for implicating an endogenous opiate mechanism in antinociceptive phenomena. First, Experiments 9 and 10 demonstrated that the antinociceptive effect of abnormal motion can be blocked by the opiate antagonist naloxone. Second, Experiment 11 demonstrated that the antinociceptive effect of abnormal motion shows cross-tolerance with the antinociceptive effects of morphine administration.

Although it seems clear that an opiate mechanism is involved in the mediation of this effect, the exact nature of this opiate mechanism is not known. Experiment 12 suggested that the mechanism is not a peripheral stress-sensitive one; neither the pituitary-adrenal axis nor the adrenal medullary system appear to influence the degree of antinociception produced by abnormal motion. It remains to be determined which endogenous opiate peptide is involved in the mediation of this phenomenon. Both B-endorphin and the enkephalins have been shown to produce antinociception when administered acutely and tolerance when administered chronically (Adler, 1980; Kosterlitz, 1979; Miller & Cuatrecasas, 1979; Rossier & Bloom, 1979) but there are differences among these peptides. The major differences lie in their structure, localization, analgesic potency, and stability (Adler, 1980; Bishop, 1980). The differences in structure and localization have been discussed

previously and the differences in analgesic potency and stability are discussed below.

It appears that when B-endorphin or the enkephalins are administered intracranially or intravenously, B-endorphin has more analgesic potency than either the enkephalins or morphine when compared on a molar basis (Liebeskind, 1978; Miller & Cuatrecasas, 1979; Rossier & Bloom, 1979). In addition, B-endorphin has been shown to be much more stable than the enkephalins (Bishop, 1980). Enkephalins are generally believed to have extremely short half lives (Bishop, 1980; Kuhar & Uhl, 1979; Miller & Cuatrecasas, 1979) and are degraded rapidly upon administration (Kastin, Jemison, & Coy, 1979), possibly by enzymatic degradation.

Supporting the hypothesis that a long-acting peptide such as B-endorphin is not involved is the fact that the antinociceptive effect of abnormal motion decays quickly when compared to other forms of stress-induced analgesia (such as immobilization or cold-water swim-induced analgesia) and further, does not appear to be affected by disruption of the pituitary adrenal axis. This would suggest that a highly responsive, short-acting opiate peptide system such as the enkephalinergic system is involved. Unfortunately, the present data do not allow this issue to be further resolved.

It would also seem that the opiate analgesia mechanism is not tonically active in the rat. If this were so, one would expect naloxone to have lowered tail withdrawal latencies in the naloxone-treated restraint groups relative to the vehicle-injected restraint groups of Experiments 9 and 10. As was shown

in Figures 15 and 16, this was not the case. This finding is consistent with the suggestion of Goldstein (1979) and others that opiate pain modulation systems are quiescent until activated by an appropriate stimulus. Other researchers however, have found that naloxone is able to increase the sensitivity of the organism to noxious stimuli (e.g., Bonnet, Alpert, Klinerock, 1978). Goldstein (1978) has suggested that these effects may well represent a procedural artifact. If the animals were 'stressed' by the handling and testing procedures in these experiments, the apparent decrease in nociceptive thresholds by naloxone may represent nothing more than a stress-induced elevation of nociceptive thresholds in the control groups against which the naloxone treated groups were evaluated.

It would seem then, that the antinociceptive effect of abnormal motion is mediated by an endogenous opiate pain modulation system that is activated in response to abnormal motion but is not tonically active. The fact that abnormal motion and hence abnormal vestibular stimulation activates an endogenous opiate system that liberates endorphins in the CNS may have important implications for other effects of abnormal vestibular stimulation. That is, it is possible that some of the other effects of abnormal vestibular stimulation such as motion sickness may be mediated by mechanisms similar to those of the antinociceptive effect. Some of these possibilities were investigated in Section IV.

SECTION IV - Other Behavioural Effects of Abnormal Motion

Although the previous sections were almost exclusively concerned with one behavioural effect of abnormal motion, the antinociceptive effect, there are other behavioral effects of abnormal motion. As discussed previously in the general introduction, motion sickness and a possible calming effect may also result from exposure to abnormal motion environments. The general purpose of Section IV was to further investigate these additional behavioural effects of abnormal motion and, in the case of motion sickness, their possible relationship to the mechanisms of the antinociceptive phenomenon.

Since the discovery of the endogenous opiate peptides, they have been implicated in a wide variety of behaviours and behavioural effects in addition to their role in pain modulation. In animals, opiate peptides have been implicated in sexual behaviour (Myers & Baum, 1979; Quarantotti, Corda, Paglietti, Biggio, & Gessa, 1978), preference for signalled versus unsignalled shock (Fanselow, 1979), aggressive behaviour (Fanselow, Sigmundi, & Bolles, 1980), brain stimulation reward mechanisms (Stein, 1978; Stein & Belluzi, 1978), learned behaviours (Rigter, Hannan, Messing, Martinez, Vasquez, Jensen, Veliquette, & McGaugh, 1980), changes in open field behaviour (Fanselow & Bolles, 1979), and other behavioural responses. In humans, endorphins have been implicated in various psychopathological states including depression (Berger, 1978), schizophrenia (Herz, Blasing, Emrich, Cording, Aree, Kolling, & Zerseen, 1978; Terenius, 1978), and anxiety (Grevert & Goldstein, 1977; Grevert & Goldstein, 1978). It would seem

then, that the endorphins may have a wider role in behaviour than their role in pain modulation would indicate. This would suggest that the endorphins may well mediate other behavioural effects produced by treatments that activate endogenous opiate systems. The purpose of Experiments 13 and 14 was to investigate some of the possible implications of activating the endogenous opiate system by abnormal motion. Specifically, both experiments were concerned with a possible role for opiate peptides in the neural mediation of motion sickness in the rat.

Experiment 15, on the other hand, investigated a different aspect of the behavioural effects of abnormal motion. This experiment explored the putative "calming" or "anxiolytic" effects of vestibular stimulation in a behavioural test that is sensitive to anxiolytic agents.

Experiment 13

Money (1970) has suggested that the motion sickness syndrome is produced by a chemical liberated in significant amounts during exposure to the motion environment. One implication of this statement is that if one could prevent the release of this chemical or block its effect at the site of action, one could treat or effectively prevent motion sickness.

Attempts to characterize the chemical mediator of motion sickness have, for the most part, been unsuccessful (Reason & Brand, 1975; Wood, 1979). A wide variety of drugs from various pharmacological classifications have been used in attempts to prevent or treat motion sickness. These different pharmacological treatments have met with varying degrees of

success, but none has proven totally effective (Reason & Brand, 1975; Wood, 1979).

The drugs that have been shown to be effective in motion sickness do not appear to exert their therapeutic effects in terms of their major pharmacological actions (Wood, 1979). Scopolamine, for example, is an anti-cholinergic agent that is somewhat effective in treating motion sickness yet other anticholinergic drugs such as atropine have little usefulness. The same is true for dimenhydrinate, an anti-histamine, and promethazine, a phenothiazine derivative: other anti-histamines and other phenothiazines have little therapeutic effectiveness in treating motion sickness. Thus, that it may be some common action of these drugs other than their main pharmacological action that is useful in the prevention and treatment of motion sickness. This common action has yet to be clearly identified and hence the chemical mediator of motion sickness remains unknown.

There is evidence from a variety of sources to suggest that this chemical mediator of motion sickness may be opiate in nature. The preceding portions of this thesis have suggested that an opiate mechanism is activated as a result of complex forms of abnormal motion. It also appears that there is some relationship between motion sickness, vestibular function, and opiate mechanisms.

One of the myriad effects of opiate (morphine) administration in humans is nausea and vomiting (Gutner, Gould, & Batterman, 1952; Jaffe & Martin, 1975). This nausea and vomiting is seen much more frequently in ambulatory patients

than in patients who are confined to bed and restricted in their movements. It appears that vestibular stimulation and morphine interact in some manner to produce this increased frequency of side effects (Gutner et al., 1952), possibly through their action on a similar underlying mechanism. Money (1970) has also noted that apomorphine-induced nausea and vomiting is less prevalent in subjects whose movements are restricted. It is also known (Money, 1970) that sub-maximal doses of emetic drugs summate or synergise with abnormal motion to accelerate the development of motion sickness.

With respect to the nausea and vomiting induced by morphine administration, Snyder (1977) and Kuhar and Uhl (1979) have suggested that this effect may be due to the activation of a pool of opiate receptors located in the area postrema. This structure is strongly implicated in the central emetic triggering processes in a variety of species (Brizze, Ordy, & Mehler, 1980; Wang & Borison, 1952). If the central emetic mechanisms are damaged by lesioning, the subject is rendered insensitive to the emetic effects of abnormal motion (Brizze, Ordy, & Mehler, 1980; Money, 1970) and various centrally-acting emetic drugs (Coil & Garcia, 1977; Wang & Borison, 1952).

The signs and symptoms of motion sickness also seem to bear a strong resemblance to the effects of morphine treatment. The signs and symptoms of motion sickness are compared to those of morphine administration in Table 1. Data concerning the symptoms of motion sickness were compiled from Reason and Brand (1975) and Money (1970), whereas those for morphine were compiled from Jaffe and Martin (1975). It is readily apparent

Table 1.

Comparison of some signs and symptoms elicited by opiate (morphine) administration and by exposure to abnormal motion (motion sickness). The presence or absence of a particular symptom is indicated by Yes or No, and the questionable existence of a symptom or lack of evidence for a symptom by ?.

<u>Symptoms and signs</u>	<u>Motion</u>	<u>Opiates</u>
Nausea	Yes	Yes
Vomiting	Yes	Yes
Pallor	Yes	No -skin flushed
Cold sweating	Yes	Yes
Sighing, yawning	Yes	?
Increased respiration	Yes(?)	No -depressed
Panting in dogs	Yes	Yes
Dysphoria	Yes	Yes-occasionally
Increased salivation	Yes	No
Feeling of body warmth	Yes	Yes
Constipation	Yes	Yes
Drowsiness	Yes	Yes
Increased ADH output	Yes	Yes
EEG changes	Yes	Yes
Pupillary constriction	?	Yes
Analgesia	Yes(?)	Yes

from Table 1 that a degree of commonality does exist between the symptoms of motion sickness and those of morphine administration.

