c.1

SEROTONIN AND EXERCISE

by

MICHAEL LEONARD WALSH

B. P. E.

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF PHYSICAL EDUCATION

in

THE FACULTY OF GRADUATE STUDIES

School Of Physical Education And Recreation

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

February 1983

© Michael Leonard Walsh, 1983

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Physical Education, February, 1983

The University of British Columbia
2075 Wesbrook Place
Vancouver, Canada
V6T 1W5

Date:

Abstract

The effects of altering serotonin (5-HT) concentration on physical exercise were investigated in adult, male, hooded rats. The rats were trained to run on a treadmill at a speed of 40 m/min, then subjected to an exhaustive run. Serotonin levels were decreased by para-chlorophenylalanine (300 mg/kg; intragastric) and increased by 5-HT (50 ug; intraventricular). Rats with lowered 5-HT levels had a 30% increase in running time to exhaustion whereas their controls only had a 1% increase. Elevating 5-HT levels decreased running time 44% whereas appropiate controls had a 7% increase in running time. In some animals the effect of exercise on 5-HT levels in the cerebellum, medulla oblongata, hypothalamus, midbrain, striatum, hippocampus, and cortex were measured. When compared to yoked, shocked controls, exercised rats had no difference in the absolute levels of 5-HT except for a lesser amount in the hypothalamus. These results suggest that although exercise did not increase absolute 5-HT levels, changing resting levels of 5-HT can markedly alter subsequent running time to exhaustion.

Table of Contents

Abstract ii
List of Tables iv
List of Figures v
Acknowledgements vi
INTRODUCTION 1
METHODS 3
Subjects 3
Surgery 3
Injections 3
Serotonin Analysis 4
Apparatus 4
Procedure 5
Histology 7
RESULTS 9
Running Time 9
Serotonin Analysis 11
Locomotor Activity 13
Histology 13
DISCUSSION 14
REVIEW OF LITERATURE 16
1 Introduction 16
2 Serotonin As A Modulator 17
2.1 Introduction 17
2.2 Anatomical Evidence 17
2.3 Physiological Evidence 18
2.4 Behavioural Evidence 20
3 Serotonin Interactions With Other Neurotransmitters .24
3.1 Introduction 24
3.2 Serotonin Interaction With Noradranaline 26
3.2.1 Introduction 26
3.2.2 Anatomical Evidence 26
3.2.3 Biochemical And Physiological Evidence 27
3.2.4 Behavioural Evidence 30
3.3 Serotonin Interaction With Dopamine 31
3.3.1 Introduction 31
3.3.2 Anatomical Evidence 31
3.3.3 Biochemical And Physiological Evidence 32
3.3.4 Behavioural Evidence 34
4 Possible Loci And Mechanisms By Which Serotonin May Inhibit Physical Activity 37
4.1 Introduction 37
4.2 Thermoregulation 37
4.3 Inhibition Of Cortical Neurones 38
4.4 Action On Spinal Motorneurones 41
4.5 Air Ionization 43
4.6 Serotoninergic Inhibition At Motor Endplates ...44
4.7 Serotoninergic Inhibition Of Glucocorticosteroid Action 45
4.8 Serotoninergic Inhibition Of Adrenal Tyrosine Hydroxylase 47
4.9 Other Possible Loci Of Inhibtion 48
5 Conclusions 49
REFERENCES 51

List of Tables

1. Exercise Regime 6
2. Running Times To Exhaustion 10
3. Serotonin Concentrations In Rat Brain 12

List of Figures

1. Percent Change In Running Time 11
2. Motor Activity Spectrum 16

Acknowledgement

I gratefully acknowledge the encouragement, excellent discussions, and technical assistance of my committee members: Dr D.J. Albert, Dr S. Brown, Dr K. Coutts, and Dr A. Pearson. Further helpful disscussion and technical assistance offered by Dr L. Burtnick, Dr K. Gallicano, and Dr P. Gallo was also greatly appreciated.

I also like to acknowledge the excellent technical assistance offer by Ben Clifford, Wayne Karlsson, Wendy Longley, Walter Martindale, Janice P. O'Brien, Linda Walsh, and Lyle Whittimore.

INTRODUCTION

Based on a large number of studies, Trulson and Jacobs (1979b) have put forward a hypothesis that cranial serotonin modulates an animal's activity level ranging from sleep to wakefulness to simple locomotor activity. They hypothesize that low serotonin (5-HT) levels, which occur during sleep, promote locomotor activity; high 5-HT levels occurring during prolonged locomotor activity induce resting. This hypothesis suggests that the modulatory effects of 5-HT serve as a safety mechanism against over-stressing the organism with too little or too much activity.

From a behavioural perspective, there is no reason why Trulson and Jacobs' hypothesis should be limited to the range of sleeping to walking. It is reasonable to infer that the activity spectrum could be extended beyond walking to include intense motor activity (exercise).

This extrapolation of Trulson and Jacobs' hypothesis to include intense motor activity has obvious and readily testable implications. The first is that the alteration of serotonin levels should alter exercise performance. To date, there have been no systematic studies which have altered serotonin levels and recorded subsequent performance of intense motor activity. However, Feldberg and Sherwood (1954) did make a peripheral observation that serotonin (intraventricular) produced apparent muscular weakness.

The second implication of extending Trulson and Jacobs' hypothesis is that exercise should cause an increase in cranial 5-HT levels. Rats that are forced to exercise are confronted

with two different stresses: (1) the motor activity required and (2) the deterring condition which augments the performance of the exercise (eg. an electric grid at the rear of a running chamber or water immersion during swimming). Research by Thierry et al (1968), demonstrates that mild electric shock increases 5-HT levels in the brainstem. A few studies have indicated that serotonin does increase during exercise (Barchas and Freedman, 1963; Bliss, 1973; Romanowski, 1967; Romanowski and Grabiec, 1974). These studies, however, used only sedentary animals as controls and hence their data do not indicate whether the increased 5-HT is the result of the shock, the exercise, or both.

It is the purpose of this study to lower and raise serotoninergic levels in the rat brain and record subsequent running time to exhaustion. Furthermore, by determining 5-HT concentration in various areas of the brain after exercise and using non-exercised control rats that receive a shock regime comparable to the exercised rats, it will be determined if 5-HT levels do indeed increase during exercise.

METHODS

Subjects

The subjects were 48 adult male hooded rats obtained from Charles River, Canada. The rats weighed 180-200 g at the time of surgery and 220-240 g by the final test. The animals were housed individually in wire mesh cages with free access to food and water. The colony room was maintained on a normal 12:12 hour light:dark cycle.

Surgery

Nineteen of the 48 animals underwent surgery. Surgery was performed using a Kopf stereotaxic instrument and sodium pentobarbital anaesthesia (50 mg/kg). Bilateral 23 gauge stainless steel cannulas were permanently implanted into the lateral ventricles. The bevelled tips of the cannulas were aligned posteriorly. The coordinates, based on the atlas of Pelligrino and Cushman (1967), were AP: -0.2, ML: ±1.8, DV: -2.7 mm from the cortical surface. The upper incisor bar was set 5 mm above the interaural line.

When not in use the cannulas were capped with 30 gauge stainless steel plugs. Animals were allowed 1 week of postsurgical recovery.

Injections

To deplete serotonin, 10 animals were given an intragastric injection of para-chlorophenylalanine (pCPA; 300 mg/kg; 30 mg/ml) while anaesthetized with ether. The pCPA was prepared immediately before use by adding 0.1 ml Tween 80 to the pCPA in saline then homogenizing the solution. Ten controls received an equivalent volume of vehicle. The injections were performed 3

days prior to the final exercise session.

To increase cranial serotonin levels, 9 rats received a bilateral intraventicular injection of serotonin creatinine monophosphate (50 ug in 5 ul) through two 30 gauge injection needles placed in the cannulas. A Sage Instruments pump, fitted with two 50 ul syringes, injected the 5 ul over a period of 3 min 45 sec. Passage of 5-HT solution into the ventricles was confirmed by the movement of a 1 ul bubble in the infusion line.

Serotonin creatinine monophosphate was dissolved in saline and adjusted to a pH of 6.5 just prior to use. Nine rats received a similarly administered vehicle solution.

Serotonin Analysis

After the final test session, designated animals were quickly sacrificed by cervical dislocation. Their brains were excised within 20 sec, cooled in ice water for 40 sec, and divided into seven regions within 3 minutes. The 7 regions were: the cerebellum, medulla oblongata, hypothalamus, striatum, midbrain, hippocampus, and cortex according to the method of Glowinski and Iversen (1966). Each brain region was put into a plastic bag and frozen in dry ice and acetone, then stored at -20°C for a maximum of 2 weeks. Each region was spectrofluorometrically analyzed (Farand 810) for 5-HT content using a modification of the method of Curzon and Green (1970) as recommended by Dr. A. Pearson (personal communication).

Apparatus

Locomotor activity was measured in a 60 x 60 x 60 cm grey box with 3 cm of San-i-cel on the floor. The floor was divided into 9 equal squares by marking the San-i-cel with ink. The

activity was recorded by an overhead camera and monitored on television screen in an adjacent room.

The motorized treadmill consisted of 3 running alleys 32 x 10 x 10 cm, with the forward 14 cm painted black. The electric grid, 12 x 10 cm, located at the rear of each running alley, was 2 cm below the running surface.

The control shock box was 35 x 13 x 35 cm, the floor being an electric grid. Simultaneous electrification of the control shock box grid and treadmill grid was attained by having a low resistance photoelectric relay in line with the treadmill grid and plugged into the external control of the shock generator going to the control shock box.

Procedure

There were 6 groups of animals: the pCPA-injected group (N=10), the control group for the pCPA-injected rats (N=10), the serotonin-injected group (N=9), the controls for the serotonin group (N=8), the yoked, shocked, control group (N=6), and the sedentary group (N=3).

The four running groups (pCPA-injected, 5-HT-injected, and their respective vehicle-injected controls) received the same training regime and fatigue runs (Table 1). This entailed 3 days of training followed by a pretest fatiguing run at 40 m/min. Four days later, day 8, the rats performed their second fatiguing run (posttest). A rat was considered fatigued if it displayed a non-running response exceeding 8 seconds. The time to exhaustion was recorded. Each yoked, shocked, control rat was paired with a rat from the pCPA-injected control group. Each time a pCPA-injected control rat was run, the paired rat in

TABLE 2

RUNNING TIMES TO EXHAUSTION

Group	Fatigue 1	Fatigue 2
pCPA	810±109	953±89
control	832±132	871±179
5-HT	620±112	408±127
control	603±134	604±128

Results are given as mean ± S.E.M. in seconds.

the yoked, shocked, control group was put in the control shoick box.

On day 5, one day after the first fatigue run (F1) the pCPA-injected group and its control group received their injection. Twenty-five minutes prior to the second fatigue run (F2) 5-HT-injected group and its control group received their injection.

The locomotor activity was recorded in 3 five minute periods 20 minutes prior to F2.

To determine if cranial levels of serotonin change during exhaustive exercise, rats from the shocked control group and selected rats from the controls for the pCPA-injected group were immediately sacrificed after exhaustion. Their brains were rapidly removed and later analyzed for serotonin.

Serotonin analysis was also done on a group of sedentary rats as a comparison to the exercised and shock stressed rats. This data was used for comparison to previous literature on the subject.

Histology

A few days after F2 the rats from the 5-HT-injected group and its control group were anaesthetized with sodium pentobarbitol. The rats were then injected with 10 ul of India ink over a 7 1/2 min period. Shortly after this their brains were removed and fixed in formalin solution.

After fixing, the brains were frozen to -18°C in a cryostat. Anterior and posterior to the cannulae placement, coronal sections 90 um thick were taken to verify ink distribution throughout the ventricles. At the level of the

placement 30 um sections were taken to further verify the placement of the cannula tips.

RESULTS

Running Time

For animals injected with pCPA, the running to exhaustion tended to be longer than those injected with saline (see Table 2). To compare any change that occured from F1 to F2, the time to exhaustion for F2 was expressed as a percentage of the time to exhaustion for F1 (i.e., F2/F1 X100). The pCPA-injected group showed an average increase in running time of 31% whereas its control group only increased 1% (see fig. 1). A one-tailed Student's t test for independent groups indicates the difference between the injected and control group barely missed significance ($p<.06$).