Although the evidence is somewhat circumstantial, the research described above seems to point to a possible role for opiates in the neural mediation of motion sickness. If this hypothesis is correct, then drugs which are effective in preventing or treating the nausea, vomiting, and other symptoms induced by opiate treatment should be effective in blocking the motion sickness syndrome. Two such drugs are naloxone and naltrexone. These opiate antagonist drugs have little or no agonist activity, and are highly effective in reversing all of the effects of morphine including nausea and vomiting (Jaffer & Martin, 1975; Snyder & Matthysse, 1975). They will also reverse the nauseating and emetic actions of apomorphine, a dopamine agonist that is thought to exert its emetic actions by way of an opiate receptor mechanism while having little analgesic action. Naloxone will also block and reverse the emetic actions of very small quantities of morphine administered intraventricularly in the cat (Stewart, Wiesbrodt, & Burks, 1976). Naloxone then, may have some potential as a treatment for motion sickness. In addition to the advantages of directly antagonizing the mechanisms responsible for motion sickness, naloxone would appear to have other potential advantages in a therapeutic role. Naloxone, unlike current motion sickness drugs, which produce drowsiness, dry mouth, and a variety of other side effects (Reason & Brand, 1975; Wood, 1979), has few no major side effects when administered to normal subjects in doses which will

completely antagonize the effects of morphine (Grevert & Goldstein, 1978).

The purpose of Experiment 13 then, was to test the hypothesis that motion sickness is mediated by an endogenous opiate mechanism activated by abnormal vestibular stimulation. Subjects in the present experiment were pre-treated with the opiate antagonist naloxone in the expectation that if endogenous opiate mechanisms were involved, naloxone would block the development of motion sickness in animals so treated.

One difficulty in the study of motion sickness in the rat is the fact that rats appear to be incapable of emesis (Coil & Garcia, 1977; Hatcher & Weiss, 1923), the most commonly accepted indicator of motion sickness (cf. Brizzee, Ordy, & Mehler, 1980; Money, 1970; Suri, Crampton, & Daunton, 1979). It is clear however, that rats are extremely sensitive to vestibular stimulation (Weismann & Gottlieb, 1969) and a variety of indicators have been proposed to assay motion sickness in the rat. These indicators include: latency to drink immediately after exposure to motion (Haroutunian, Riccio, & Gans, 1976), suppression of operant responding in a rotating environment (Riccio & Thach, 1968), changes in locomotor activity in a rotating environment, the formation of conditioned taste aversions as a function of exposure to abnormal motion (Green & Rachlin, 1973, 1976), and the ingestion of non-nutritive substances following periods of abnormal motion (Mitchell, Krusemark, & Hafner, 1977).

Of these indicators, only two would appear to be free from possible confounding non-specific effects of vestibular

stimulation. It is difficult to understand how motion-induced illness could be the only factor producing a suppression of motor-activity, operant response rate, or speed with which a animal will drink. The formation of a conditioned taste aversion following motion and the consumption of non-nutritive substances following rotation on the other hand, would seem to be much more appropriate behavioural assays for motion sickness in the rat. Conditioned taste aversion refers to the finding that an animal that has been poisoned or otherwise made ill following exposure to a novel taste will subsequently avoid that taste (Garcia, 1975; Gustavson, 1975). Conditioned 'pica', the consumption of non-nutritive substances such as clay or dirt, refers to the recent finding that rats will dramatically increase their intake of a clay or dirt mixture following either poisoning (Mitchell, Winter, & Morisaki, 1977) or a period of abnormal motion (Mitchell, Krusemark, & Hafner, 1977). It has been argued that some form of illness or gastric disturbance is necessary for the development of both conditioned taste aversions (Coil & Garcia, 1977) and conditioned pica (Mitchell, Krusemark, & Hafner, 1977; Mitchell, Laycock, & Stephens, 1977). If gastro-intestinal disturbance is necessary for these effects, it suggests that motion is somehow producing gastric disturbances in the rat that are analogous to motion sickness in other species. Of these two techniques, the conditioned taste aversion would perhaps be the most insensitive to confounding non-specific effects as the strength of the taste aversion can be tested well after the pairing of the novel flavour and abnormal motion. Thus, the taste aversion was chosen here to

test the possible blocking effects of an opiate antagonist, naloxone, on the formation of a motion-induced conditioned taste aversion in rats.

METHOD

Subjects

The subjects were 24 male black hooded rats weighing approximately 375 gm that had served in the restraint condition of Experiment 5. All subjects were individually housed in standard hanging cages as previously described and food was freely available throughout the experiment.

Procedure

The present experiment consisted of two phases: a 6 day baseline phase in which each subject's preference for a novel saccharin drinking solution was assessed, followed by a testing phase in which the effects of naloxone and abnormal motion on saccharin preference were assessed.

Baseline phase. On each of the 6 days of the baseline phase of the experiment, each rat was allowed 10 min access to both tap water and a .1% (w/v) sodium saccharin drinking solution. The solutions were presented in two side-by-side graduated drinking tubes attached to the front of each cage. The positions of the tap water and saccharin solutions were reversed each day to avoid possible position preferences. Immediately prior to the 10 min drinking period, each rat was injected (i.p.) with a sterile saline solution (.9% w/v, 1 ml/kg). The purpose of the saline injection was to accustom the rats to the injection procedure and hence to attenuate any disruptive effects of the injection procedure in the test phase

of the experiment. Following the 10 min drinking period, the volumes of each solution consumed were recorded and a percentage saccharin preference score calculated based on the total fluid consumption. No other drinking fluid was available at any time throughout the course of the experiment.

Test phase. On the sixth day, 12 of the animals received naloxone injections (1.0 mg/kg) in lieu of the previous saline injections. Naloxone hydrochloride (Endo) was dissolved in sterile saline at a concentration of 1 mg/ml, thus ensuring that the injection volume was equivalent to the previous saline injections. The remaining 12 animals received saline injections.

After the 10-min drinking period, six animals from each of the saline (SAL) and naloxone (NAL) injected groups were randomly assigned to either the motion (MOT) or restraint condition (REST). The design was thus a 2 X 2 factorial design with motion versus restraint and saline versus naloxone as the two levels of each factor. The abnormal motion consisted of horizontal rotation (30 RPM) in combination with vertical oscillation (50 cycles/min) for a period of 15 min. This motion was identical to that described in previous experiments and was similar to that described by Brizzee and co-workers (Brizzee, Ordy, & Mehler, 1980; Ordy & Brizzee, 1980) in their studies of motion-induced food aversions in the squirrel monkey. As the device used to administer the motion was capable of holding six rats simultaneously, the experiment was conducted in two squads of 12 animals each. Each squad contained three rats from each of the 4 groups. The restraint condition involved placing the

rats in the restraining tubes and placing the six tubes in a wire mesh carrier similar to that used in the motion device. The carrier was then merely placed on a table adjacent to the motion device for the 15 min duration of the motion condition.

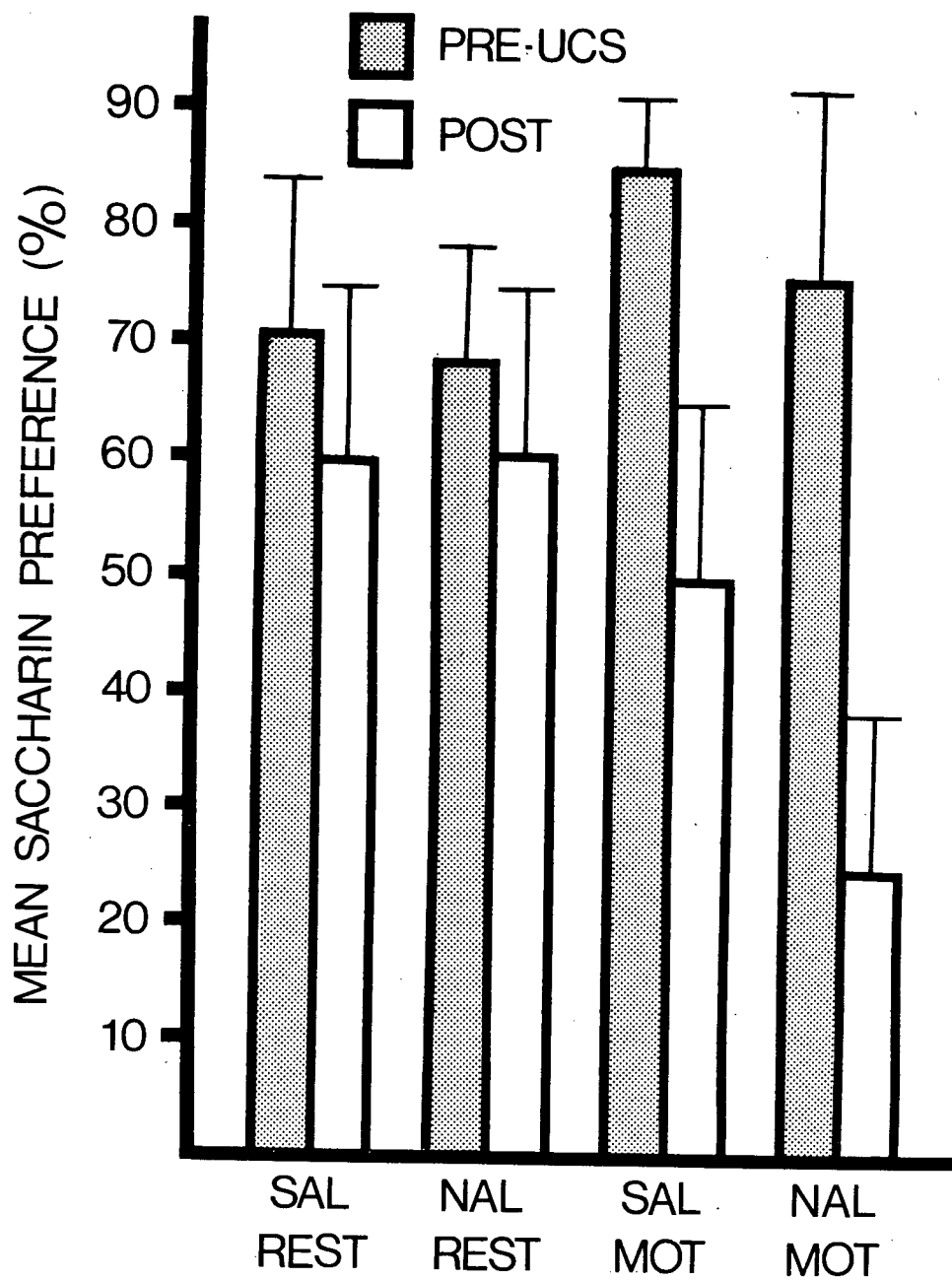
The entire procedure of Day 6 was repeated on test Days 7 and 8. Saccharin preference scores for Day 7 and 8 then, reflect the effect of the motion and drug treatments of the preceding day of testing. Day 7 preference scores for example, represent the effect of pairing saccharin and motion on Day 6; whereas Day 8 preference scores represent the effect of pairing saccharin and motion on Day 7.

RESULTS

For each rat, a mean preference score for baseline days 5 and 6 combined and a mean preference score for test days 7 and 8 were calculated to allow comparison of the pre- and post-treatment preference scores. Group means for these pre- and post-treatment scores are shown in Figure 21.