The running performance of the rats injected intraventricularly with 5-HT decreased 44% whereas its control group increased 7%; this was significant ($p<.005$).

Serotonin Analysis

Serotonin concentrations in each area of the brain examined are given in Table 3. The exercise group showed no difference when compared to its shocked control group except in the hypothalamus.

For the exercise group, the medulla oblongata and hypothalamus showed increases when compared to sedentary controls. For the shocked control group, the medulla oblongata, hypothalamus and midbrain showed increases when compared to controls. Whole brain 5-HT levels, obtained by pooling the individual brain areas, were not significantly different between groups.

TABLE 1
EXERCISE REGIME

	Day				
Bout	1	2	3	4	8
1	5+18 (1)(2)	22 (2)	24 (2)	24 (2)	21→40→21 (2)
2	21 (2)	25 (2)	30 (1)	33 (1)	40 (fatigue)
3	24 (2)	27 (2)	33 (1)	37 (1)	
4	25 (2)	29 (2)	35 (1)	40 (1)	
5				40 (fatigue)	

Table 1 gives the running speed (m/min) for each bout of exercise. The duration of each bout of exercise is given in brackets (min). There was a 10 min rest between each bout of exercise except for a 30 min rest between bout 4 and 5 of day 4.

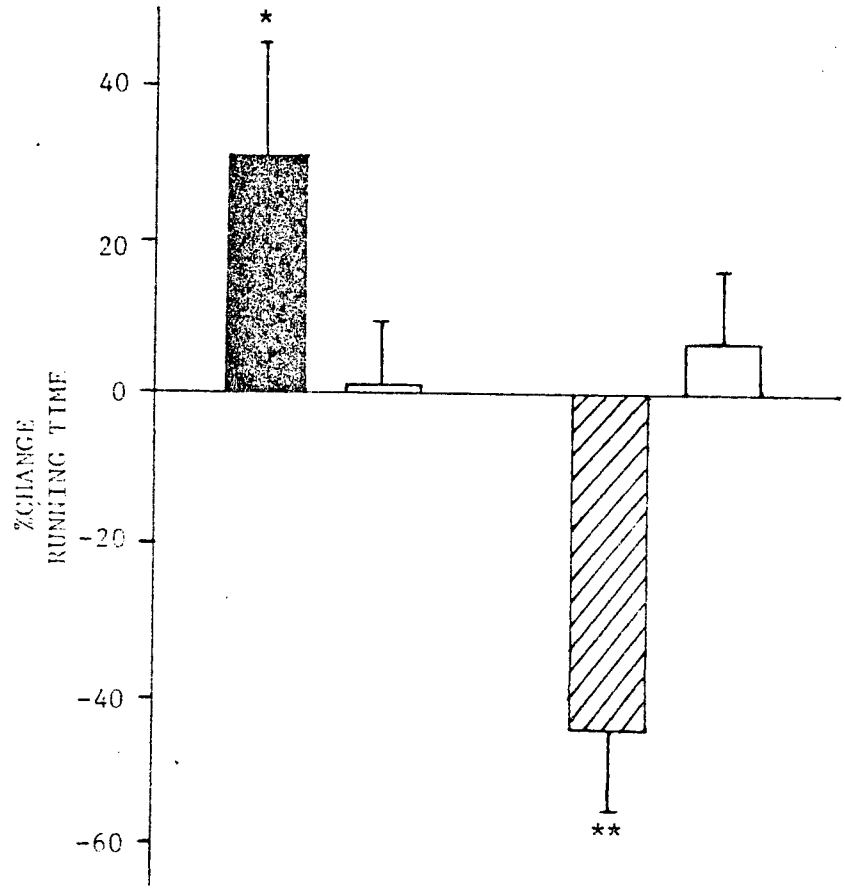

FIG. 1. Percent change in running time from F1 to F2 (means±SEM). Black column (pCPA group); striped column (5-HT group); open column (respective control group). *=p<.06; **=p<.005.

TABLE 3

SEROTONIN CONCENTRATIONS IN THE RAT BRAIN AFTER EXERCISE, SHOCKED CONTROL, AND SEDENTARY CONTROL CONDITIONS

Behavioural Condition	Brain Area						
	Cerebellum	Medulla Oblongata	Hypothalamus	Midbrain	Striatum	Hippocampus	Cortex
Exercise	.24+.02 (6)	.91+.15a (7)	1.58+.25bf (7)	1.12+.21 (7)	.99+.25 (7)	.78+.17 (7)	.45+.06 (7)
Shocked Control	.27+.03 (5)	1.02+.15d (6)	1.93+.25be (6)	1.18+.14c (6)	.90+.18 (6)	.78+.10 (6)	.47+.05 (6)
Sedentary	.24+.02 (3)	.71+.05ad (3)	1.40+.10ef (3)	.95+.05c (3)	.85+.03 (3)	.66+.02 (3)	.43+.02 (3)

Results are given as mean ug/g+S.D. The number of rats used is given in brackets.
a,b,c=$p<.05$; d=$p<.01$; e,f=$p<.001$.

Locomotor Activity

The pCPA-injected group averaged 129 crossings over the 15 min period. Its respective control averaged 127. Analysis of variance of the locomotor activity divided into 5 min intervals indicated no difference between groups ($p>.80$), a significant effect of time ($p<.001$), and no significant interaction of the groups by time ($p>.60$).

The 5-HT-injected group averaged only 80 crossings in 15 min whereas its control averaged 157 crossings. Analysis of variance showed a significant group effect ($p<.001$), a significant time effect ($p<.001$), and a nonsignificant interaction ($p>.20$).

Histology

In 5 of the 10 placements in the 5-HT-injected group ink injections indicated that both cannula tips were located in the ventricles. Four other animals in the 5-HT group had unilateral placements in the ventricles and in 1 animal both canula tips were located outside of the 3rd ventricle. This last animal was not included in the statistical analysis. The 4 animals with unilalteral placements were included in the statistical analysis because there was no signicicant differences in their running times ($t=.64$; $p>.50$) or their locomotor activity (F group=2.52, $p>.13$; F groupXtime=.27, $p>.75$) when compared to animals with bilateral placements.

The controls for the 5-HT-injected group had 6 bilateral placements in the ventricles, 2 unilateral placements, and 1 animal that had neither cannula located in the ventricles. This animal was discarded from the statistical analysis.

DISCUSSION

The trend of the data does support the extension of Trulson and Jacobs' hypothesis that lower 5-HT levels promote an increase in the duration of fatiguing exercise. pCPA injections, which lowered 5-HT levels, increased running time to exhaustion by 30% when compared to controls. However, this barely failed to reach significance ($p<.06$) hence a firm conclusion cannot be made. Increasing 5-HT levels in the brain caused the opposite effect: a significant decrease in running time of 50% when compared to control animals.

Compared to sedentary controls the yoked, shocked controls increased absolute 5-HT levels in the medulla oblongata, hypothalamus, and midbrain. The exercised rats only had increases in the medulla oblongata and hypothalamus. Contrasting the serotonin levels of exercised rats and shocked controls, only the hypothalamus revealed a significant difference: the concentration was elevated in the shocked control animals. There was no differnece between any of the groups when whole brain 5-HT levels were compared.

The results of the serotonin analysis is in agreement with the literature. Thierry et al (1968), found small but not always significant increases in 5-HT levels in the brain stem-mesencephalon and in the whole brain. Serotonin levels may not be higher during exercise because concurrent with the acceleration of 5-HT synthesis there is an acceleration of 5-HT catabolism. This is observed during minimal muscular exercise (treadwheel activity @3.7m/min) (Elo and Tirri, 1972) and during foot shock (Bliss et al, 1968). The increased catabolic

activity may prevent a summation of 5-HT levels during compound stresses creating a ceiling effect. The lack of summation is in agreement with Heym, Trulson, and Jacobs (1982). These authors found an excitation of serotoninergic neurones with phasic auditory and visual stimuli but did not observe any summation when the stimuli were presented simultaneously.

The effects of changing 5-HT levels on locomotor activity were as expected. Although lowering 5-HT levels does increase locomotor activity, the effect is only observed in familar environments and not in novel situations (Mackenzie et al, 1978). Since the animals were not previously exposed to the testing box, the similar scores for the pCPA-injected group and its control group are not contradictory. In accordance with other studies, the 5-HT injected group performed significantly fewer crossings than did its control group (Green et al, 1976a; Green et al, 1976b; Jacobs and Eubanks, 1974; Warbritton, 1978).

In conclusion, alterations of 5-HT can increase and decrease the endurance time to physical exhaustion. The effect can be predicted from extending Trulson and Jacobs' motor activity spectrum to include exercise. A limitation of the evidence is the failure to find any overall difference in 5-HT levels when comparing exercised rats to yoked, shocked controls. Thus although manipulation of serotonin levels produce the predicted change in motor performance, it could not be demonstrated that involuntary exhaustive exercise will directly produce changes in the absolute levels of serotonin.

REVIEW OF LITERATURE

1 Introduction

Although most studies relating fatigue and exercise investigate only the peripheral locus, i.e., within the muscle, there is other research to support an inhibitory effect at the central level, i.e. within the central nervous system. Figure 1 is an extension of the hypothesis that serotonin (5-HT) is a modulator of activity (Trulson and Jacobs, 1979b); the right end has been extended to include intense locomotor activity.

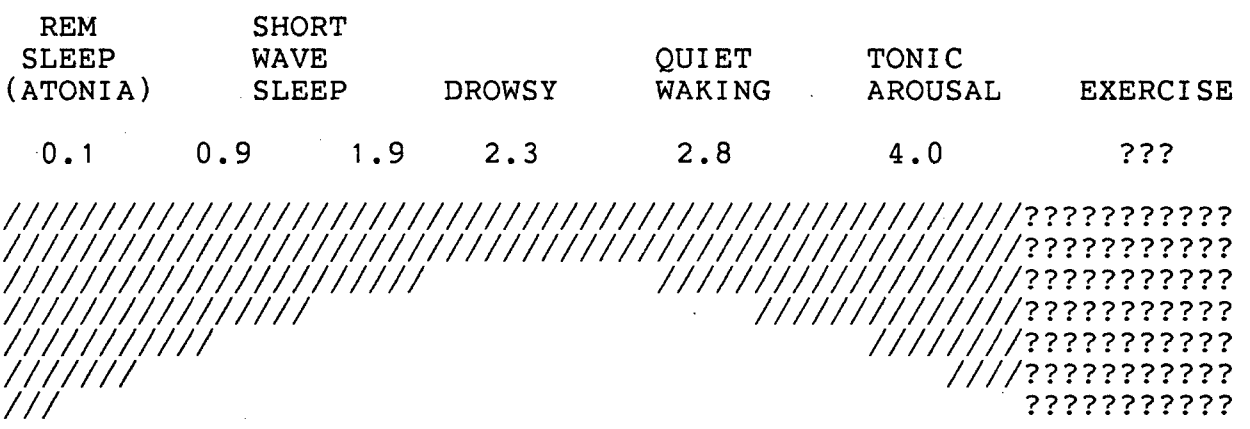

Figure 2. The motor activity spectrum including exercise as a proposed extension. The numbers represent the firing frequency (spikes/sec) of serotonin-containing neurones. See text for further explanation.

Before this hypothesis can be accepted, the anatomical, biochemical, pharmacological, physiological, and behavioural literature relating 5-HT to modulatory functions and locomotor activity must be reviewed.

2 Serotonin as a Modulator

2.1 Introduction

It is generally accepted that the majority of serotonin's effects are inhibitory. Some authors have expanded the role of serotonin, suggesting it is a modulator of behavioural arousal (Harvey et al, 1975; Trulson and Jacobs, 1979b). When brain 5-HT levels are high there is a concomitant decrease in motor activity preventing a hyperactive state. Conversely, when behavioural arousal is low, 5-HT decreases; this results in removal of inhibition of motor activity thus preventing hypoactivity. This hypothesis implies that 5-HT acts to maintain the organism's activity in the middle range of a motor activity spectrum (see Fig. 1) thus acting as a safeguard against detremental extremes of activity. For Figure 1, the amount of shaded area (/////) is proportional to behavioural change that would be incurred by a maximal antagonizing change in the serotoninergic system. An extension to the right, to include exercise, has been added to the motor spectrum.