It is apparent from Figure 21 that exposure to abnormal motion appears to result in a substantial attenuation of the rats' preference for a previously preferred substance: a conditioned taste aversion. Further data reduction was accomplished by calculating difference scores between pre- and post-treatment preference scores for each animal. These difference scores were then subjected to a constant addition transform to allow further analysis. Analysis of variance on the transformed difference scores indicated only a significant effect of motion ($F=7.35$, $df=1/20$, $p<.05$) on saccharin preference, thus confirming that abnormal motion is capable of

FIGURE 21. Mean saccharin preference before (PRE-UCS) and after (POST) pairing of saccharin and motion (MOT) or restraint (REST) in rats that had been treated with naloxone hydrochloride (NAL) or saline (SAL) in Experiment 15.



producing a conditioned taste aversion in rats. Naloxone however, had no significant effect ($F=.47$, $df=1/20$, $p>.05$) on the formation of a conditioned taste aversion to abnormal motion. There was also no significant interaction ($F=.12$, $df=1/20$, $p>.05$).

DISCUSSION

Naloxone hydrochloride, at least at the dose used here, failed to block the taste aversion produced by abnormal motion. In addition, the trend indicated in Figure 21, although not statistically significant, would suggest that naloxone may have an aversive component of its own that is detectable in the taste aversion paradigm.

Possible explanations for the failure of naloxone to block the development of a conditioned taste aversion are many and varied. The most likely explanation is that the hypothesis is incorrect. Although this may be true, it should be noted that one test of the hypothesis at one dose level does not constitute an adequate test of the hypothesis.

The dose level chosen may not have produced sufficient receptor blocking to block the appearance of the conditioned taste aversion. LeBlanc and Cappell (1975), and van der Kooy and Phillips (1977), using morphine as an unconditioned stimulus (UCS) rather than abnormal motion, have shown that the dose of naloxone adequate to block a taste aversion to a given dose of morphine lies within a very narrow range. Above and below this dosage, the taste aversion appears quite strong and is thought to represent the effects of morphine and an effect of excess naloxone. However, attempts in our laboratory to block

conditioned taste aversions resulting from abnormal motion with a variety of naloxone doses (.0125 to 7.5 mg/kg) have been unsuccessful (unpublished data).

The aversive nature of naloxone in the taste aversion paradigm has also been noted by other authors. Pilcher, Stolerman, and D'Mello, (1978) for example, have noted that naloxone is an effective stimulus for inducing conditioned taste aversions in rats and Stolerman, Pilcher, and D'Mello(1978) have confirmed this effect at doses as low as 1.0 mg/kg. These authors have also demonstrated that this taste aversion inducing property is stereospecific, suggesting a direct action on a particular binding site (Snyder & Pert, 1975).

Another possible explanation for the failure of naloxone to block the conditioned taste aversion is somewhat more speculative, and relies on the pharmacodynamics of naloxone in rats (Ngai, Berkowitz, Yang, Hempstead, & Spector, 1976). It is possible that the naloxone treatment may produce supersensitivity of the opiate receptor upon recovery from naloxone. This supersensitivity does appear to exist for at least chronic naloxone treatment (Schulz, Wurster, & Herz, 1979). If the opiate receptor is supersensitive following naloxone treatment, then the return of endogenous opiates to the receptors previously occupied by naloxone may produce an effect similar to that of the opiate system activation by abnormal motion, and thus effectively produce a taste aversion. Naloxone has a very short duration of action in rats and this effect could occur relatively close in time to the effects of abnormal motion in the saline-injected animals. Given the wide range of

delays between the conditioned stimulus (flavor) and the UCS that will still produce a conditioned taste aversion (Garcia & Hankins 1975; Gustavson, 1975), the time difference between the motion UCS and the naloxone withdrawal UCS may not be detectable in a preference test 24 hr later.

These two difficulties, the short duration of action and the taste aversion inducing properties of naloxone, prompted a further study of possible endogenous opiate involvement in motion sickness using a different opiate antagonist, naltrexone.

Experiment 14

Experiment 14, like Experiment 13, explored the possible attenuating effects of an opiate antagonist on conditioned taste aversions produced by exposure to abnormal motion in rats. Because naltrexone has a longer duration of action than does naloxone (Jaffe & Martin, 1975) and also appears to have fewer aversive properties of its own compared to naloxone in the conditioned taste aversion paradigm (Stolerman, Pilcher, & D'Mello, 1978), naltrexone was the opiate antagonist employed in the present experiment. The dose of naltrexone chosen (3.0 mg/kg) was one that has been previously shown to effectively block opiate receptor mechanisms while having little effectiveness in producing taste aversions (Stolerman et al., 1978). It is also possible that repeated administration of naloxone and abnormal motion was a confounding factor in the previous experiment. In the present experiment, the taste aversion paradigm was modified to a single forced exposure trial followed one day later by a single two bottle preference test.

METHOD

Subjects

Serving as subjects in the present experiment were 60 naive male hooded rats, weighing approximately 300 gm. The animals were purchased as previously described and were housed individually in hanging wire cages for a period of 14 days prior to the start of the experiment.

Procedure

The entire experiment was carried out over a 3-day period. On Day 1, water bottles were removed from the cages and no further fluid was available until the saccharin exposure trial on Day 2. Twenty-four hr following removal of the water bottles, 30 animals were injected with naltrexone hydrochloride (3.0 mg/kg, i.p.), and the remaining 30 animals were injected with the saline vehicle. Naltrexone hydrochloride was dissolved in sterile saline (3.0 mg/ml) and vehicle injections were equivolume injections of sterile saline. Immediately following the drug injections, a sodium saccharin solution (.1% w/v) was presented to each rat for a 15 min period. The volume of solution consumed in the 15 min period was recorded to the nearest ml. Within 5 min following the saccharin exposure trial, 15 animals from each of the naltrexone and saline injection groups were placed in the restraining tubes and subjected to the horizontal rotation and vertical oscillation stimulus used in Experiment 13 for a 15-min period. The remaining 15 animals from each of the naltrexone and saline groups underwent a 15-min period of restraint, in a manner identical to that previously described. The experimental design

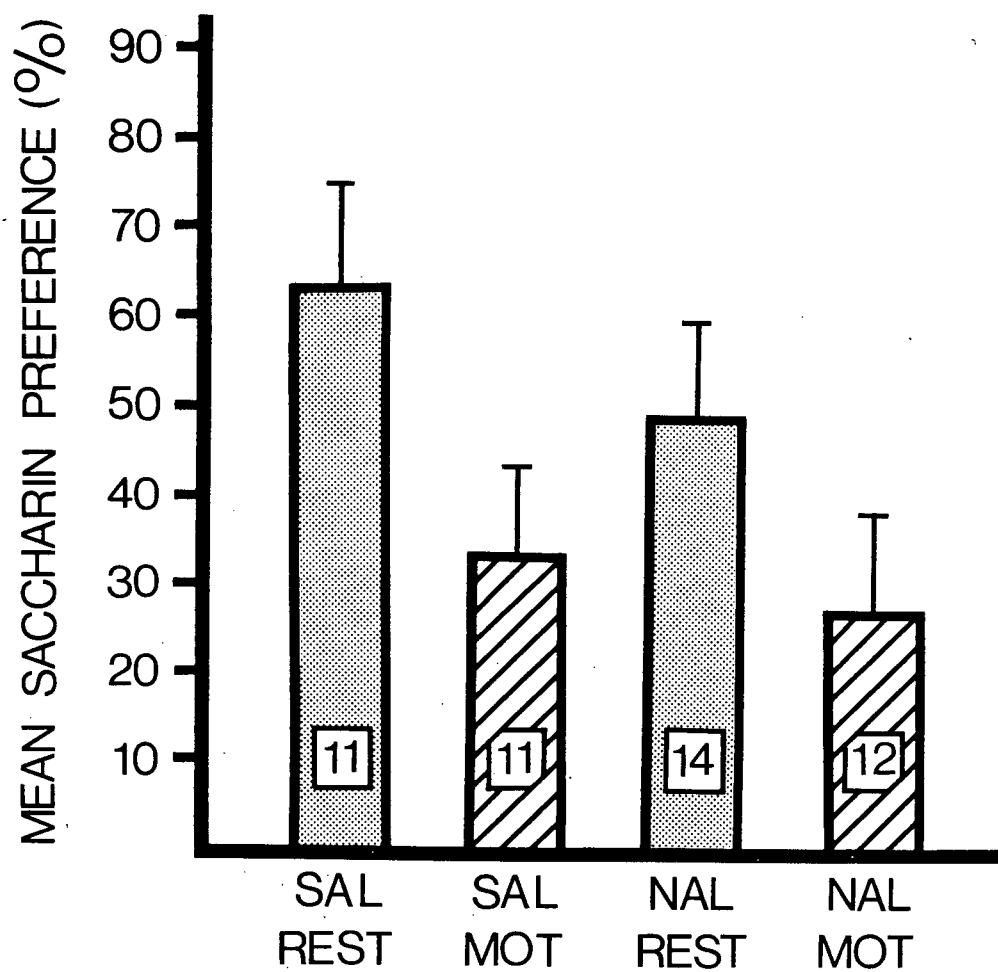
was thus a 2 X 2 factorial design with naltrexone or saline and motion or restraint as the levels of the two factors. As the device used to administer the motion had a six rat capacity, rats were run in squads of 12 animals each, composed of three rats from each of the four conditions.

On Day 3, 24 hr after the motion or restraint treatment, a two choice preference test was conducted. Two drinking tubes, one containing sodium saccharin solution (.1% w/v) and the other tap water, were attached to the front of the cage and the rats allowed to drink for a 15 min period. Following the 15 min test period, the volume of each fluid consumed was recorded and the percentage of saccharin solution consumed relative to the total volume consumed was calculated. Rats that drank no saccharin solution on either Day 2 or 3 were deleted from further analysis and the number of animals per group was reduced accordingly.

RESULTS

As Shown in Figure 22, exposure to abnormal motion resulted in a dramatic decrease in subsequent saccharin preference following a single exposure to saccharin prior to abnormal motion. As in Experiment 13, administration of an opiate antagonist prior to the administration of abnormal motion had little effect on subsequent saccharin preference save for a slight trend towards increased avoidance of the solution. Analysis of variance confirmed the presence of a conditioned taste aversion in the abnormal motion groups ($F=6.06$, $df=1/44$, $p<.05$). There was no significant effect of naltrexone ($F=.32$, $df=1/44$, $p>.05$) nor was the interaction between naltrexone and abnormal motion significant ($F=.58$, $df=1/44$, $p>.05$).

FIGURE 22. Mean saccharin preference after pairing of saccharin presentation and motion (MOT) or restraint (REST) in rats that had been pre-treated with naltrexone (NAL) or saline (SAL) in Experiment 14. Numbers within the bars refer to the number of animals per group.



DISCUSSION

It would appear from the results of the present experiment and the preceding experiment that there is no simple or obvious relationship between opiate antagonists and the mechanisms of motion sickness. Neither naloxone nor naltrexone, two relatively pure opiate antagonist drugs, appeared to prevent the development of a conditioned aversion to a novel flavor when abnormal motion was used as the provocative stimulus.

Although the most parsimonious explanation for the results of these two experiments is that the hypothesis is incorrect, there are a number of alternate hypotheses that may also explain the failure of opiate antagonists to block the development of the conditioned taste aversion.

First, it appears that there are a number of different opiate receptors in the central nervous system that are differentially sensitive to opiate antagonist drugs (Cheng & Pomeranz, 1980; Lord, Waterfield, Hughes, & Kosterlitz, 1976; Ward, Metcalf, & Rees, 1978). If the opiate receptor mechanism that potentially mediates motion-induced taste aversions is insensitive to blockade with opiate antagonist drugs, one would not expect opiate antagonist drugs to block the illness-inducing properties of abnormal motion.

The existence of the differentially specific subpopulations of opiate receptors is not only feasible, but many authors have suggested (see Adler, 1980; Cheng & Pomeranz, 1980, Goldstein, 1978) that the many different behavioural effects of opiates could be individually mediated by different receptor populations.

It is also possible then, that the opiate receptor mechanism responsible for mediating motion-induced taste aversion is less specific for opiate antagonists than for the endogenous ligand. If this were true, it is possible that the endogenous peptides released by abnormal motion could displace the naloxone molecule from the receptor site and hence exert their normal opiate-like effects.

A second hypothesis involves the difficulty in establishing the appropriate dosage relationship of the opiate antagonist to the endogenous opiate peptide. As mentioned previously, naloxone will block the taste aversion inducing properties of morphine administration but only at certain morphine-naloxone dosage combinations (LeBlanc & Cappell, 1975; van der Kooy & Phillips, 1977). A similar situation may have existed in the present experiments such that the dose of antagonist used may have been inappropriate for the degree of endogenous opiate involvement.

A third explanation rests on the appropriateness of the conditioned taste aversion paradigm as an index of motion sickness in the rat. It may be that the development of a conditioned taste aversion is not analogous to the motion sickness phenomenon.

It appears that there are a wide variety of neural processes involved in conditioned taste aversion (Coil & Garcia, 1977) and a variety of hypotheses concerning the development of taste aversions (e.g. Braveman, 1975; Gamzu, 1975). To date, the only reliable evidence suggesting that motion sickness and conditioned taste aversion may be analogous is the fact that

both may be induced by exposure to abnormal motion. This commonality does not, of course, imply that both phenomena are necessarily subserved by identical underlying mechanisms. Hence, in attempting to investigate the underlying mechanisms of motion sickness through a conditioned taste aversion, one may in fact be studying only the mechanisms of the taste aversion. This point is offered here only as a possible explanation for the results of Experiments 13 and 14 but is considered in greater detail in a subsequent discussion.

Although administration of opiate antagonists did not block the formation of a conditioned taste aversion following exposure to abnormal motion, the fact remains that a strong taste aversion was produced by the motion. If endogenous opiates are not involved in mediating the cue properties of the aversive stimulus, then what sort of system may be involved? One possible explanation for the formation of the taste aversion has been proposed by Braveman (1975). This hypothesis suggests that the unconditioned stimulus acts as a 'stressor' and it is the activation of the pituitary-adrenal system by this stressor that mediates the illness-cue properties of the stimulus. The fact that exposure to one of a variety of stressors will block the effectiveness of another unconditioned stimulus in producing a taste aversion, and the fact that exposure to these stimuli is accompanied by increased corticosteroid levels (Braveman, 1975) suggests that these different stimuli may act through a common mechanism, the pituitary-adrenal system. Recent evidence demonstrating that dexamethasone will attenuate taste aversions and that ACTH will prolong extinction of taste aversions

(Hennesy, Smotherman, & Levine, 1980) provides support for this hypothesis. It is possible that a similar stress effect was responsible for the taste aversion-inducing properties of abnormal motion seen here. As discussed previously, exposure to abnormal motion produces physiological changes consistent with the proposed role of abnormal motion as a stressor. This hypothesis may also explain the slight facilitating effect of opiate antagonists in Experiments 13 and 14. Eisenberg (1980) has recently demonstrated that naloxone may act as a stressor at least as measured by increased corticosterone levels as a result of naloxone administration.

Although the endorphin hypothesis of motion sickness cannot be eliminated, neither can it be supported. Following the completion of Experiments 13 and 14, it was discovered that this hypothesis has also been independently tested in another laboratory. Money and his co-workers (personal communication, 1980) have investigated the effects of opiate antagonists on motion-induced vomiting in the dog. No change was found in either the latency to vomit or the characteristics of the emetic response.

Experiment 15

Experiment 15 attempted to investigate the 'calming' or anxiolytic effect of abnormal motion. Vestibular stimulation has been found to reduce crying time and other signs of distress in human infants (Korner & Thoman, 1972; Pederson & Ter Vrugt, 1973; Weeks, 1979) and is thought to be more effective in soothing infants than are other common techniques (Korner &

Thoman, 1972). Pederson and Ter Vrugt (1973) have found that the calming effects of vestibular stimulation can far outlast the duration of the stimulus in human infants and that there is an optimal frequency of vertical rocking that is most effective in producing this effect. Although it has been suggested that this rather poorly defined calming effect is due to vestibular stimulation, non-specific effects of the stimulus such as apparatus noise, mere stimulus repetition, etc., were confounding factors in the above-mentioned experiments.

Aside from these few studies in human infants, little systematic research has been conducted concerning the possible calming effects of vestibular stimulation in the adult. "Drowsiness" and "lethargy" (Reason & Brand, 1975) have been noted as symptoms of motion sickness and may reflect the same mechanism as the calming effects in infants although neither have been extensively studied. Weeks (1979) points out that there exists much anecdotal evidence concerning the efficacy of rocking or swinging movements in inducing relaxation and drowsiness.

This possible calming effect has also not been extensively investigated in animals. Thoman and Korner (1971) have demonstrated that vestibular stimulation in infant rats reduces signs of distress in a manner similar to that described for human infants. However, this study has been extensively criticized on methodological grounds (LaBarba & Stewart, 1978). Staubli and Huston (1979) in a recent report describing a new avoidance task, noted that the animals tested in the paradigm were subjected to a period of swinging prior to being placed on

a shock grid. This brief period of swinging was said to "calm" the animals and facilitate placement on the grid.

It is clear from this brief discussion that little research exists concerning the putative 'calming' effects of vestibular stimulation and that which does exist is poorly controlled and difficult to interpret. The purpose of the present experiment then, was to investigate the possible calming effects of abnormal vestibular stimulation in rats in a well-controlled experimental environment.

A number of behavioural assays have been proposed to investigate 'calming' or anxiolytic effects in animals (Glick, 1976). These paradigms have been primarily used to investigate the anxiolytic actions of various pharmacological treatments and almost all rely on observing changes in behaviour when the animal is exposed to an aversive or 'fear-producing' stimulus. Attenuation of the animals normal response to the aversive stimulus by a drug or other treatment is generally assumed to reflect a calming or anxiolytic action of that treatment.

Pinel and Treit (in press, 1981) and Treit (1981) have recently described a reliable and easily administered behavioural assay for anxiolytic agents in rats: the defensive burying paradigm. The growing literature concerning the defensive burying phenomenon indicates that rats exposed to a variety of aversive or novel stimuli will approach the source of these stimuli and spray bedding material or other suitable material toward or pile material around the source of the stimulus in such a way as to 'bury' the stimulus source (cf. Pinel & Treit, 1978; Terlecki, Pinel, & Treit, 1979). This

behaviour may be elicited by a contingent presentation of a noxious stimulus (e.g., shock) with an otherwise innocuous object (the conditioned defensive burying procedure) or by presentation of a complex novel object (the unconditioned defensive burying procedure). Treit (Pinel & Treit, in press, 1981; Treit, 1981) has demonstrated that clinically utilized anxiolytic agents such as diazepam will reduce both conditioned and unconditioned defensive burying in a dose-dependent manner and has suggested that this reduction in defensive burying may well reflect the anxiolytic or fear-modulating actions of the benzodiazepines.

If vestibular stimulation does have some anxiolytic or calming effect, then this effect should be detectable in the defensive burying paradigm as a reduction in the amount of burying behaviour elicited by a particular stimulus.

In the present experiment, the effects of abnormal motion on subsequent defensive behaviour were studied in the unconditioned defensive burying paradigm described by Terlecki et al. (1979). This paradigm was chosen as it does not require the use of shock or any other noxious stimulus whose functional strength could be attenuated by the motion induced analgesia phenomenon described previously. In addition, the unconditioned burying test session is of a fixed length and can be administered at any time following the treatment; whereas, the conditioned defensive burying paradigm involves variable delays from the start of the test session until the aversive stimulus is administered. This consistency in the unconditioned defensive burying paradigm may be important if the calming effect of abnormal motion is of short duration.

It is possible that any effect of abnormal motion on defensive burying behaviour may be due to a general stress effect whereby any stressor applied prior to testing would have the same effect on burying behaviour as would abnormal motion. To examine this possibility, a group of animals that received only footshock prior to testing in the unconditioned burying paradigm were included in the present experiment.

METHOD

Subjects

Thirty naive male hooded rats served as subjects in the present experiment. The subjects weighed between 250 and 350 gm and were group housed in hanging cages under a reversed 12 hr light/dark cycle. Food and water were continuously available in the home cage.