2.2 Anatomical Evidence

The now classical studies of Dahlstrom and Fuxe (1964; 1965) elucidated the anatomy of the serotoninergic pathways within the central nervous system. The sources of cranial serotonin are discrete nuclei within the caudal brainstem. The authors labelled these nuclei, caudal to rostral, B1-B9. The major, though not only, sources of the ascending serotoninergic system are the B7 (dorsal raphe), B8 (median raphe), and B9 nuclei (Lorens, 1978; Ungerstedt, 1971). The descending system originates mainly from B1 (raphe obscurus), B2 (raphe pallidus),

and B3 (raphe magnus) (Dalhstrom and Fuxe, 1965; Loewy and Mckellar, 1981; Satoh, 1979; Tohyama et al, 1979; Ungerstedt, 1971).

The ascending serotoninergic system is as much diffuse as it is topographical. It is a widely distributed, highly collaterized, unmyelinated system (Moore et al, 1978). This is exemplified by immunohistochemical evidence indicating the ascending serotoninergic system may contact every cell in the cortex (Lidov et al, 1980). It is very likely that individual serotoninergic neurones themselves account for the large arrays of terminals and limited topography noted under autoradiography (Moore et al, 1978).

2.3 Physiological Evidence

Although Figure 1 illustrates only the motor activity spectrum, other activity spectra including biochemical and physiological phenomena may also be modulated by serotonin.

Most spontaneous fast-firing somatosensory neurones of the cat are inhibited by electrophoretically applied 5-HT. Conversely, most slow-firing neurones are excited by 5-HT. A very high correlation of r=.98 was determined between the percentage of cells depressed by 5-HT and their spontaneous firing rates (Szabadi et al, 1977). The action potentials of cat lateral geniculate neurones with large amplitudes are decreased by 5-HT adminstration, while simultaneously, the action potentials in individual neurones with low amplitudes are increased by 5-HT administration directly into the nucleus (Rinaldi et al, 1975). Within the systemic system, the vascular response of the dog's gracilis muscle to 5-HT is found to be

dependent upon the initial level of vascular resistance (Emerson et al, 1973). The resistance of vessels with a low baseline resistance is increased while the converse is true for vessels with a high vascular resistance.

Serotonin administration (into the solitary tract nucleus or i.p.) causes a tranquilizing effect upon cortical activity (Key and Mehta, 1977; Monnier and Trissot, 1958). The dorsal raphe nucleus (B7) and the median raphe nucleus (B8) may be involved in this observation. The unit activity of the dorsal raphe nucleus is inversely related to EEG synchronization (Trulson and Jacobs, 1979a). Electrolytic lesioning of the median raphe causes a persistent arousal in EEG pattern (Kostowski et al, 1968; 1969). Iontophoretic administration of 5-HT into the deep neurones of the sensomotor cortex or electrolytic stimulation of the median raphe inhibits the cortical neurones (Sastry and Phillis, 1977b). These effects are diminished by metergoline (a selective 5-HT antagonist (Sastry and Phillis, 1977a)) and prolonged by fluoxetine (a selective 5-HT uptake blocker (Wong et al, 1975)) (Sastry and Phillis, 1977b). Reader (1980), has shown that the inhibition resulting from 5-HT injection (10^{-12}M) into the cortex lasts over a time span of seconds through to minutes. This long duration suggest that in addition to ionic changes, metabolic and biochemical changes are also occurring.

Figure 1 illustrates the positive correlation between serotonin neurone firing rate and motor activity. It is possible to dissociate atonia and REM sleep by lesioning by the pontine tegmentum at the level of the locus coeruleus. When

this dissociation is created, raphe uniit activity still remains correlated to motor output (Trulson and Jacobs, 1981).

2.4 Behavioural Evidence

Injections (i.p. or intraventricularly) of low doses of serotonin or its precursors, tryptophan and 5-hydroxytryptophan (5-HTP), produce a sedation effect and apparent muscular weakness in rats (Green et al, 1976a; Green et al, 1976b; Jacobs and Eubanks, 1974; Warbritton, 1978), in cats (Feldberg and Sherwood, 1954; Monnier and Tissot, 1958; Patkina and Lapin, 1976), and in monkeys (Raleigh et al, 1980). Decreasing serotoninergic levels with injections of para-chlorophenylalanine (pCPA), a specific inhibitor of serotonin synthesis (Koe and Weissman, 1966), produces the reverse effect, i.e., insomnia and increased locomotor activity in mice (Chrusciel and Herman, 1969; Hutchins and Rogers, 1973), in rats (Fibiger and Campbell, 1971; Jacobs et al, 1975; Kayser and Hildwein, 1977; Mackenzie et al, 1978), and in monkeys (Raleigh et al, 1980). Para-chlorophenylalanine blocks the conversion of tryptophan to 5-HTP but does not effect the conversion of 5-HTP to 5-HT (Koe and Weissman, 1966). One would therefore expect 5-HTP administration to reverse the effect of pCPA whereas tryptophan administration would have no effect. Pujol et al (1971), did find that 5-HTP antagonized the pCPA-induced increase in locomotor activity and Raleigh et al (1980) found that tryptophan did not affect pCPA-induced behavioural effects. In rats, electrolytic lesions (Costall et al, 1976; Geyer, 1978; Gulmulka et al, 1970; Jacobs et al, 1974; 1975; Jacobs and Cohen, 1976; Kostowski et al, 1968; 1976; Mackenzie et al, 1978;

Srebro and Lorens, 1975) or 5,7-dihydroxytryptamine(5,7-DHT; a serotonin neurotoxin) lesions (Deakin et al, 1979; Mackenzie et al, 1978) of the median raphe nucleus elicit an increase in spontaneous motor activity.

Some authors (Hole et al, 1976; Lorens et al, 1976) have concluded that central serotoninergic fibres are not involved in lesion-induced increases in spontaneous activity. Although electrolytic lesions increase activity, more effective and specific 5,7-DHT lesions do not. These authors tested activity in the open field and not in the home cage. Mackenzie et al (1978), using both environments when measuring locomotor activity found the 5,7-DHT lesions increase activity only in the home setting. The authors concluded that the home cage and novel environment settings are not measuring the same type of locomotion. This finding is not surprising since the behaviour of rats in an unfamiliar environment is the result of a complex interaction between fear and curiosity (Blanchard et al, 1974).

Semenova et al (1981), took a different approach to investigating 5-HT and locomotor activity. Instead of altering 5-HT levels and recording subsequent motor activity, these authors grouped rats according to their activity level and measured cranial 5-HT in each group. Their results indicate the larger the ratio of cortical to caudal brainstem 5-HT concentration the more passive a rat would be.

There are only a few studies that have altered 5-HT levels in human subjects and have recorded some aspect of muscular performance. The subjects used in these studies are usually prisoners or people with neurological disorders. Myoclonus is a

movement disorder characterized by involuntary , irregular contraction of muscles. When 5-hydroxyindolacetic acid (5-HIAA; serotonin's major metabolite) is measured the cerebral spinal fluid of people with myoclonus, the levels are found to be reduced. Treatment of this disorder with 5-HTP plus a decarboxylase inhibitor dramatically decreases the frequency and intensity of myoclonic contractions (Van Woert and Sethy, 1975). With reference to human motor activity, one study indicated that 22 out of 25 children that were hyperactive had low levels of blood 5-HT (Coleman, 1971).

As noted above there are many studies relating changes in cranial serotonin levels to locomotor activity. These studies have generally found that low cranial serotoninergic levels increase locomotor activity while high serotoninergic levels inhibit locomotor activity. However, very few studies have investigated the role of serotonin under activity conditions more intense than general walking behaviour.

The first study of the relation between 5-HT level and exercise reported very significant increases ($P<.001$) in cranial 5-HT, in the rat, immediately following 15-30 min of swimming (Barchas and Freedman, 1963). Significant increases ($p<.05$) in 5-HT after longer durations of swimming or running wheel activity were also recorded.

The most significant work in relating 5-HT to the stress of physical exercise has been performed by Romanowski and co-workers. Romanowski and co-workers built their studies upon the finding of a substance, extracted from the brains of resting rats, which inhibits acetylcholine actions (Pataky and Pfeifer,

1955; Pfeifer and Pataky, 1955). Similar brain extracts from exercised rats inhibit acetylcholine-stimulated frog rectus trunci muscle and, when injected intraperitoneally, make rats drowsy and immobile (Romanowski and Janota-Lukaszewska, 1967). It was subsequently found that the brain 5-HT concentration increases in the exercised rat, and that 5-HT mimics the effect of the extract on frog rectus trunci muscle at concentrations comparable to those found in the brain (Romanowski, 1967; Romanowski and Grabiec, 1974). Ruled out as biochemical bases for the effects of the inhibitory extract are lactate, sodium, calcium, potassium, aspartic acid, ethanolamine, serine, glycine, alanine, lysine, threonine, leucine, isoleucine, valine, acetylcholine, lipids, anuerin, AMP, ADP, ATP, histamine, adrenaline, substance P, and choline (Pfeifer and Pataky, 1955; Romanowski, 1967; Romanowski and Janota-Lukaszewska, 1967).

Exploring possible mechanisms of serotonin's inhibitory action, Romanowski and Grabiec (1979) found that 5-HT and the extract inhibit an in vitro oxidative reaction and that 5-HT hyperpolarizes brain cell surface potentials.

Relative to rest, spontaneous activity increases the cranial level of dopamine's major metabolite, homovanillic acid (HVA), in mice. There is no change in the cranial levels of serotonin's major metabolite, 5-hydroxyindolacetic acid (HIAA). Under the more phasic condition of swimming (1 hr) there is an increase in both HVA and HIAA levels, indicating an increase in the turnover of dopamine and 5-HT respectively (Bliss, 1973).

3 Serotonin Interactions With Other Neurotransmitters

3.1 Introduction

The role of 5-HT in behavioural arousal has also been approached by integrating the serotoninergic system with the catecholaminergic system. In 1954, Hess postulated two competing systems: (1) an ergotropic system "which is coupled with energy expenditure" and (2) a trophotropic system which is for "protection and restitution" (Hess, 1954; p60). Later noradrenaline (NA) was postulated to be the chemical mediating the ergotropic responses and 5-HT to be the chemical mediating trophotropic responses (Brodie and Shore, 1957).

Numerous experiments have investigated the ergotropic and trophotropic systems individually and these supported Brodie and Shore's hypothesis. Review articles conclude that any experimental tool that increases the cranial activity of noradrenaline or dopamine (DA) or both typically enhances behavioural arousal, of which locomotor activity was one index. Conversely, any method that diminishes the function of these catecholamines produces a decrease in locomotor activity (Schildkraut and Kety, 1967; Weiss and Laties, 1969). Evidence for serotonin's role in the trophotropic system has already been discussed (see section 2 inclusive).

A serotoninergic system that inhibits catecholamine arousal (dopamine and noradrenaline were not investigated individually) is inferred from the observations that (1) 5-HT depletion via pCPA increases behavioural arousal, (2) pCPA potentiates arousal induced by amphetamines (catecholamine stimulants), (3) 5-HTP reverses the increase in behavioural arousal induced by pCPA,

(4) 5-HTP eliminates the potentiation of amphetamine-induced arousal by pCPA, and (5) pCPA treatment augments behavioural arousal induced by reserpine (a potent depletor of biogenic amines) (Mabry and Campbell, 1973). Increasing 5-HT levels by 5-HT infusion to the lateral ventricle (Warbritton, 1978), administering l-tryptophan (i.p.) (Hollister et al, 1976), treatment with pargyline (an inhibitor of monoamine oxidation) (Hollister et al, 1974) or decreasing 5-HT levels by lesioning of the median and dorsal raphe nuclei (Carey, 1976; Neill et al, 1972), using a tryptophan free diet (Hollister et al, 1976), and administration of pCPA (Hollister et al, 1974; Hollister et al, 1976) support Mabry and Campbell's findings that there is a serotoninergic system that inhibits amphetamine-induced arousal. Similar effects are also obtained using 5,6-dihydroxytryptamine (75ug; intracisternal) (a potent and specific serotoninergic neurotoxin with the effect delimited to the CNS when administered in this manner (Baumgarten et al, 1971)) which further indicates that the locus of serotoninergic inhibition of amphetamine-induced arousal is probably central (Breese et al, 1974).