Procedure

On each of the 3 days prior to testing, all animals underwent 30-min habituation sessions (see Pinel & Treit, 1978). In each habituation session, the rats were placed in groups of six into 43 X 30 X 44 cm Plexiglas test chambers containing approximately 5 cm of commercial bedding material (San-i-cel, Paxton Processing Co.) and were allowed to move about freely. On the fourth day, 10 rats were randomly assigned to each of three treatment conditions: the motion condition, a no-treatment control condition, and a shock condition. Rats in the motion condition were placed in restraining tubes and subjected to 10 min of the horizontal rotation and vertical oscillation motion described previously. Rats in the shock condition were placed in a grid floor shock chamber and subjected to a series of 20 .8

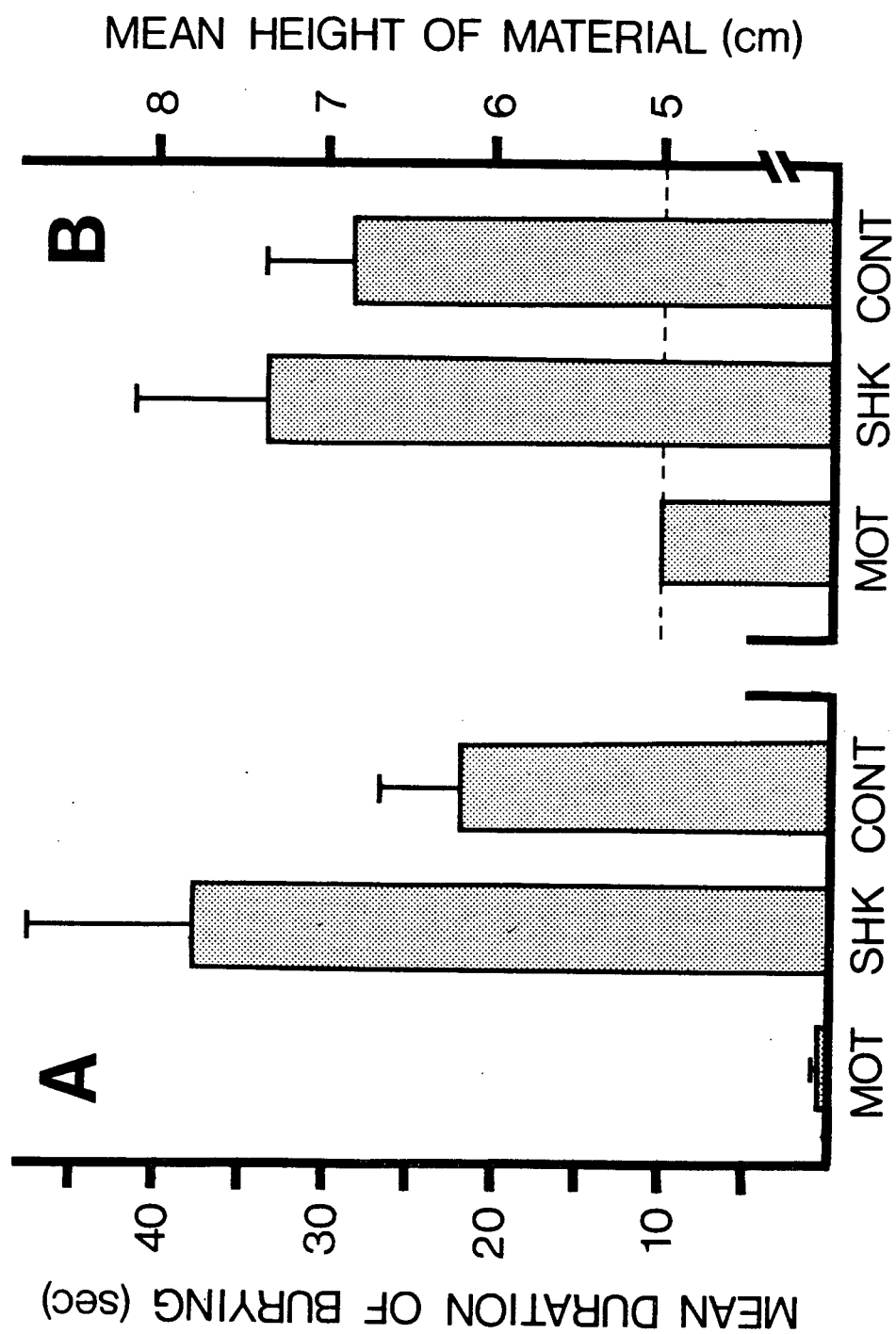
mA, 5 sec duration scrambled footshocks spaced 25 sec apart. Rats in the no-treatment control condition were merely placed in the restraining tubes and allowed to remain in the tubes for a 10 min period (n = 5) or were placed in the non-functional shock apparatus for a 10 min period (n = 5). Data from these two groups were combined in the analysis of the results.

Within 2 min of the termination of the treatment period, each rat was placed in the centre of a test chamber containing 5 cm of bedding material and an unset mousetrap affixed to the centre of one wall, 2 cm above the level of the bedding material (cf. Terlecki et al., 1979). The behaviour of the rat was monitored from outside the room by closed circuit television and burying behaviour was scored throughout the 15 min test session. Burying behaviour is easily observed and is highly stereotyped: rats orient towards the trap and push or spray bedding material at it with rapid pushing movements of the forepaws (Pinel & Treit, 1978). The duration of burying score reported here was the cumulative duration of all instances of directed forelimb spraying that occurred throughout the test session. Following the 15-min test session, an additional measure of burying behaviour was obtained by measuring the height of bedding material that had accumulated at the prod.

RESULTS

As shown in Figure 23, the abnormal motion treatment administered prior to exposure to a novel object resulted in an almost complete suppression of defensive burying behaviour. Only one of the 10 rats in the motion treatment condition demonstrated a single burst of burying and the duration

FIGURE 23. Effects of pre-exposure to brief periods of abnormal motion (MOT), electric shock (SHK), or a control condition (CONT) on defensive burying behaviour in rats (Experiment 15). Panel A illustrates duration of burying scores and Panel B indicates the height of material accumulated at the trap at the end of the test session.



of this burst (1.9 sec) was insufficient to alter the height score. Rats in the shock and no-treatment control conditions, on the other hand, showed appreciable amounts of burying behaviour. One-way analysis of variance for each measure confirmed a significant treatment effect ($F=4.54$, $df=2/27$, $p<.05$ for duration; $F=5.06$, $df=2/27$, $p<.05$ for height) and post-hoc analysis (Tukey) indicated that scores in the motion condition were significantly less than those in the shock or control conditions. Post-hoc analysis further indicated that shock and control group scores did not differ significantly in either the duration or height measure.

DISCUSSION

The results of the present experiment indicate that exposure to a brief period (10 min) of abnormal motion results in a dramatic alteration in the rat's subsequent reaction to a novel object. Rats that had experienced a period of abnormal motion exhibited almost no defensive burying behaviour in response to an unset mousetrap, a stimulus that was effective in eliciting burying behaviour in rats that had been pre-exposed to either a period of footshock or to a control condition.

This attenuation in defensive burying behaviour may represent an empirical demonstration of the putative anxiolytic or calming effects of abnormal motion. It is clear that the attenuation was specific to abnormal motion and was not merely a general effect of pre-exposure to a noxious or "stressful" stimulus. Treit (Pinel & Treit, in press, 1981; Treit, 1981) has demonstrated a similar suppression of burying behaviour following pre-treatment with drugs that are used clinically for

their anxiolytic effects (e.g. diazepam, chlordiazepoxide). Other classes of drugs such as stimulants (amphetamine, picrotoxin) or major tranquilizers (chlorpromazine) either had no effect on defensive burying behaviour, caused a slight increase in the amount of burying behaviour, or produced patterns of effects on defensive burying which were different from the effects of the anxiolytic agents.

It would seem possible then, that abnormal motion represents a non-pharmacological means for the control of anxiety or fear. That is, abnormal motion may activate an endogenous anxiolytic mechanism. There are however, a number of difficulties associated with this interpretation.

First, it is possible that some other effect of abnormal motion other than an anxiolytic effect is responsible for the suppression of burying observed in the present experiment. The abnormal motion may have produced a gross motor deficit in the subsequent test. If the rats were dizzy for example, one would expect their ability to manipulate the bedding material to be somewhat impaired. Although this hypothesis cannot be eliminated, it is unlikely that the motor deficit or 'dizziness' would persist for the entire 15-min test period (see also Sections II and III). Observations of the test session also suggest that although overall activity levels appeared somewhat suppressed, the animals in the motion condition walked about the chambers with little apparent difficulty. It is also possible that the rats had been made 'ill' as a result of exposure to abnormal motion. Abnormal motion does appear capable of producing some internal state that is capable of supporting a

conditioned taste aversion (see Experiments 13 and 14) and this internal state (motion sickness?) may have produced a suppression of burying behaviour. This alternative explanation again cannot be eliminated but appears unlikely for two reasons. First, motion induced illness decays rapidly following cessation of the motion stimulus (Reason & Graybiel, 1970) and it is unlikely the rats were debilitated to an extent that would prevent burying for the entire 15-min test period. Observations again indicated the rats did not appear to be suffering gross debilitation. Second, Treit (1981) indicates that drugs that are capable of producing illness and taste aversions in rats do not have consistent effects on defensive burying. Stimulants such as amphetamine for example, do not suppress burying but do produce conditioned taste aversions, even in doses that animals will self-administer (Gamzu, 1975). It seems unlikely then, that illness would have any consistent effect on defensive burying.

The results and conclusions of the present experiment must be considered preliminary in terms of a non-pharmacological anxiolytic mechanism. The possible anxiolytic effects of abnormal motion could be more clearly delineated in a variety of ways. The conditioned defensive burying paradigm for example, has been used by Pinel and Treit (in press, 1981) to control for possible interfering side effects of drugs in the benzodiazepine-induced suppression of burying phenomenon. Drug-treated rats received either a low or high intensity shock from a prod mounted on the wall of the test chamber. Benzodiazepines, in a variety of doses, did not suppress burying

at the high shock level whereas burying elicited by the low shock level was suppressed. The fact that anxiolytic drugs did not affect burying behaviour elicited by a high shock level allowed gross motor impairment and other possible side effects (such as analgesia) to be eliminated as explanations for the effects of anxiolytic drugs. A similar analysis could be conducted for the effects of abnormal motion on defensive burying.

The specificity of the possible anxiolytic effects of abnormal motion could be established by testing the effects of abnormal motion in behavioural paradigms that are used as screening devices for anxiolytic drugs. The reader is referred to Glick (1976) for an overview of these techniques.

It would seem that both of these steps must be completed before any firm analogy is drawn between the behavioural effects of abnormal motion and the effects of clinical anxiolytic agents, and thus the present results represent a preliminary stage in the investigation of non-pharmacological anxiolytic mechanisms.

It is tempting however, to speculate on the possible underlying mechanisms for a non-pharmacological anxiolytic phenomenon. There are at least two exciting possibilities for this mechanism. The first of these involves endogenous opiate peptides. The experiments contained in previous portions of this thesis strongly indicate that endogenous opiate activity is enhanced by abnormal motion. Endogenous opiate peptides have been suggested to play an anti-anxiety role in humans. Grevert and Goldstein (1977) have found that human subjects receiving

naloxone showed more anxiety, tension, and hostility on standard mood scales than did saline-treated subjects after exposure to a stressful situation. Presumably, the stressful situation activated an endorphin mechanism which was responsible for the change in mood in the saline controls but was blocked in the naloxone-treated subjects. Naloxone administration to human patients in other studies (Grevert & Goldstein, 1978) has also been reported to result in vague feelings of anxiety and tension that did not result from treatment with a saline vehicle. Morphine, the prototypical opiate antagonist, also appears to exert some anxiolytic actions in addition to its many other effects (Jaffe & Martin, 1975; Terenius, 1978). Pilot studies attempting to block the motion-induced suppression of burying behaviour with naloxone in our laboratory however, have thus far been unsuccessful.

Another possible mechanism for the motion-induced suppression of burying behaviour involves the recent discovery of benzodiazepine-specific receptors in the brain (Tallman, Paul, Skolnik, & Gallagher, 1980). The presence of benzodiazepine receptors suggests that an endogenous benzodiazepine molecule may also exist within the central nervous system. Although this endogenous ligand has not yet been identified, it is possible that an endogenous "anti-anxiety" system exists within the brain and may be activated by stimuli such as abnormal motion.

In conclusion, it appears that abnormal motion may have an identifiable anxiolytic or calming effect. Although the results described here are provocative, and much more research is

necessary to quantify and describe the nature of these effects, they do raise the interesting and potentially useful possibility of the control of clinical anxiety syndromes through non-pharmacological means.

GENERAL DISCUSSION

The present thesis has uncovered and investigated a variety of behavioural effects that occur in response to a brief period of abnormal motion in rats. These behavioural effects include analgesia, aversion to a previously preferred taste, and a possible anxiolytic effect.

Sections I, II, and III of the present investigation were devoted primarily to exploring the antinociceptive effects of exposure to abnormal motion and the physiological mechanisms underlying this newly discovered effect. Section I confirmed the earlier indications from our laboratory of the existence of an antinociceptive effect of abnormal motion in rats. This antinociceptive effect was found following only relatively complex forms of abnormal motion and was of a relatively brief duration when compared to other forms of non-pharmacological pain modulation (e.g. Hayes, Bennet, Newlon, & Mayer, 1978). The hot-water tail withdrawal test was used as the primary measure of analgesia but the analgesia produced by abnormal motion was not restricted to this one measure of analgesia as a significant antinociceptive effect was also found in the hot-plate paw-lick jump-escape task. It was also found that the analgesic effect of abnormal motion required some minimal period of exposure to the motion in order to appear (or be detected) in the analgesia test and once the analgesic effect had developed, little change in its magnitude was apparent with longer periods of exposure to the motion.

Section II was devoted to investigating the role of the vestibular system in the modulation of the antinociceptive

effect of abnormal motion. Destruction of the peripheral vestibular apparatus completely eliminated the antinociceptive response to a period of abnormal motion, thus implicating the vestibular system in antinociception produced by abnormal motion. Lesions and electrical stimulation of some discrete components of the central vestibular system however, revealed no consistent involvement of any single central vestibular component. These results were interpreted to suggest that although the vestibular system is essential for the production of the pain modulating effect of abnormal motion, more than one or different central vestibular components are probably involved.

Section III presented concrete evidence that this antinociceptive effect is mediated by an endogenous opiate pain modulating mechanism. The antinociceptive effect of abnormal motion was blocked by the opiate antagonist drug naloxone and also demonstrated cross-tolerance with chronic morphine administration. Unlike some other forms of non-pharmacological or stress-induced antinociception (Bodnar, Kelly, & Glusman, 1979; Chance & Rosecrans, 1979; Lewis, Cannon, & Liebeskind, 1980; Spiaggia, Bodnar, Kelly, & Glusman, 1979), motion-induced analgesia appears to be produced through a mechanism that involves endogenous opiate peptides. The exact locus of this opiate peptide mechanism was not found, although it is apparently independent of the hypothalamic-pituitary axis unlike other apparently opiate-regulated forms of non-pharmacological pain modulation (Cheng & Pomeranz, 1978; Cheng, Pomeranz, & Yu, 1979).

Section IV investigated a possible implication of the activation of an endogenous opiate system in response to abnormal motion. There are a number of similarities between the effects of exogenous opiate administration and the symptoms and signs of motion sickness and this similarity suggested that motion sickness could be mediated by an endogenous opiate mechanism. Exposure to abnormal motion produced a dramatic aversion to a preferred novel fluid after pairing of the fluid and abnormal motion. However, opiate antagonists were unsuccessful in blocking a motion-induced conditioned taste aversion, a putative rodent analogue of motion sickness. Also included in this section was a preliminary investigation of a possible "calming" or "anxiolytic" effect of vestibular stimulation. A brief period of abnormal motion was found to suppress performance of a species-typical defensive response: defensive burying. These results are consistent with the effects of anxiolytic drugs on the defensive burying response and suggest, somewhat prematurely perhaps, that an endogenous anxiolytic mechanism may be activated by vestibular stimulation.

From this brief review of the findings of the present thesis, it would seem that there are a variety of implications of these findings for pain control, motion sickness, and a possible endogenous anxiolytic mechanism. This final section of the thesis is devoted to a discussion of these implications and possible applications. This general discussion is divided into three separate parts, each a discussion of the three main subject areas investigated here: pain modulation, motion sickness, and anxiety modulation.

MOTION-INDUCED ANTINOCICEPTION

Exposure to a brief period of abnormal motion activates an endogenous opiate system that appears responsible for the antinociceptive effects of motion observed in the hot-water tail withdrawal and hot plate tests. The significance of this finding for endogenous pain modulation mechanisms and possible applications to pain control are discussed below.

Physiological mechanisms of motion-induced antinociception

Experiments 9, 10, and 11 of Section III strongly implicate an endogenous opiate pain modulation system in the antinociceptive effect of abnormal motion. Naloxone at very low doses (0.5 mg/kg) completely blocked the antinociceptive effect of abnormal motion and the antinociceptive effect demonstrated cross-tolerance with chronic morphine treatment, thus suggesting similar mechanisms for morphine and motion-induced analgesia. Although endorphins appear to be involved in mediating the pain-modulating properties of abnormal motion, it is not clear which specific opiate peptides are involved or where in the nervous system they are exerting this modulating influence on pain transmission.

There are three endogenous opiate peptides that have been implicated in endogenous pain modulation: B-endorphin, met-enkephalin, and leu-enkephalin (Barchas, Akil, Elliot, Holman, & Watson, 1978; Basbaum & Fields, 1978; Bishop, 1980; Kosterlitz, 1979; Liebeskind, 1978). The enkephalins, met- and leu-enkephalin, are thought to be degraded extremely rapidly in the nervous system and hence produce analgesia of relatively short duration (Frederickson, Smithwick, & Shuman, 1978; Miller &

Cuatrecasas, 1979). In contrast, B-endorphin is degraded very slowly and produces a long-lasting analgesic effect (Rossier & Bloom, 1979; Tseng, Loh, & Li, 1976). Based on analgesic potency, B-endorphin is considered to be more potent than morphine when compared on a molar basis (Tseng, Loh, & Li, 1976; Yaksh & Henry, 1978). The short duration of the analgesic effect of abnormal motion demonstrated in Section I and the fact that motion did not at any time produce a degree of analgesia in any way comparable to that produced by morphine, would seem to suggest that it is the enkephalins rather than B-endorphin that are responsible for the analgesic effects of abnormal motion. Additional support for this hypothesis is provided by the failure to find an effect of adrenalectomy on the motion-induced analgesia phenomenon in Experiment 12. B-endorphin is restricted almost exclusively to the pituitary gland (Barchas et al., 1978; Rossier & Bloom, 1979) and is thought to be secreted concomitantly with ACTH (Guillemin, Vargo, Rossier, Minick, Ling, Rivier, Vale, & Bloom, 1977). Any manipulations that affect the regulation of ACTH secretion should thus affect circulating levels of B-endorphin and mask or eliminate the antinociceptive effect of abnormal motion. Cheng, Pomeranz, and Yu (1979) for example, have shown that naloxone-reversible acupuncture analgesia is attenuated by pretreatment with dexamethasone, a synthetic glucocorticoid that acts to suppress ACTH secretion through a feedback mechanism in the hypothalamus (Martini, Motta, & Muller, 1964). This inhibition of ACTH secretion, and thus B-endorphin secretion, from the pituitary is thought to explain the attenuation of analgesia.

Adrenalectomy, which increases ACTH secretion (Martini, Motta, & Muller, 1964), had no effect on the appearance of the motion-induced analgesia phenomenon in the present experiments. The lack of effect of adrenalectomy then, would suggest that B-endorphin is not involved in the antinociceptive effect of abnormal motion and, by elimination, implicates the enkephalins.

If one can eliminate B-endorphin as the endogenous opioid peptide involved in the antinociceptive effect, it would seem likely that the antinociceptive effect of abnormal motion is mediated through a central nervous system mechanism that does not involve the hypothalamic-pituitary axis. Hence, the antinociceptive effect of abnormal motion is most likely produced by an enkephalinergic pain modulating system located within the central nervous system. Concentrations of enkephalinergic neurons are found in conjunction with pain pathways (Basbaum & Fields, 1978; Kuhar & Uhl, 1979) throughout the ascending paleospinalthalamic system. The paleospinalthalamic system is thought to predominantly carry information concerning 'slow' or 'burning' pain rather than 'fast' pain (Adler, 1980; Basbaum & Fields, 1978; Kosterlitz, 1979; Pert, 1978). Large concentrations of enkephalinergic neurons are found in the substantia gelatinosa of the spinal cord and at various other points throughout the ascending course of the spinothalamic pathway (Basbaum & Fields, 1978; Kuhar & Uhl, 1979). Any one or all of these groups of enkephalinergic neurons could modulate the transmission of pain information in this pathway, and the studies contained within the present thesis allow no further localization of this modulating effect.

No direct anatomical link has been established between the pain pathways and the vestibular system (although some interaction in the reticular formation is possible). Possible mechanisms for the modulation of pain transmission in the central nervous system have been extensively discussed elsewhere (Melzack, 1973; Melzack & Wall, 1968; Nathan, 1976) and the reader is referred to these sources for a comprehensive treatment of this topic.

It was suggested in Section III of the present thesis that the motion-induced analgesia phenomenon may represent a phenomenon analogous to the "stress-induced analgesia" (SIA) phenomenon that has been the target of intensive research activity in recent years. The purpose of the following section is to examine current findings concerning stress-induced analgesia and their relationship to the motion-induced analgesia phenomenon.

Stress-induced and motion-induced analgesia.

Recently, a great deal of interest has been generated by the finding that a short period of footshock is sufficient to induce antinociception in the rat (Akil, Madden, Patrick, & Barchas, 1976). This study was one of the first to clearly demonstrate the existence of a non-pharmacological pain control mechanism that could be activated by physiological 'stress'. Since publication of this study, a large number of additional investigations of stress-induced analgesia have been performed. The results of these studies present a rather complicated role for 'stress' in the SIA phenomenon and also suggest that different physiological stressors may activate one or a number of antinociceptive mechanisms.

Bodnar and his co-workers (Bodnar, Kelly, Brutus, Greenman, & Glusman, 1980; Spiaggia, Bodnar, Kelly, & Glusman, 1979) have suggested that endogenous pain modulation may be mediated by one or both of two different types of systems: one opiate in nature and the other non-opiate. In the following brief review, these systems will be considered separately and the types of stressors thought to activate them will be discussed.