A combination of harmine and apomorphine induces an extreme catecholaminergic arousal. This arousal, typified by violent jumping, can be potentiated by pCPA or methysergide (a serotonin blocker) and reduced by 5-HT treatment (Takashi and Kuga, 1981).

Clinical studies also indicate a serotonin-catecholamine interaction. Minimal brain dysfunction is symptomized in part by hyperkinetic behaviour, outbursts of aggressive acts, and failure to respond to reprimand or punishment. A review by

Brase and Loh (1975), relating 5-HT and catecholamines to minimal brain dysfunction (especially the symptom of hyperactivity) concludes there is an inhibitory serotoninergic system controlling catecholaminergic arousal. With regards to other symptoms of minimal brain dysfunction serotonin is thought to (1) subserve a punishment function by inhibiting normal catecholamine goal-directed reward systems (Stein and Wise, 1974; Wise et al, 1973) and (2) inhibit aggressive behaviour (Albert and Walsh, 1982). In mice treated with pCPA, aggressive behaviour has been significantly correlated with gross motor behaviour (Matte and Tornow, 1978).

3.2 Serotonin Interaction with Noradrenaline

3.2.1 Introduction

Gromova et al, (1976; p149), pointed out that there is a "remarkable similarity in the distribution of the terminals and axons which proceed from serotoninergic and noradrenergic neurones and give rise to tracts both ascending to the forebrain and descending to the spinal cord....also some common enzymes...participate in the metabolism of serotonin and noradrenalin." From this the authors concluded there must be a functional interrelationship between these two monoamines.

3.2.2 Anatomical Evidence

Anatomical studies supply physical evidence for the connections between the locus coeruleus (the main source of noradrenergic perikarya) and serotoninergic nuclei. The use of horse radish peroxidase, degeneration, and autoradiography indicate the locus coeruleus receives afferent input from serotoninergic nuclei (Bobillier et al, 1976; 1979; Conrad et al

, 1974; Morgane and Jacobs, 1979; Sakai et al, 1976). Also, 5-HT containing terminals ($10^7/mm^3$) have been indentified in the locus coeruleus (Leger and Decarries, 1978; Pickel et al, 1977). The reverse, catecholamine terminals contacting serotoninergic neurones in raphe nuclei, has been demonstrated via fluorescence (Dalhstrom and Fuxe, 1964; Fuxe, 1965).

3.2.3 Biochemical and Physiological Evidence

Biochemical analysis has demonstrated high levels of noradrenaline in the source nuclei of 5-HT as well as high levels of 5-HT in the source nuclei of noradrenaline (Saaverda et al, 1976).

Lesioning of the dorsal raphe nucleus decreases 5-HT levels in the locus coeruleus (McRae-Degueurce et al, 1982; Palkolvits et al, 1977). Depletion of 5-HT by pCPA (Crespi et al, 1980; McRae-Degueurce et al, 1982), by 5,6-DHT (McRae-Degueurce et al, 1982; Pujol et al, 1979; Renaud et al, 1975), or by electrolytic lesioning of the dorsal raphe (DR) or median raphe (MR) nuclei (Lewis et al, 1976; McRae-Degueurce et al, 1982), increases the activity of the NA synthesis enzymes, tyrosine hydroxylase and dopamine-b-hydroxylase, in the locus coeruleus. The increased enzymatic activity is greatly reduced if 5-HTP is simultaneously administered with pCPA, suggesting an antagonism of the catecholaminergic system by 5-HT (Crespi et al, 1980). The reverse has also been indicated, i.e., catecholaminergic antagonism of the serotoninergic system, by the observation that 5-HT synthesis and utilization increases in the cortex, brainstem, mesencephalon, and cerebellum after an intracisternal injection of the catecholamine neurotoxin 6-hydroxydopamine (6-

OHDA) (Blondaux et al, 1973). Also, the infusion of the catecholamine precursor 3,4-dihydroxyphenylalanine (l-DOPA; 20mg i.p.) causes an increase in noradrenaline levels and a decrease in 5-HT levels in the cortex and hypothalamus (Gromova et al, 1976). The reciprocal interaction between 5-HT and NA is further supported by (1) noting an increase in the NA metabolite 3-methoxy-4-hydroxy-phenylglycol sulphate after electrolytic lesioning of the midbrain raphe nuclei and (2) observing an increase 5-HIAA after bilateral lesioning of the locus coeruleus (Kostowski et al, 1974). Injections (i.p.) of the powerful dopamine-b-hydroxylase inhibitor, 1-phenly-3-(2-thiazolyl)-2-thiourea, caused a 79-98% depletion of noradrenaline levels in the brain, including the serotoninergic raphe nuclei. Concurrent with the noradrenaline depletion there was an increase in serotonin levels in the medial raphe nucleus and the raphe magnus (Saaverda et al, 1976) and in the whole brain (Johnson et al, 1972). No change in 5-HT levels were observed in the dorsal raphe (Saaverda et al, 1976). In rat hippocampal slices, NA inhibits the depolarization-induced 5-HT release. This process is thought to occur directly via α-receptors (Frankhuyzen and Mulder, 1980).

At the spinal level, fluorescence techniques have indicated a concentration of 5-HT terminals in the sympathetic lateral column (Carlsson et al, 1964). Stimulating the raphe pallidus or raphe obscurus and recording the effect on sympathetic outflow at the thoracic level indicates the function of these serotoninergic terminals is one of inhibition (Gilbey et al, 1981). Coote and Macleod (1974), found that although 5-HTP

(intravenous) had no effect on spontaneous sympathetic renal nerve activity, 5-HTP did depress reflex activity of the nerve. This observation illustrates the phasic nature of serotonin modulation in many instances. A change in the state of the system to be modulated had to occur before an antagonistic change in the serotoninergic system could have a significant effect.

There are studies that indicate the serotonin-noradrenaline interaction is not reciprocal. Noradrenaline terminals present in the dorsal raphe mediate a tonically active adrenergic influence upon which the firing of serotoninergic cells depend. The impairment of noradrenergic transmission by reserpine (Baraban et al, 1978) or low doses (30ug/kg) of clonidine (Svensson et al, 1975) reduces serotoninergic cell firing and noradrenergic cell firing. Serotoninergic cell activity is also suppressed by the systemic administration of drugs which block adrenergic activity (Baraban and Aghajanian, 1980; Gallager and Aghajanian, 1976). Furthermore microiontophoretically applied adrenergic agonists can reduce the suppression caused by alpha adrenergic antagonists (Baraban et al, 1978; Baraban and Aghajanian, 1980; Svensson et al, 1975). This data, recorded from anaesthetized animals, led Aghajanian and co-workers to conclude there is a tonic noradrenergic input (in the dorsal raphe) which drives 5-HT cell firing. However, Heym et al (1980), have shown that even with noradrenergic transmission impaired, the serotoninergic system still functions in a state dependent manner.

3.2.4 Behavioural Evidence

As noted earlier in section 2.4, increasing 5-HT levels attenuate motor activity and decreasing 5-HT levels promote motor activity. The reverse is true for noradrenline. Depletion of noradrenaline levels with disulfiram (Goldstein et al, 1964) or 6-OHDA (Laverty and Taylor, 1970) decrease motor activity. Increasing cranial noradrenaline levels by injection of the neurotransmitter (50ug-3mg) into the third ventricle or cisterna magna produces wakefulness and excitation (Cordeau et al, 1971).

Intraventicular injections of 6-OHDA (200ug) decrease NA levels by 70-80% in the dorsal raphe, median raphe, and raphe magnus (Saaverda et al, 1976). Six-hydroxydopamine administered in this manner also decreases locomotor activity, yet 5,6-DHT injections (intraventricularly) do not cause the opposite effect. If the two neurotoxins are administered simultaneously there is no change in locomotor activity. These results led Richardson et al, (1974) to conclude the decreased motor activity caused by 6-OHDA is due to an increase in 5-HT levels and not the decrease in NA levels. The above observations once more indicate a phasic nature of serotonin.

Miller and Maickel (1969), altered 5-HT and NA levels in rats and observed the effects on a continuous avoidance response. The benzoquinolizine, Ro 4-1284 (a drug that releases both 5-HT and NA, 5-HT being released in greater quantities), causes behavioural depression of the avoidance task. pCPA had no effect on the task. However, pCPA treatment prior to Ro 4-1284 reversed the effects of Ro 4-1284 treatment. The authors

concluded it is the balance of free 5-HT/NA that is the deciding factor in the behavioural depression induced by benzoquinolizines. It should again be noted that activation of the noradrenergic system was required before alteration of the serotoninergic system could have an effect.

3.3 Serotonin Interaction with Dopamine

3.3.1 Introduction

The relationship that Gromova et al (1976) indicated between serotonin and noradrenaline (see 4.3.2.1) is also true for serotonin and dopamine in the brain. Ascending tracts of serotoninergic and dopaminergic neurones terminate in the neostriatum and limbic forebrain. Monoamine oxidase is responsible for the oxidation of 5-HT and DA. High concentrations of both monoamines are found in the source nuclei of 5-HT and DA. Hence one must accept the possibility of a functional interrelationship between serotonin and dopamine.

3.3.2 Anatomical Evidence

There are two major ascending dopaminergic pathways: the nigro-neostriatal pathway (including the substantia nigra and superior colliculs) and the mesolimbic dopamine system (including the medial accumbens and tuberculum olfactorium) (Anden et al, 1966; Ungerstedt, 1971). Early studies of the anatomy of serotoninergic and dopaminergic systems indicate common areas of termination including the neostriatum and limbic forebrain (Anden et al, 1966). Localized injections of horseradish peroxidase and ^{3}H-leucine provide strong evidence for a dorsal raphe nucleus projection (Fibiger and Miller, 1977; Moore et al, 1978) and a median raphe nucleus projection

(Bobillier et al, 1979; Dray et al, 1976; Moore et al, 1978) to the substantia nigra (SN; a major source of cranial dopamine). This coincides with the observation of large number of serotoninergic fibres forming axo-dendritic synapses within the SN (Parizek et al, 1971). A large number of catecholamine terminals can also be seen on the surface of 5-HT producing neuronal perikarya (Dalhstrom and Fuxe, 1964; Fuxe, 1965).

3.3.3 Biochemical and physiological evidence

Biochemical and physiological techniques are used to substantiate an interaction between the source nuclei of DA and 5-HT. Within the SN there are substantial concentrations of 5-HT (Palkovits et al, 1974; Palkovits et al, 1977) and high tryptophan hydroxylase activity (Brownstein et al, 1975). In the serotoninergic raphe nuclei (B1-B9) dopamine concentrations are high and levels of tyrosine hydroxylase are of the same order of magnitude as tryptophan hydroxlase (Saaverda et al, 1976). Electrolytic (Fibiger and Miller, 1977) or 5,7-DHT (Deakin et al, 1979) lesioning of the DR decreases nigral and striatal 5-HT content. Stimulation of the DR inhibits unit activity in the SN; this effect is blocked by pCPA pretreatment (Fibiger and Miller, 1977) and mimicked by 5-HT application into the striatum (Davies and Tongroach, 1978). However, pCPA treatment alone does not alter DA utilization in the mesolimbic nor nigro-striatal systems (Fibiger and Miller, 1977). These observations led the authors to conclude the inhibitory serotoninergic projection from the DR influences dopaminergic cells in the SN in a phasic but not a tonic manner.

This phasic nature of serotoninergic influence on dopamine

may explain the negative fidnings of Gumulka et al (1970) and Rommelspacher and Strauss, (1980). These authors found that electrolytic lesions in the DR or MR do not alter the striatal dopamine content.

Serotonin-dopamine interaction has also been observed under more tonic conditions. Serotonin uptake inhibitors potentiate and 5-HT receptor blockers antagonize the increased dopamine metabolism induced by haloperidol (Waldmeier et al, 1979). Unilateral injections of 5,7-DHT into the SN cause an ipsilateral increase in striatal DA turnover (Giambalvo and Snodgrass, 1978). Chronic treatment with pCPA or metergoline (Roberge, 1979) or electrolytic lesioning of the dorsal and median raphe nuclei (Herve et al, 1979; 1981) enhance dopamine utilization in the nucleus accumbens. Electrical stimulation of the MR causes, mainly, the depression of single neurone activity in the SN (Dray et al, 1976). Microiontophoretically applied 5-HT to the SN produces mainly inhibition of neuronal activity (Dray et al, 1976). Discrete electrolytic lesions of the MR decrease 5-HT in the SN and increase striatal dopamine levels (Dray et al, 1976). 5,7-DHT injections into the MR decrease 5-HT uptake in the SN (Giambalvo and Snodgrass, 1978). The data collected by these authors strongly suggest a direct inhibitory pathway from the MR to the SN that influences nigro-striatal dopaminergic activity. Unilateral lesions of the DR decrease 5-HT and 5-HIAA and increase dopamine metabolism in the ipsilateral SN (Nicolaou et al, 1979). Unilateral lesions of the MR produced similar effects in the corpus striatum (Nicolaou et al, 1979). The authors concluded that the DR and MR send

projections differentially to the SN and corpus striatum, respectively, which exert tonic inhibition of DA metabolism. Nigral dopamine administration (10^{-7}M) decreases 5-HT in the caudate putamen and SN and similar application of alpha-methylparatyrosine (a dopamine depletor) has the opposite effect (Hery et al, 1980). In an in vitro striatal synaptosome preparation, 3uM 5-HT depresses dopamine synthesis from tyrosine (Andrews et al, 1978).

Somewhat contrary to the above results, evidence presented by Lyness and Moore (1981) does not support a 5-HT-DA interaction. These authors recorded an increase in d-amphetamine- and apomorphine-induced locomotor activity after 5,7-DHT injections into the lateral cerebral ventricle or the nucleus accumbens septi but did not find a concurrent change in dopaminergic neurone activity as indicated the DOPAC concentration or l-DOPA accumulation.

3.3.4 Behavioural Evidence

Motor activity is reduced by electrolytic lesions of the SN (Gumulka et al, 1970) and by bilateral 6-OHDA lesions in dopamine's mesolimbic system (Koob and Robins, 1979). Stimulation of central dopamine receptors by apomorphine (i.p.) induces hyperactivity in rats (Grabowska and Michaluk, 1974; Westermann et al, 1976). Serotoninergic depletion by pCPA (i.p.) or 5,6-DHT (injected into the MR) enhances the hyperactivity. Serotoninergic elevation with harmine (a monoamine oxidase inhibitor) pretreatment reduces the apomorphine-induced hypermotility and the extra enhancement caused by pCPA or 5,6-DHT (Westermann et al, 1976). An

enhancement of apomorphine- and d-amphetamine-induced locomotion is also observed after injections of 5,7-DHT into the lateral ventricle or bilaterally into the nucleus accumbens septi (Lyness and Moore, 1981). The authors also concluded the enhanced activity was not due to a change in dopaminergic activity as determined by 3,4-dihydroxyphenylacetic acid concentrations and l-DOPA accumulation.

A dose-dependent increase in locomotor activity is produced by injections of dopamine into the nucleus accumbens (Carter and Pycock, 1979; Costall et al, 1976; Costall et al, 1980; Pijnenburg et al, 1976). Serotonin injections, at the same site, reduce locomotor activity (Carter and Pycock, 1979; Costall et al, 1976; Jones et al 1981; Pijnenburg et al, 1976). Electrolytic median raphe lesions enhance dopamine-induced hyperactivity and markedly decrease the threshold and maximal doses of dopamine (Costall et al, 1976). Serotonin injections into the nucleus accumbens, of rats pretreated with dopamine into the same site, causes an immediate reduction in motor activity (Costall et al, 1976).

Serotonin also interacts with dopamine stimulated activity in the nigro-striatal system. 6-OHDA lesions of the SN (the origin of DA perikarya for the nigro-striatal system), although not affecting apomorphine-induced hyperlocomotion, does prevent further augmentation of the hyperactivity induced by 5,6-DHT lesions (Westermann et al, 1976).

Lesioning of the superior colliculus (part of the nigro-striatal system) and observing the effects upon amphetamine-induced locomotor activity, Pope et al (1980) concluded the

nigro-striatal system is not necessary for the increased locomotor behaviour induced by amphetamine. However, a review by Cole (1978) concludes that both the mesolimbic and nigro-striatal dopamine systems are involved in amphetamine-induced locomotor activity and that inhibition of these systems inhibits the amphetamine-induced locomotion.

4 Possible Loci and Mechanisms by Which Serotonin May Inhibit Physical Activity

4.1 Introduction

The possible mechanisms discussed, by which serotonin may inhibit physical activity, are those in the literature that have a reasonable documented basis. It should not be assumed that any of the possible loci and mechanisms are mutually exclusive.

4.2 Thermoregulation

The integrity of the monoamine system is vital for correct functioning of the hypothalamus in temperature regulation (Cronin and Baker, 1977; Jacob and Girault, 1979; Woolf et al, 1975). Many aspects of the role of 5-HT in thermoregulation remain to be elucidated. Conflicting observations due to species, drug dosage, and site of injection have been reported (see Clark and Clark (1980) and Jacob and Girault (1979) for an extensive review). The conflicting data may, in part, be elucidated by the proposition that 5-HT synapses in the rostral and caudal portions of the hypothalamus of cats mediate functionally opposing thermoregulatory effects (Komiskey and Rudy, 1977). This may explain the finding that DR lesions decrease catecholamine activity in the hypothalamus whereas MR lesions increase catecholamine activity in the hypothalamus (Rommelspacher and Strauss, 1980). Certain 5-HT pathways do act to increase heat loss and decrease heat production (Bligh et al, 1971). It is known that, in the rat, an increase in ambient temperature causes an increase in 5-HT turnover and intraventricular injections of 5-HT cause a decrease in core

temperature (Feldberg and Lotti, 1967; Jacob and Girault, 1979; Weiss and Aghajanian, 1971). In anesthetized cats, most neurones in and around caudal midbrain raphe nuclei increased there firing frequency within 30 sec when the temperature was increased 5°C by water thermodes (Cronin and Baker, 1977)

During high intensity exercise the fast twitch fibres of the active muscle are preferentially recruited (Essen and Kayser, 1976; Gillespie et al, 1974; Gollnick et al, 1974; Karlsson and Komi, 1976). If the exercise is not of high intensity or exhaustive, fast twitch fibres will not be activated. These fast twitch, glycolitic fibres are responsible for the major portion of muscle temperature increase (Bolstad and Ersland, 1978). Here 5-HT, potentially, can function as dual safety mechanism for an animal performing high intensity exercise. Firstly, 5-HT can inhibit the motor activity thus reducing the organism's heat production. Secondly, 5-HT can stimulate heat loss, reducing the organism's core temperature.

4.3 Inhibition of Cortical Neurones

Lidov et al (1980) investigated the ascending serotoninergic pathways of the B7-B9 nuclei using a new and very sensitive immunohistological procedure. These researchers found such a ubiquitous array of 5-HT terminals in the cerebral cortex as to state "the raphe neurones may contact every cell in the cortex" (p.207). Ontologically, high concentrations of serotonin are present in the motor cortex at birth and in the early stages of postnatal development in the rat. These levels slowly decrease to adult levels (Uzbekov et al, 1979).

Stimulation of the DR, in anaesthetized rats, causes a

frequency-dependent release of 5-HT in the parietal cortex (Fujiwara, 1981). Electrophoretic, iontophoretic, arterial injection, and dorsal and median raphe stimulation studies indicate serotonin has inhibitory (Bloom et al, 1973; Frederickson et al, 1972; Huang and Marrazzi, 1973; Johnson et al, 1970; Olpe, 1981; Phillis et al, 1968a; Reader et al, 1979; Reader, 1980; Sastry and Phillis, 1977b; Sharma, 1977) or both excitatory and inhibitory effects (Szabadi et al, 1977) upon cortical neurones. Although the exact location of the cortical neurones were not always stated, the inhibitory effects of 5-HT were observed in the posterior cruciate cortex (Frederickson et al, 1972), the deep neurones of the sensomotor cortex (Sastry and Phillis, 1977b; Szabadi et al, 1977) and pyramidal, pericruciate cortex cells (Huang and Marrazzi, 1973).

Kostowski et al, (1968) showed that electrolytic lesioning of the MR nucleus causes (1) a decrease of forebrain 5-HT and 5-HIAA levels, (2) an increased in general activity, (3) the establishment of a persistent EEG arousal pattern, and (4) an increase in spontaneous motor activity. More recent lesion studies have confirmed that the MR nucleus is responsible for the increased locomotor activity observed in rats when the ascending pathways are lesioned (Geyer, 1978; Jacobs et al, 1974; Jacobs and Cohen, 1976; Lorens, 1978).

The hippocampus is thought to play a major role in mediating the effects of median raphe lesions. Anatomical data indicates that there are two distict pathways of median raphe fibres to the hippocampus: one pathway is supracallosal travelling with the cingulum bundle and the other is

infracallosal associating with the fornix-fimbria system (Azmitia and Segal, 1978). Later, Azmitia (1981) used horseradish peroxidase and ^{3}H-5-HT in a double labelling technique to show that the DR also has an efferent pathway to the hippocampus. Research by Pasquier and Reinoso-Suarez (1977) indicates the dorsal raphe efferents terminate primarily in the dorsal hippocampus whereas the median raphe projects neurones throughout the entire hippocampus.

A comparison of DR and MR lesions indicate that only MR lesions significantly decrease hippocampal serotonin (Geyer, 1978; Geyer et al, 1976; Herr and Roth, 1976; Jacobs et al, 1974; Keller et al, 1977; Lorens and Guldberg, 1974; Trimbach as indicated by Mabry and Campbell, 1973; Van de Kar and Lorens, 1979) whereas DR lesions have little effect on hippocampal 5-HT levels (Geyer, 1978; Jacobs et al, 1974; Keller et al, 1977; Lorens and Guldberg, 1974; Trimbach according to Mabry and Campbell, 1973; Van de Kar and Lorens, 1979). Contrarily, Deakin et al (1979) showed that 5,7-DHT lesions of the DR and MR produced similar decreases in hippocampal 5-HT levels and Rommelspacher and Strauss, (1980) found thermal lesions of DR also decrease hippocampal 5-HT although not nearly to extent as MR lesions.

Approximately ninety percent of hippocampal pyramidal cells are inhibited by iontophoretic administration of 5-HT and 40% of hippocampal pyramidal cells are inhibited by median raphe stimulation (Segal, 1975; 1980; 1981). In vitro studies also support 5-HT inhibition of hippocampal cells. Serotonin caused hyperpolarization of all rat CA1 hippocampal cells studied in

vitro (Cobbett and Cottrell, 1980). The hyperpolarization is believed caused by activation of potassium channels (Segal, 1980).

Contrarily, Hole et al (1977) found that lesioning the mesencephalic medial serotoninergic bundle (the major ascending serotoninergic system) with 5,7-DHT had no effect on motor activity. However, the motor activity was measured 20 days after lesioning and by this time regeneration of some 5-HT neurones (Svendgaard et al, 1975; Wiklund et al, 1978) or increases in 5-HT sensitivity (Blackburn et al, 1981; Seeman et al, 1980; Stewart et al, 1976; Trulson and Jacobs, 1978), or both, could have occurred. The locomotor activity was also measured in the open field—an environment not conducive to measuring activity in 5-HT depleted animals (see section 2.4).

The observations that prior hippocampectomy blocks the ability of pCPA or electrolytic lesions to produce hyperactivity (Jacobs et al, 1975) provides strong evidence for hippocampal involvement in serotoninergic modulation of activity.