Endogenous opiate mechanisms. An endogenous opiate pain modulation system has been proposed to account for the antinociceptive effects of a variety of different types of stressors. In most of these, the analgesic effects of the particular stressor have been shown to be reversible with the opiate antagonist naloxone, and in some cases, cross-tolerance with morphine has been established. Electroacupuncture (Cheng & Pomeranz, 1978), immobilization (Amir & Amit, 1978), electrical brain stimulation (Akil, Mayer, & Liebeskind, 1976), food deprivation (McGivern, Berka, Berntson, Walker, & Sandman, 1979) and footshock (Buckett, 1979) are all treatments that are thought to produce an opiate mediated antinociceptive effect. Additional support for opiate involvement arises from studies demonstrating increased endorphin levels (e.g. Akil, Madden, Patrick, & Barchas, 1976; Terenius, 1978), and decreased receptor binding capacity (Chance, White, Krynock, & Rosecrans, 1978; DeVries, Chance, Payne, & Rosecrans, 1979) following exposure to stressors and an attenuation of the analgesic effects of stressors following treatments that reduce endorphin levels (Cheng, Pomeranz, & Yu, 1979).

The antinociceptive effect of abnormal motion discussed in

the present thesis also seems to fit in the category of an endorphin-mediated antinociceptive effect by virtue of its sensitivity to naloxone and the ability to develop cross-tolerance with chronic morphine treatment.

Not only have the endorphins been strongly implicated in the antinociceptive effects of these different stressors, but it appears that the B-endorphin and enkephalinergic systems have the capacity to be differentially activated. Electroacupuncture for example, appears to involve pituitary B-endorphin (Cheng, Pomeranz, & Yu, 1979), although the antinociceptive effects of abnormal motion likely involve the enkephalin systems. Buckett (1979) has also demonstrated a very short duration antinociceptive effect of footshock in mice that likely involves the enkephalins rather than the B-endorphin system.

Nonopiate mechanisms. In contrast to the types of stressors mentioned above, there are a number of stressors that produce analgesia that is neither affected by naloxone nor shows cross-tolerance with morphine. For example, it has been reported that cold-water swimming (Bodnar, Kelly, Steiner, & Glusman, 1978), insulin administration (Bodnar, Kelly, Mansour, & Glusman, 1979), 2-deoxy-D-glucose (2-DG) administration (Bodnar, Kelly, & Glusman, 1979), footshock administration (Hayes, Bennet, Newlon, & Mayer, 1978), and conditioned analgesia (Chance & Rosecrans, 1979a, 1979b) act through an endogenous pain modulating system that is not opiate in nature. Although the possible mechanisms of non-opiate SIA are for the most part unknown, recent evidence has suggested two possible nonopiate pain modulating mechanisms. Vasopressin (anti-

diuretic hormone), is released from the pituitary and has recently been implicated in the SIA phenomenon. Rats with diabetes insipidus, a condition accompanied by very low vasopressin levels, are insensitive to the antinociceptive effects of cold-water swimming (Bodnar, Zimmerman, Nilaver, Mansour, Thomas, Kelly, & Glusman, 1980). Vasopressin has also been found to exist in the rat brain (Glick & Brownstein, 1980) and has a potent analgesic action when administered intracranially or systemically (Berntson & Berson, 1980). The vasopressin hypothesis may explain why hypophysectomy attenuates analgesia induced by cold-water swimming and 2-DG (Bodnar, Glusman, Brutus, Spiaggia, & Kelly, 1979) without endogenous opiate involvement.

Dopamine (DA) has also been implicated in the non-opiate forms of SIA. Bodnar et al. (1980) for example, have found that apomorphine, a DA agonist, attenuates cold-water swim analgesia. Consistent with this finding, Crowley, Rodriguez-Sierra, and Komisurak (1977) have found that DA agonists attenuate, and DA antagonists facilitate, antinociception induced by vaginal probing in rats.

In contrast, Kulkarni (1980) has suggested that drugs that inhibit catecholamine function such as alpha-methyl-para-tyrosine, reserpine, haloperidol, and chlorpromazine will abolish analgesia induced by heat stress or immobilization. It is not known if the differential involvement of catecholamines in these studies reflects a differential involvement of catecholamine systems in analgesia induced by different stressors (i.e. cold-water, heat, or immobilization) or is

merely the result of procedural differences among the studies. It is also possible that the drugs used were acting in a different manner than is normally assumed. Apomorphine for example, is thought to bind to at least some opiate receptor sites but has little analgesic effect. Jaffe and Martin (1975) indicate that the emetic actions of apomorphine may be abolished by naloxone, an opiate antagonist.

It should be noted that it has been suggested that footshock activates both an opiate and a nonopiate pain modulation system. Even within the same study, footshock has been shown to produce naloxone-reversible and naloxone-insensitive antinociceptive effects (Lewis, Cannon, & Liebeskind, 1980). Three mins of continuous footshock produced an antinociceptive effect that was not sensitive to naloxone; whereas, 30 min of intermittent footshock produced an antinociceptive effect that was attenuated by both naloxone and dexamethasone treatment. The same stressor then, is capable of activating either an opiate or a non-opiate pain modulating system, depending on the administration parameters. All of the stressors discussed above have not only been administered in different forms, but have widely different physical parameters associated with them. Cold-water swim stress for example, has much different physical and temporal parameters than does footshock. It is possible that the parameters of cold-water swim stress could be adjusted so as to activate an opiate-type pain modulation system. The possibility of escaping the stressor may also be important in the activation of an endogenous pain control system. Jackson, Maier, and Coon (1980)

have recently demonstrated that escapable versus inescapable footshock produced different degrees of antinociception.

It would seem from the above discussion that the term 'stress-induced analgesia' is somewhat of a misnomer in that 'stress' does not necessarily activate a specific pain modulation system. In fact, some treatments that qualify as stressors produce no detectable degree of anti-nociception (Hayes, Bennet, Newlon, & Mayer, 1978, Willer, Boureau, & Albe-Fessard, 1979). Not only may different types of stressors activate different pain modulation systems, but the duration of the stressor and the perceived ability to control the stressor may determine which type of system, if any, is activated. The significance of these multiple systems and the reasons for the apparently arbitrary manner in which they are activated in response to stress remains unknown.

Applications of the motion-induced analgesia phenomenon.

It is possible that abnormal motion may have some usefulness as a nonpharmacological means of pain control in humans and other animals. The usefulness of this procedure has been clearly demonstrated in the present thesis if one is concerned with the administration of an acute noxious stimulus to laboratory animals. A brief period of abnormal motion produces a large but short-lived reduction in the reaction to the noxious stimulus. The use of this procedure should be encouraged as it minimizes the trauma to the animal generated by administration of the noxious stimulus. It also follows that this procedure should not be used if one is interested in either the reaction of the animal to noxious stimuli (e.g. Staubli &

Huston, 1979) or in various biochemical assays that may be affected by the activation of an opiate peptide system.

In humans, nonpharmacological means of pain modulation offer a number of potential advantages over more conventional pharmacological methods of pain control. First, they likely do not have the same addictive potential or would be as susceptible to abuse as the opiate and opiate-derived analgesic drugs (Jaffe & Martin, 1975; Snyder, 1977). Second, nonpharmacological pain control techniques likely do not have the many undesirable side effects of typical analgesic drugs (see Jaffe & Martin, 1975).

In addition to these advantages, which are common to all nonpharmacological means of pain modulation, abnormal motion would seem to have some unique advantages. It is easy to administer, requiring only a motion device to stimulate the vestibular organs. The device used to stimulate the vestibular system could be as simple as a rotating chair in which the patient could sit and have his head moved repeatedly out of the plane of rotation. This technique (Graybiel, Wood, Miller, & Cramer, 1968; Cowings, Billingham, & Toscano, 1978) generates 'coriolis accelerations' within the semi-circular canals and can be of sufficient intensity to induce motion sickness. The experience of abnormal motion, although possibly not pleasant, is possibly not as noxious as some other techniques could be (e.g. trans-cutaneous electrical stimulation). There are few side effects of abnormal motion that outlast the period of stimulation and even motion sickness, should it develop, can be controlled by adjusting the intensity of the stimulus so that the unpleasant effects may be minimized (Reason & Brand, 1975).

At this time however, empirical confirmation of an antinociceptive effect of abnormal motion in humans does not exist.

The antinociceptive effect of abnormal motion, even if it does exist in humans, may be of somewhat limited usefulness in human pain control. Most pain of clinical concern is reasonably long lasting and all demonstrations to date of the antinociceptive effect of abnormal motion have concentrated on a reduction of responsiveness to acute painful stimuli. This acute test for antinociception may reveal nothing about the effectiveness of the abnormal-motion treatment in pain states of longer duration.

A very large portion of the pain-control literature concerns methods for alleviating pain of relatively long duration, and it would seem that if an antinociceptive effect of abnormal motion is to be clinically useful, it must alleviate pain of longer durations than that caused by exposure to brief stimuli. Perhaps one way of conducting this examination would be to examine the effect of the abnormal motion treatment in an animal model of "tonic" pain. Such a test has recently been described by Dennis and Melzack (1979). This test appears to provide a pain stimulus of relatively long duration and hence could be used to evaluate the long-term antinociceptive effects of abnormal motion.

It may seem that a clinically useful role for abnormal motion can be rejected on the grounds that the analgesia produced is of too short a duration to be useful. This is not necessarily the case however, and it is possible that acute

exposure to abnormal motion would have some usefulness in chronic pain conditions. Although it is true that acute non-pharmacological pain control techniques (such as transcutaneous electric shock) produce brief analgesia in normal animals tested with acute painful stimuli (Hayes et al., 1978), it is also true that these same techniques can produce prolonged pain relief lasting weeks in humans (Melzack & Dennis, 1978; Melzack, 1973). The possible usefulness of abnormal motion in human clinical pain syndromes then, cannot be rejected out of hand and abnormal motion may prove to be a valuable adjunct to other forms of pain control.

MOTION SICKNESS

Experiments 13 and 14 of the present thesis confirmed previous reports (Green & Rachlin, 1973, 1976; Haroutunian & Riccio, 1975) indicating that abnormal motion can act as the unconditioned stimulus in the conditioned taste aversion paradigm. Attempts to reverse the development of the conditioned taste aversion in rats pretreated with two different opiate antagonists failed. The failure to reverse or block the development of a conditioned taste aversion in response to motion by the use of opiate antagonists was interpreted to suggest that endogenous opiate peptides released in response to abnormal motion have no easily discernible role in the development of the conditioned taste aversion.

It is also possible however, that opiate peptides may act on receptor mechanisms that are insensitive to naloxone or naltrexone. Cheng and Pomeranz (1980) for example, have shown that acupuncture analgesia is mediated by one type of opiate

receptor (naloxone-sensitive) and suggest that other behavioural effects of opiate peptides may be mediated by another (naloxone-insensitive) type of receptor (see also Lord, Waterfield, Hughes, & Kosterlitz, 1976; Ward, Metcalf, & Rees, 1978, for further discussion of multiple opiate receptors). This possibility seems unlikely as an explanation for the present results as the nausea, vomiting, and taste aversion-inducing properties of morphine can be blocked or attenuated by naloxone (Jaffe & Martin, 1975; Le Blanc & Cappell, 1975; van der Kooy & Phillips, 1977).