4.4 Action on Spinal Motorneurones

The posterior raphe nuclei (B1-B3) are the major source of descending serotoninergic tracts which terminate in the spinal cord. Minor contributions of descending 5-HT neurones come from B5, B7, B8, and B9 (Bowker et al, 1981; Satoh, 1979; Shimizu et al, 1981; Tohyama et al, 1979).

Serotonin concentrations are highest in spinal segments that contain motorneurones which innervate the limbs (Anderson, 1972). Moreover, using microassay, microdissection, and fluorescence techniques it was determined that the ventral

horns, the location of motorneurone perikarya, have the highest 5-HT concentration in the spinal cord (Anderson and Holgerson, 1966; Carlsson et al, 1964; Oliveras et al, 1977; Segu and Calas, 1978). It is postulated that the source of the high 5-HT levels in the ventral horn is from descending serotoninergic neurone terminals directly contacting alpha motorneurones (Dalhstrom and Fuxe, 1965; Naftchi et al, 1972; Torskaya and Goloborodo'ko, 1977; Ungerstedt, 1971). Spinal cord transection produces diminished amounts of 5-HT below the transection indicating the source of 5-HT to be of brain origin (Anderson, 1972; Naftchi et al, 1972; Oliveras et al, 1977).

Only a few studies have attempted to elucidate the effects of 5-HT on motorneurones and the results are conflicting. Extracellular application of 5-HT (150nA; iontophoretic) or noradrenaline (100nA) to spinal motorneurones causes membrane polarization suggesting both transmitters act as inhibitory agents (Phillis et al, 1968b). The serotonin antagonists cinanserin and methysergide abolish long latencies of ventral root potentials evoked by brainstem stimulation indicating a tonic inhibition of motorneurone potentials (Proudfit and Anderson, 1973). Contrarily, it has been noted that 5-HTP (75mg/kg; i.v.) (Myslinski and Anderson, 1978) or 5-HT (.16M; iontophoretic) (Barasi and Roberts, 1974; White and Neuman, 1980) increases the excitability of spinal motorneurones. Perhaps elucidating these contradictory results Komissarov and Abramets (1980) reported that low concentrations of 5-HT (10^{-5}M) depolarize spinal motorneurones whereas high concentrations (10^{-4}-10^{-3}M) hyperpolarize motorneurones.

4.5 Air Ionization

Another possible mechanism of 5-HT action is air ionization. With a high barometer there is a decrease of positive ions in the air (Schreiber, 1967). Positive ionization of ambient air increases blood and cranial 5-HT and, likewise, negative ionization decreases blood and cranial 5-HT (Krueger et al,1966; Krueger and Kotaka, 1969). Negative ionization also decreases cortical 5-HT levels (Diamond et al, 1980). With regard to these observations, one would expect a rising barometer to increase spontaneous activity and a falling barometer to decrease spontaneous activity. This is what happens according to Krueger and Smith (1960).

In rats, there is an increase in 5-HIAA excretion after negative ionization treatment (Olivereau, 1971). It is postulated that negative ionization accelerates enzymatic oxidation of 5-HT thus decreasing bodily 5-HT levels (Olivereau, 1971). The mechanism by which positive ions increase blood 5-HT is believed via a cation exchange. The release of 5-HT from blood cells such as mast cells and platelets is via a displacement of positive ions into the cells causing 5-HT to be released from the cells into the blood stream (Unvas, 1978).

Further evidence supporting a relationship between air ionization and 5-HT is as follows:

(1) negative ions have been shown to decrease alpha wave frequency 2-4Hz, increase EEG amplitude, increase spread of alpha waves, increase synchronization of EEG between hemispheres, increase alertness, and increase working capacity (Assael et al, 1974).

(2) negative ions have been shown, is some cases, to increase muscular endurance in rats (Olivereau, 1973).

(3) weather conditions that augment positive ionization and increase 5-HT cause the Serotonin Irritation Syndrome in about one third of the human population (Sulman et al, 1975). This syndrome, as manifested by headaches, dizziness, and irritation of the respiratory pathways, is relieved by treatment with negative air ionization. This syndrome can be induced, in humans, by treatment with positive ions (Winsor and Bechett, 1958).

(4) negative ions increase oxygen uptake of isolated mouse liver cells (Bhartendu and Menon, 1978).

It is a possibility that the increased pressure and temperature that take place in the lungs and muscles during exercise will increase blood 5-HT enough to cause a significant physiological effect on muscular performance.

4.6 Serotoninergic Inhibition at Motor Endplates

Serotonin decreases the electrophysiological and associated mechanical responses of acetylcholine applied to the frog neuromuscular junction (Akasu et al, 1981; Colomo et al, 1968; Hirai et al, 1981; Magazanik et al, 1976 according to Akopyan et al, 1980; Romanowski, 1967). Serotonin ,in itself, does not alter the postsynaptic membrane conductance but is able to impair the acetylcholine-activation of ionic channels (Magazanik et al, 1976) by reducing the affinity of acetylcholine to the recognition site of acetylcholine receptors (Hirai et al, 1981). The concentration of 5-HT required is the same as found in the brain extracts of exercised rats (Romanowski, 1967).

4.7 Serotoninergic Inhibition of Glucocorticosteroid Action

Adrenalectomy decreases running wheel time. Synthetic corticosterone treatment of adrenalectomized rats results in an immediate increase in running wheel activity (Moberg and Clark, 1976; Pedersen-Bjergaard and Tonnesen, 1954). The rise in glucocorticosteriod secretion during the late resting phase results in an increase in glycogen catabolism—yielding fuel for the subsequent activity phase. Elimination of the serotoninergic innervation to the suprachiasmatic nuclei (SCN) of the hypothalamus either via electrolytic lesion of B7 and B8 nuclei or destruction of 5-HT neurones in the SCN by 5,7-DHT (1ug in 1ul) treatment, decreases adrenocorticotropic hormone (ACTH) amplitudes and levels and increases corticosterone amplitudes and levels (Szafarczyk et al, 1980). Concurrent with the increase in corticosterone above control levels, the locomotor activity of the animal was also elevated relative to controls for both lesion procedures. There was no change in either the phase relationship of the corticosteroid or the ACTH circadian rhythm to the light-dark cycle (Balestrery and Moberg, 1976; Szafarczyk et al, 1980). Electrical stimulation of midbrain raphe nuclei reduces the stress induced increase of plasma corticosterone—an effect that is blocked by methysergide (a 5-HT antagonist) (Kovacs et al, 1976). These observations led Kovacs et al (1976), to speculate the existence of serotoninergic inhibition of hypothalamo-pituitary-adrencortical activation in rats.

The 5-HT-corticosterone interaction may also exist in the reverse direction. Normally, it appears corticosterone mediates

a negative feedback mechanism on serotonin. Bilateral adrenalectomy and concurrent decreases in corticosterone levels elevates brain tryptophan levels but decreases the concentrations of cranial 5-HT and 5-HIAA (Miller et al, 1980; Sze, 1976). The locus of action for this effect is probably tryptophan hydroxylase, for bilateral adrenalectomy also decreases tryptophan hydroxylase activity and 5-HT uptake. This effect is reversed with corticosteriod treatment (Azmitia et al, 1970; Dekloet et al, 1982; Sze, 1976; Vermes, 1976). Increases in corticosteroids augment tryptophan uptake and its subsequent metabolism to 5-HT (Sze, 1976). Sze (1976), concludes that corticosteriods have a fast action upon 5-HT by regulating tryptophan uptake and a slow action on 5-HT by regulation of tryptophan hydroxylase activity. Vermes et al (1976), goes even further, suggesting that corticosteroid hormones might play a modulatory role in maintaining a certain functional activity level of central serotoninergic neurones.

The locus of the negative feedback of corticosteroids upon the serotoninergic system may occur in the raphe nuclei, or even the hippocampus. Twenty to thirty percent of the small blood vessels in the DR and MR have direct apposition with serotoninergic perikarya and dendrites (Felten and Crutcher, 1979). Histochemical fluorescence and pharmacological manipulation provide strong support for the existence of 5-HT terminals in the supra-ependymal layer of the lateral cerebral ventricles (Richards et al, 1973). The hippocampus, which borders the ventral surface of the lateral ventricles, has the highest corticosteriod uptake and binding capacity of any

structure in the brain (Grosser et al, 1973; McEwen et al, 1969).

The possibility of a 5-HT-corticosterone interaction influencing motor activity is strongly documented.

4.8 Serotoninergic Inhibition of Adrenal Tyrosine Hydroxylase

Lesioning of the adrenal medulla reduces the time to exhaustion in long duration exercise (Richter et al, 1981). Prior to and during exercise, sympathetic activity releases adrenaline and noradrenaline from the adrenal glands into the blood stream. These catecholamines markedly enhance glycogenolysis mediated by motor nerve activity (Richter el al, 1981). This enhancement can come about via stimulating glycogenolysis (Mayer, 1970), stimulating calcium release from the sarcoplasmic reticulum (Mayer et al, 1970), stimulating lipolysis (Carlson, 1965; Newsholme and Start, 1973; Fizack, 1965; Schimmel, 1976), stimulating muscle (Na+,K+)-ATPase (Cheng et al, 1977; Flatman and Clausen, 1978), stimulating substrate cycling in the muscle (Newsholme, 1976) and inhibiting glycogen synthesis (Mayer, 1970). The force of contraction is also facilitated by catecholamines, but only in fast twitch fibres and only by beta adrenergic stimulation (Holmberg et al, 1979).

The key regulatory enzyme for synthesizing these sympathetic hormones is tyrosine hydroxylase (TOH) (Nagatsu et al, 1964). There is a slight (18%), though significant, increase in adrenal TOH activity following 5-HT depletion with pCPA (Breese et al, 1974). If the TOH activity is increased via chronic amphetamine administration prior to pCPA treatment, there is a very large increase (100%) in TOH activity (Breese et

al, 1974; Hollister et al, 1974). These observations indicate that 5-HT inhibition of catecholamine synthesis in the adrenals is much greater when the catecholamine system is activated. Most likely, the central nervous system mediates the effects of pCPA. Central serotoninergic neurones inhibit sympathetic outflow from the spinal cord (Coote and Macleod, 1974) and adrenal TOH activity (Quirk and Sourkes, 1977). Furthermore, 5-HT has been localized in the cytoplasm and nucleus of adrenal medulla cells (Csaba and Sudar, 1978). The authors elucidating the serotoninergic action on the adrenal medulla used a time scale of days for their observations. On a shorter time scale, i.e. during exercise of a long duration, adrenal production of catecholamines is inhibited (Matlina, 1976). The possiblity that 5-HT may inhibit adrenal tyrosine hydroxylase during exercise must be considered.

4.9 Other Possible Loci of Inhibition

Other possible loci where 5-HT may have its inhibitory effect on locomotor activity have already been discussed in section 3. The loci include the dopaminergic nigro-striatal and mesolimbic systems and the locus coeruleus.

5 Conclusions

Numerous investigative procedures have documented serotonin as a modulator. Anatomically, 5-HT neurones are unmyleinated, highly collateralized, and have a large number of terminal aborations. Many direct contacts are made between 5-HT cell bodies and the circulatory system. There is a vast array of 5-HT terminals lining the ventricles. Biochemically, 5-HT and tryptophan hydroxylase are found within the ergotropic system; contrarily NA, DA, and their synthesis enzymes are found within the trophotropic system. Physiologically, the tonic low firing rate of 5-HT neurones and their long temporal effects are not conducive to an on-off system. Pharmacologically, the many drugs that have been used to alter the state of the ergotropic and trophotropic systems support the modulatory influence that 5-HT has upon the ergotropic system. Behaviourally, increases or decreases in serotoninergic functioning cause the reciprocal effect in locomotor activity. Considering the above, it appears the serotoninergic system is better suited for functioning in modualtory capacity—setting the response levels of innervated neurones to modify input from other neurones, rather than an on-off system of information processing.

One can speculate that a modulator that opposses either extreme of activity (be the activity biochemical, physiological, or behavioural in nature) to have a stronger modulatory influence at the extremes of an activity continuum. The numerous instances of serotonin modulation under phasic conditions only (Breese et al, 1974; Coote and Macleod, 1974; Fibiger and Miller, 1977; Miller and Maickel, 1969; Richardson

et al, 1974), support this hypothesis.

The studies mentioned in this review lead me to a similar conclusion as Heym, Trulson, and Jacobs (1982): since the activity of 5-HT neurones is influenced by- and influences the output of central motor systems and that these cells are also responsive to sensory input suggest 5-HT plays a modulatory role in sensomotor integration.

REFERENCES

Akasu, T., K. Hirai, and K. Koketsu. 5-Hydroxytryptamine controls Ach-receptor sensitivity of bullfrog sympathetic ganglion cells. Brain Res. 211: 217-220, 1981.

Akopyan, A.R., N.K. Chemeris, V.I. Iljintand, and B.N. Veprintseu. Serotonin, dopamine and intracellular cyclic AMP inhibit the responses of nicotinic cholinergic membrane in snail neurons. Brain Res. 201: 480-484, 1980.

Albert D.J. and M.L. Walsh. The inhibitory modulation of agonistic behavior in the rat brain: A review. Neurosci. Biobehav. Rev. 6: 125-143, 1982.

Anden, N.-E., A. Dahlstrom, K. Fuxe, K. Larsson, L. Olson, and U. Ungerstedt. Ascending monoamine neurons to the telencephalon and diencephalon. Acta Physiol. Scand. 67: 313-326, 1966.

Anderson, E.G. Bulbospinal serotonin-containing neurons and motor control. Fed. Proc. 31: 107-112, 1972.

Anderson, E.G. and L.O. Holgerson. The distribution of 5-hydroxytryptamine and norepinephrine in the cat spinal cord. J. Neurochem. 13: 479-485, 1966.

Andrews, D.W., R.L. Patrick, and J.D. Varchas. The effects of 5-hydroxytryptamine on dopamine synthesis and release in rat brain striatal synaptosomes. J. Neurochem. 30: 465-470, 1978.

Assael, M., Y. Pfeifer, and F.G. Sulman. Influence of artificial air ionization on the human electroencephalogram. Int. J. Biometeor. 18: 306-312, 1974.

Azmitia. E.C. Bilateral serotonergic projections to the dorsal hippocampus of the rat: Simultaneous localization of ^{3}H-5HT and HRP after retrograde transport. J. Comp. Neurol. 203: 737-743, 1981.

Azmitia, E.C. Jr., S. Algeri, and E. Costa. In vivo conversion of ^{3}H-L-tryptophan into ^{3}H-serotonin in brain areas of adrenalectomized rats. Science 169: 201-203, 1970.

Azmitia, E.C. and M. Segal. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J. Comp. Neurol. 179: 641-668, 1978.

Balestrery, F.G. and Moberg, G.P. Effect of midbrain raphe nuclei lesions on the circadian rhythm of plasma corticosterone in the rat. Brain Res. 118/3: 503-508, 1976.

Baraban, J.M. and G.K. Aghajanian. Suppression of firing

activity of 5-HT neurons in the dorsal raphe by alpha-adrenocepter antagonists. Neuropharmacology 19: 355-363, 1980.

Baraban, J.M., Wang, R.Y., and G.K. Aghajanian. Resperine suppression of dorsal raphe neuronal firing: Mediation by adrenergic system. Eur. J. Pharmacol. 52: 27-36, 1978.

Barasi, S. and M.H.T. Roberts. The effects of stimulation of nucleus raphe and iontophoretically applied 5 hydroxytryptamine on spinal motorneurones. J. Physiol. (London) 236/1: 11P-12P, 1974.

Barbeau, A. The pathogenesis of Parkinson's disease: A new hypothesis. Can. Med. Assoc. J. 87: 802-807, 1962.

Barchas, J.D. and D.X. Freedman. Brain amines: Response to physiological stress. Biochemical Pharmacol. 12: 1232-1235, 1963.

Baumgarten, H.G., A. Bjorklund, L. Lachenmayer, A. Nobin, and U. Stenevi. Long lasting selective depletion of brain serotonin by 5,6-dihydroxytryptamine. Acta Physiol. Scand., Suppl. 373: 1-15, 1971.

Bhartendu and I.A. Menon. Effects of atmospheric small negative ions on the oxygen consumption of mouse liver cells. Int. J. Biometeor. 22: 43-52, 1978.

Blackburn, T.P., B. Cox, C.G. Heapy, T.F. Lee, and D.N. Middlemiss. Supersensitivity of nigral serotonin receptors and rat rotational behaviour. Eur. J. Pharmacol. 71: 343-346, 1981.

Blanchard, R.J., M.J. Kelly, and D.C. Blanchard. Defense reactions and exploratory behavior in rats. J. Comp. Physiol. Psychol. 87: 1129-1133, 1974.

Bligh, J., W.H. Cotle, and M. Maskrey. Influence of ambient temperature on the thermoregulatory responses to 5-hydroxytryptamine, noradrenaline and acetylcholine injected into the lateral cerebral ventricles of sheep, goats and rabbits. J. Physiol. 212: 377-392, 1971.

Bliss, E.L. Effects of behavioural manipulations upon brain serotonin and dopamine. In: Serotonin and Behaviour, edited by J. Barchas and E. Usdin. New York: Academic Press, 1973, 315-324.

Bliss, E.L., J. Ailion, and J. Zwanziger. Metabolism of norepinephrine, serotonin and dopamine in rat brain with stress. J. Pharmacol. Exp. Ther. 164: 122-134, 1968.

Blondaux, C., A. Juge, F. Sordet, G. Chouvet, M. Jouvet, and J.F. Pujol. Alteration of serotonin metabolism in rat brain by 6-hydroxydopamine (French). Brain Res. 50: 101-

114, 1973.

Bobillier, P., S. Seguin, A. Degueurce, B.D. Lewis, and J.F. Pujol. The efferent connections of the nucleus raphe centralis superior in the rat as revealed by radioautography. Brain Res. 166: 1-8, 1979.

Bobiller, P., S. Seguin, F. Petitjean, D. Salvert, M. Touret, and M Jouvet. The raphe nuclei of the cat brain stem: a topographical atlas of their efferent projections as revelaed by autoradiography. Brain Res. 113: 449-486, 1976.

Bolstad, G. and A. Ersland. Energy metabolism in different human skeletal muscles during voluntary isometric contractions. Eur. J. Appl. Physiol. 38: 171-179, 1978.

Bowker, R.M., K.N. Westlund, and J.D. Coulter. Serotonergic projections to the spinal cord from the midbrain in the rat: An immunocytochemical and retrograde transport study. Neuroscience Letters 24: 221-226, 1981.

Brase, D.A. and H.H. Loh. Possible role of 5-hydroxytryptamine in miminal brain dysfunction. Life Sci. 16: 1005-1016, 1975.

Breese, G.R., B.R. Cooper, and R.A. Mueller. Evidence for involvement of 5-hydroxytryptamine in the actions of amphetamine. Brit. J. Pharmacol. 52: 301-314, 1974.

Brodie, B.B. and P.A. Shore. A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Annals N.Y. Acad. Sci. 66: 631-642, 1957.

Brownstein, M.J., M. Palkovits, J.M. Saavedra, and J.S. Kizer. Trytophan hydroxylase in the rat brain. Brain Res. 97: 163-166, 1975.

Carey, R.J. Effects of selective forebrain depletions of norepinephrine and serotonin on the activity and food intake effects of amphetamine and flenfluramine. Pharmacol. Biochem. Behav. 5: 519-523, 1976.

Carlson, L.A. Inhibition of mobilization of free fatty acids from adipose tissue. Ann. N.Y. Acad. Sci. 131: 119-142, 1965.

Carlsson, A., B. Flack, K. Fuxe, and N.-A. Hillarp. Cellular localization of monoamines in the spinal cord. Acta physiol. Scand. 60: 112-119, 1964.

Carter, C.J. and C.J. Pycock. The effects of 5,7-dihydroxytryptamine lesions of extrapyramidal and mesolimbic sites on spontaneous motor behavior, and amphetamine-induced stereotype. Naunyn-Schmied. Arch. Pharmacol. 308/1: 51-54, 1979.

Cheng, L.C., E.M. Rogus, and K. Zierler. Catechol, a structural requirement for ($Na^+ + K^+$)-ATPase stimulation in rat skeletal muscle membrane. Biochem. Biophys. Acta 464: 338-346, 1977.

Chrusciel, T.L. and Z.S. Herman. Effect of dopalanine on behaviour in mice depeted of norepinephrine or serotonin. Psychopharmacologia 14: 124-134, 1969.

Clark, W.G. and Y.L. Clark. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants. Neurosci. Biobehav. Rev. 4: 281-375, 1980.

Cobbett, P. and G.A. Cottrell. Actions of 5-hydroxytryptamine on CA1 pyramidal neurones of rat hippocampus in vitro . J. Physiol. 305: 101P-102P, 1980.

Cole, S. Brain mechanisms of amphtamine-induced anorexia , locomotion , and sterotype: A review. Neurosci. Biobehav. Rev. 2: 89-100, 1978.

Coleman, M. Serotonin concentrations in whole blood of hyperactive children. J. Pediat. 78: 985-990, 1971.

Colomo, F., R. Rahaminoff, and E. Stefani. An action of 5-hydroxytryptamine on the frog motor end-plate. Eur. J. Pharmacol. 3: 272-274, 1968.

Condrad, L.C.A., C.M. Leonard, and D.W. Pfaff. Connections of the median and dorsal raphe nuclei in the rat: an autoradiographic and degeneration study. J. Comp. Neurol. 156: 179-206, 1974.

Coote, J.H. and V.H. Macleod. The influence of bulbospinal monoaminergic pathways on sympathetic nerve activity. J. Physiol. 241: 453-475, 1974.

Cordeau, J.P., J. DeChamplain, and B. Jacks. Excitation and prolonged waking produced by catecholamines injected into the ventricular system of cats. Canad. J. Physiol. 49:627-631, 1971.

Costall, B., S.-C.G. Hui, and R.J. Naylor. Denervation in the dopaminergic mesolimbic system: Functional changes followed úsing (-)N-n-propylorapomorphine depend on the basal activity levels of the rat. Neuropharmacol. 19: 1039-1048, 1980.

Costall, B., R.J. Naylor, C.D. Marsden, and C.J. Pycock. Serotoninergic modulation of the dopamine response from the nucleus accumbens. J. Pharm. Pharmac. 28: 523-526, 1976.

Crespi, F., M. Buda, A. McRae-Degueurce, and J.-F. Pujol. Alteration of tyrosine hydroxylase activiity in the locus coeruleus after administration of p-chlorophenylalanine.

Brain Res. 191: 509, 1980.

Cronin, M.J. and M.A. Baker. Thermosensitive midbrain neurons in the cat. Brain Res. 128: 461-472, 1977.

Csaba, G. and F. Sudar. Localization of radioactively labelled serotonin in the nucleus of adrenal medulla cells. Acta Anat. 100: 237-240, 1978.

Curzon, G. and A.R. Green. Rapid method for the determination of 5-hydroxytryptamine and 5-hydroxyindolacetic acid in small regions of rat brain. Br. J. Pharmacol. 39: 653-655, 1970.

Dalhstrom, A. and K. Fuxe. Evidence for the existence of monoamine-containg neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta physiol. Scand. 62 Suppl. 232: 1-55, 1964.

Dahlstrom, A. and K. Fuxe. Evidence for the existence of monoamine neurons in the central nervous system. II. Experimentally induced changes in the intraneuronal amine levels of bulbospinal neuron systems. Acta physiol. Scand. 64, Suppl. 247: 1-36, 1965.

Davies, J. and P. Tongroach. Neuropharmacological studies on the nigro-striatal and raphe-striatal system in the rat. Eur. J. Pharmacol. 51: 91-100, 1978.

Deakin, J.F.W., S.E. File, J.R.G. Hyde, and N.K. MaCleod. Ascending 5-HT pathways and behavioural habituation. Pharmacol. Biochem. Behav. 10/5: 687-694, 1979.