One difficulty associated with applying the results of the present experiments to the mechanisms of motion sickness is that the conditioned taste aversion paradigm has never been appropriately validated as a model of motion sickness in the rat. That is, although it is perhaps intuitively attractive to view the rats as being made 'sick' by the motion and hence developing an aversion to a novel fluid, this connection has yet to be verified. In fact, some evidence exists that suggests that the motion-induced taste aversion in rats is not directly analogous to the motion sickness found in other animal species. Lesions of the area postrema have been found to eliminate motion sickness in primates (Brizzee, Ordy, & Mehler, 1980a, 1980b) and dogs (Money, 1970) and also eliminate taste aversions produced by centrally acting emetic drugs (Coil & Garcia, 1977; Hartley, 1977). This fact suggests that both motion sickness and centrally acting emetic drugs exert their nauseogenic and emetic actions through the area postrema. In rats however, area postrema lesions have been found to eliminate taste aversions

induced by centrally acting emetic drugs but not aversions produced by abnormal motion (Hartley, 1977). This may indicate that the mechanisms by which abnormal motion and centrally acting emetic drugs exert their effects in rats are different than in other species. If this were true, then it would be unlikely that studying the mechanisms of motion-induced taste aversions in the rat would reveal any mechanisms of motion sickness that would have cross-species generality. However, it should be noted that the Hartley (1977) results appeared only in abstract form and evaluation of these results was thus impossible.

These criticisms do not however, discount the possible usefulness of the conditioned taste aversion paradigm and information derived from the study of the neural mechanisms of conditioned taste aversions in the study of the physiological mechanisms of motion sickness. Motion for example, produces both motion sickness (vomiting) and conditioned taste aversions in the squirrel monkey (Ordy & Brizzee, 1980; Roy & Brizzee, 1979). In species other than the rat, area postrema lesions eliminate both the motion sickness (Brizzee, Ordy, & Mehler, 1980) and illness produced by centrally acting emetic drugs (Coil & Garcia, 1977; Wang & Borison, 1952) that are capable of inducing conditioned taste aversions. These facts suggest that unconditioned stimuli for taste aversions and motion sickness may share similar neural mechanisms. Additional evidence for this shared mechanism is provided by the fact that doses of emetic drugs not normally effective in producing vomiting will summate with a sub-effective motion stimulus to produce vomiting

(Money, 1970). Braveman (1975) has further suggested that motion and a variety of other illness-inducing agents (morphine, lithium chloride, etc.) will develop cross-tolerance in the conditioned taste aversion paradigm. Prior exposure to morphine or lithium chloride for example, inhibits the formation of subsequent taste aversions when motion is used as the unconditioned stimulus. This cross-tolerance effect in the formation of conditioned taste aversions has also been demonstrated with a variety of other pharmacological treatments (e.g. Brown, Amit, Smith, & Rockman, 1979; Gamzu, 1975). Triesman (1977) has hypothesized that not only are the mechanisms of motion sickness and drug induced illness similar, they may be identical.

If it is true that motion sickness and conditioned taste aversions produced by centrally acting emetic drugs share common neural mechanisms, there are at least two important implications of this relationship. First, adaptation to emesis produced by repeated exposure to centrally acting emetic drugs should produce cross-tolerance to the illness-inducing properties of motion. This means that protective adaptation to motion sickness could be acquired by repeated exposures to emetic drugs. At present, protective adaptation to motion sickness occurs only when the organism is repeatedly exposed to the motion previously used to induce the motion sickness (Reason & Brand, 1975). If the central emetic mechanism could be adapted to the illness-inducing properties of centrally acting emetic drugs, this adaptation should extend to all illness-inducing treatments that share the same mechanisms.

The possible commonality between the actions of centrally acting emetic drugs and motion sickness may also explain the actions of drugs effective in preventing relatively mild forms of motion sickness. These drugs, which include some phenothiazines, some antihistamines, and some anticholinergics, do not seem to exert their antimotion-sickness effects through any one neurochemical system (Reason & Brand, 1975; Wood, 1979). That is, not all phenothiazines, antihistamines, or anticholinergics are effective in preventing motion sickness. These drugs must also be taken well before exposure to motion (Wood, 1979) and all have nausea and vomiting as side effects at high doses. It is possible that these drugs prevent motion sickness in a manner that is similar to Braveman's finding (1975) that preexposure to morphine or other drugs prevents the formation of a motion-induced taste aversion. Preexposure to drugs that are able to block or weakly stimulate the central emetic mechanisms may inhibit the subsequent activation of these mechanisms by another stimulus such as abnormal motion.

It would seem then, that the taste aversion paradigm, although it may not be a suitable assay of motion sickness in the rat, may prove useful in the investigation of the physiological basis of motion sickness.

CALMING EFFECTS OF ABNORMAL MOTION

The present thesis includes an experiment describing a possible calming or anxiolytic effect of abnormal motion. Rats that had been exposed to a brief period of abnormal motion subsequently demonstrated an inhibition of a species-typical response to novel or aversive stimuli. This species typical

response, defensive burying, has recently been shown to be affected by anxiolytic drugs in the same fashion that the response is affected by abnormal motion (Pinel & Treit, in press, 1981). Treatment with the anxiolytic agents diazepam or chlordiazepoxide suppress burying in rats in much the same manner as a brief period of abnormal motion.

This putative calming or anxiolytic effect is in complete accord with previous studies suggesting a calming effect of abnormal vestibular stimulation in both humans (Korner & Thoman, 1972; Ter Vrugt & Pederson, 1973; Reason & Brand, 1975; Weeks, 1979) and other species (Thoman & Korner, 1971; Staubli & Huston, 1979). In addition, it is in agreement with anecdotal evidence concerning the calming effects of rocking chairs, swinging or swaying motions, and the like (Weeks, 1979).

The defensive burying paradigm would seem useful for further exploration of this anxiolytic effect for a variety of reasons. First, the response is reliably elicited by a variety of novel stimuli (Terlecki, Pinel, & Treit, 1979) and by previously neutral stimuli that have been paired with an aversive stimulus such as an electric shock (Pinel & Treit, 1978). Second, the response itself is highly stereotyped and easily observed by even untrained observers (cf. Pinel & Treit, in press, 1981). Third, there is a direct and reliable relationship between the amount of burying exhibited by a subject and the intensity of the aversive stimulus (Treit, Pinel, & Terlecki, 1980) and thus the amount of burying behaviour observed is probably related to the aversiveness of the stimulus object. Fourth, Treit (Pinel & Treit, in press,

1981) has shown that by using different stimulus intensities in the conditioned defensive burying paradigm, it is possible to eliminate non-specific effects of the putative anxiolytic treatment as explanations for the suppression of burying. Diazepam, for example, suppresses defensive burying in the unconditioned burying paradigm and at low shock intensities in the conditioned defensive burying paradigm. Diazepam in the same dose however, has little effect on defensive burying behaviour when high shock intensities are used in the conditioned defensive burying paradigm. The fact that diazepam fails to affect defensive burying at high shock intensities eliminates non-specific drug actions such as motor debilitation or analgesia as plausible alternate explanations for the suppression effect at low shock intensities and in the unconditioned defensive burying paradigm.

In order for the putative anxiolytic effect of abnormal motion to be considered a valid 'anxiolytic' effect rather than the product of some non-specific motor debilitation or illness effect, the Treit (1981) procedure using different shock intensities can be used. To date, this experiment has not been conducted. In addition to meeting the criteria that Treit and Pinel (in press, 1981) have established for anxiolytic agents in the defensive burying paradigm, it is also necessary to examine the effects of abnormal motion in other behavioural tests designed to screen anxiolytic agents. These tests include conflict tests, open field exploration, locomotor activity in situations where locomotor activity is punished by footshock, and others (Corey, 1978; Glick, 1976).

Should an anxiolytic action of abnormal motion be confirmed, it will possibly be the first demonstration of the activation of an endogenous 'anxiolytic' mechanism. The existence of such a system is suggested by the presence of endogenous benzodiazepine receptors in the central nervous system (Tallman, Paul, Skolnik, & Gallagher, 1980). Because the receptors exist, it seems logical to assume that there are endogenous benzodiazepine-like molecules that activate these receptors in response to the appropriate environmental stimuli. Although it is tempting to speculate on the usefulness of a non-pharmacological anxiolytic mechanism that could be activated at will without the adverse effects attendant to drug use, it must first be demonstrated that the putative anxiolytic effect of abnormal motion is more than a possible side effect of abnormal motion such as illness. In conjunction with this however, it is interesting to note that recent evidence indicates that lithium may exert its anti-aggressive effects in rats through the area postrema, an area thought to primarily detect the presence of illness-inducing toxins such as lithium chloride (Hartley, 1977). If the area postrema is lesioned in rats, the anti-aggressive effects of lithium are abolished (McGlone, Ritter, & Kelly, 1980).

CONCLUSIONS

The experiments contained in this thesis have demonstrated three main behavioural effects of abnormal motion in the rat: antinociception, the formation of a conditioned taste aversion, and a possible anxiolytic effect. Are these behavioural effects distinct in that they represent the behavioural manifestations

of different physiological mechanisms or do they represent the behavioural effects of a common underlying mechanism in different tasks?

It has been suggested in various places throughout this thesis that endogenous opiate peptides may be the common mechanisms underlying the behavioural effects of abnormal motion. Although the activation of an endogenous peptide system appears to mediate the antinociceptive effect of abnormal motion (and possibly the anxiolytic effect), this activation does not appear to be responsible for the taste aversion-inducing properties of abnormal motion.

It is also possible that abnormal motion exerts its behavioural effects through a general stress mechanism. Although a general stress mechanism may explain the taste aversion data and possibly the antinociceptive effect, it does not explain the anxiolytic effect found in Experiment 15. In Experiment 15, it was found that exposure to abnormal motion, a stressor, suppressed performance of a defensive response whereas exposure to a different stressor, electric shock, slightly facilitated performance of the response. This dissociation would seem to render the stress hypothesis unlikely. It would seem then, that the behavioural effects of abnormal motion may represent the activation of a number of hormonal or neurochemical systems.

The present thesis has demonstrated that the vestibular system may play an important role in behaviour. Abnormal activation of this system results not only in motion-induced illness, but also in the activation of an endogenous pain

modulating system, and a possible endogenous anxiolytic mechanism. Vestibular stimulation then, may have a much greater involvement in behaviour than has been previously assumed and it is hoped that the experiments presented here will stimulate further research in the almost unexplored area of the vestibular system and its role in behaviour.

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