Dekloet, E.R., G.L. Kovacs, G. Szaba, G. Telegdy, B. Bohus, and D.H.G. Versteeg. Decreased serotonin turnover in the dorsal hippocampus of rat brain shortly after adrenalectomy: Selective normalization after corticosterone substitution. Brain Res. 239: 659-663, 1982.

Diamond, M.C., J.R. Connor Jr., E.K. Orenberg, M. Bissel, M. Yost, and A. Krueger. Environmental influences on serotonin and cyclic nucleotides in rat cerebral cortex. Science 210/4470: 652-654, 1980.

Dray, A., T.J. Gonye, N.R. Oakley, and T. Tanner. Evidence for the existance of a raphe projection to the substantia nigra in the rat. Brain Res. 113: 45-57, 1976.

Elo, H., and R. Tirri. Effect of forced motility on the noradrenaline and 5-hydroxytryptamine metabolism in different parts of the rat brain. Psychopharmacologica (Berl.) 26/2: 195-200, 1972.

Emerson Jr., T.E., P.D. Meier, and R.M. Daugherty Jr. Dependence of skeletal muscle vascular response to serotonin

upon the level of vascular resistance. Proc. Soc. Exp Biol. Med. (N.Y.) 142/4: 1185-1188, 1973.

Essen, B. and L. Kayser. Glycogen utilization in individual muscle fibres during intermittent and continuous exercise. Acta Physiologica Scandinavica: Suppl. 440: 170, 1976.

Feldberg, W. and V.J. Lotti. Temperature responses to monoamines and an inhibitor of MAO injected into the cerebral ventricles of rats. Brit. J. Pharmacol. 31: 152-161, 1967.

Feldberg, W. and S.L. Sherwood. Injections of drugs into the lateral ventricle of the cat. J. Physiol. 123: 148-167, 1954.

Felten, D.L. and K.A. Crutcher. Neuronal-vascular relationships in the raphe nuclei, locus coeruleus, and substantia nigra in primates. Am. J. Anat. 155: 467-482, 1979.

Fibiger, H.C. and B.A. Campbell. The effect of para-chlorophenylalanine on spontaneous locomotor activity in the rat. Neuropharmcol. 10: 25-32, 1971.

Fibiger, H. and J.J. Miller. An anatomical and electrophysiological investigation of the serotonergic projection from the dorsal raphe nucleus to the substantia nigra in the rat. Neurosci. 2: 975-987, 1977.

Flatman, J.A. and T. Clausen. B2-adrenoceptors mediate the stimulating effect of adrenaline on active electrogenic Na^+-K^+-transport in rat soleus muscle. Acta Physiol. Scand. 102/1: 61A-62A, 1978.

Frankhuyzen, A.L. and A.H. Mulder. Noradrenaline inhibits depolarization-induced ^3H-serotonin release from slices of rat hippocampus. Eur. J. Pharmacol. 63: 179-182, 1980.

Frederickson, R.C.A., L.M. Jordan, and J.W. Phillis. A reappraisal of the actions of noradrenaline and 5-hydroxytryptamine on cerebral cortical neurons. Comp. Gen. Pharmacol. 3: 443-456, 1972.

Fujiwara, H., M. Uemoto, and C. Tanaka. Stimulation of the rat dorsal raphe in vivo releases labeled serotonin from the parietal cortex. Brain Res. 216: 351-360, 1981.

Fuxe, K. Evidence for the existence of monoamine-containing neurones in the central nervous system. IV. Distribution of monoamne nerve terminals in the central nervous system. Acta Physiol. Scand. 64 Suppl. 247: 37-85, 1965.

Gallager, D.W. and G.K. Aghajanian. Effect of antipsychotic drugs on the firing of dorsal raphe cells. I. The role of the adrenergic system. Eur. J. Pharmacol. 39: 341-355,

1976.

Geyer, M.A. Heterogenous functions of discrete serotonergic pathways in brain. In: Biochemistry of Mental Disorders Modern Pharmacology-Toxicology. New York: Marcel Dekker, Inc., 13: 233-260, 1978.

Giambalvo, C.T. and S.R. Snodgrass. Biochemical and behavioral effects of serotonin neurotoxins on the nigrostriatal dopamine system: comparison of injection sites. Brain Res. 152: 555-566, 1978.

Gilbey, M.P., J.H. Coote. V.H. Macleod, and D.F. Peterson. Inhibition of sympathetic activity by stimulating in the raphe nuclei and the role of 5-hydroxytryptamine in this effect. Brain Res. 226: 131-142, 1981.

Gillespie, C.A., D.R. Simpson, and V.R. Edgerton. Motor unit recruitment as reflected by muscle fibre glycogen loss in a Prosimian (Bushbaby) after running and jumping. J. Neurol. Neurosurg. Psychiat. 37: 817-827, 1974.

Glowinski, J. and L.L. Iversen. Regional studies of catecholamines in the rat brain--I. The disposition of [^{3}H]norepinephrine, [^{3}H]dopamine and [^{3}H]dopa in various regions of the brain. J. Neurochemistry 13: 655-669, 1966.

Goldstein M., B. Anagnoste, E. Lauber, and M.R. McKereghan. Inhibition of dopamine-b-hydroxyalse by disulfiram. Life Sci. 3: 763-767, 1964.

Gollnick, P.D., K. Piehl, and B. Saltin. Selective glycogen depletion pattern in human muscle fibres after exercise of varying intensity at varying pedal rates. J. Physiol. 241: 45-57 1974.

Grabowska, M. and J. Michaluk. On the role of serotonin in apomorphine-induced locomotor stimulation in rats. Pharmacol. Biochem. Behav. 2: 263-266, 1974.

Green, R.A., J.A. Barchas, G.R. Elliott, J.S. Carman, and R.J. Wyatt. The tryptolines: effect of intraventricular adminstration on spontaneous motor activity of rats. Pharmocol. Biochem. Behav. 5: 383-385, 1976a.

Green, R.A., J.C. Gillin, and R.J. Wyatt. The inhibitory effect on intraventricular administration of serotonin on spontaneous motor activity of rats. Psychopharmacol. 51: 81-84, 1976b.

Gromova, E.A., T.P. Semenova, and N.L. Vekshina. Functional interactions of the serotonin systems of the brain during the process of conditioning. Doklady Biological Sciences 227: 149-151, 1976.

Grosser, B.I., W. Stevens, and D.J. Reed. Properties of

corticosterone-binding macromolecules from rat brain cytosol. Brain Res. 57: 387-395, 1973.

Gumulka, W., A.R. Del Angel, R. Samanin, and L. Valzelli. Lesions of substantia nigra: biochemical and behavioral effects in rats. Eur. J. Pharmacol. 10: 79-80, 1970.

Harvey, J.A., A.J. Scholosberg, and L.M. Yunger. Behavioral correlates of serotonin depletion. Fed. Proc. 34: 1796-1801, 1975.

Herr, B.E. and R.H. Roth. The effect of acute raphe lesion on the serotonin synthesis and metabolism in the rat forebrain and hippocampus. Brain Res. 110/1: 189-193, 1976.

Herve, D., H. Simon, G. Blanc, A. Lisoprawdki, M. Le Moal, J. Glowinski, and J.P. Tassin. Increased utilization of dopamine in the nucleus accumbens but not in the cerebral cortex after dorsal raphe lesion in the rat. Neurosci. Lett. 15/2-3: 127-133, 1979.

Hery, F., P. Soubrie, S. Bourgoin, J.L Motastruc, F. Artaud, and J. Glowinski. Dopamine released from dendrites in the substantia nigra controls the nigral and striatal release of serotonin. Brain Res. 193: 143-151, 1980.

Heym, J., M.E. Trulson, and B.L. Jacobs. Raphe unit acitivity in freely moving cats. II. Effects of adrenergic drugs. Soc. Neurosci. Abst. 6: 234, 1980.

Heym, J., M.E. Trulson, and B.L. Jacobs. Raphe unit activity in freely moving cats: Effects of phasic auditory and visual stimuli. Brain Res. 232: 29-39, 1982.

Hirai, K., T. Akasu, and K. Koketsu. Effect of 5-hydroxytryptamine on the nicotinic acetylcholine receptor-channel complex. Neuroscience Letters Supp. 6: S68, 1981.

Hole, K., K. Fuxe, and G. Jonsson. Behavioral effects of 5,7-dihydroxytryptamine lesions of ascending 5-hydroxtryptamine pathways. Brain Res. 107: 385-399, 1976.

Hole, K., G.E. Jonsson, and O.-G. Berge. 5,7-dihydroxytryptamine lesions of the ascending 5-hydroxytryptamine pathways: Habituation, motor activity, and agonistic behavior. Pharmacol. Biochem. Behav. 7: 205-210, 1977.

Hollister, A.C., G.R. Breese, and B.R. Cooper. Evidence for involvement of brain serotonin in the actions of amphetamine and other phenylethylamine derivatives. Fed. Proc. 33: 255, 1974.

Hollister, A.S., G.R. Breese, C.M. Kuhn, B.R. Cooper, and S.M. Schanberg. An inhibitory role for brain serotonin-containing systems in the locomotor effects of d-

amphetamine. J. Pharmacol. 198: 12-22, 1976.

Holmberg, E., I. Svedinger, and B. Waldeck. On the sympathometic induced effects on skeletal muscle contractions. In: Catecholamines: Basic and Clinical Frontiers, edited by E. Usdin, I.J. Kopin, and J. Barchas. New York: Pergamon Press, 1, 1979,p.986-988.

Huang, C.C. and A.S. Marrazzi. Analysis of drug block of LSD/5HT/GABA by monitoring neuronal membrane changes. Fed. Proc. 32: 303, 1973.

Hutchins, D.A. and K.J. Rogers. Some observations on the circadian rhythm of locomotor activity of mice after depletion of cerbral monoamines. Psychopharmacologica V (Berl.) 31/4:343-348, 1973.

Jacob, J.J. and J.-A.T. Girault. 5-Hydroxytryptamine. In: Body Temperature, Modern Pharmacology and Toxicology, edited by P. Lomax and E. Schonbaum. New York: Marcel Dekker Inc. 16: 183-230, 1979.

Jacobs, B.L. and A. Cohen. Differential behavioral effects of lesions of the median or dorsal raphe nuclei in rats: Open field and pain-elicited aggression. J. Comp. Physiol. Psychol. 90: 102-108, 1976.

Jacobs, B.L. and E.E. Eubanks. A comparison of the locomotor effects of 5-hydroxytryptophan administered via two systemic routes. Pharmacol. Biochem. Behav. 2/1: 137-139, 1974.

Jacobs, B.L., C. Trimbach, E.E. Eubanks, and M. Trulson. Hippocampal mediation of raphe lesion- and PCPA-induced hyperactivity in the rat. Brain Research 94: 253-261, 1975.

Jacobs, B.L., W.D. Wise, and K.M. Taylor. Differential behavior and neurochemical effects following lesions of the dorsal or median raphe nuclei in rats. Brain Research 79: 352-361, 1974.

Johnson, E.S., M.H.T. Roberts, and D.W. Straughan. Amino-acid induced depression of cortical neurones. Brit. J. Pharmacol. 38: 659-666, 1970.

Johnson, G.A., E.G. Kim, and S.J. Boukma. 5-hydroxyindole levels in rat brain after inhibition of dopamine b-hydroxylase. J. Pharmacol. 180: 539-546, 1972.

Jones D.L., G.J. Morgenson, and M. Wu. Injections of dopaminergic, cholinergic, serotoninergic and gabaergic drugs into the nucleus accumbens: effect on locomotor activity in thr rat. Neuropharmacol. 20: 29-37, 1981.

Karlsson, J. and P.V. Komi. Motion and its significance on innervation, fibre recruitment and muscle metabolism. Acta Physiol. Scand. Suppl. 440: 12, 1976.

Kayser, Ch. and G. Hildwein. Monoamines cerebrales et rythme circadien de l'activite motrice spontanee du rat. Soc. Biol. (Paris) 171: 450-455, 1977.

Keller, K.J., P.A. Brown, J. Marid, M. Bernstein, J. Vernikos-Danellis, and W.R. Mehler. Origins of serotonin innervation of forebrain structures. Experimental Neurology 56: 52-62, 1977.

Key, B.J. and V.H. Mehta. Changes in eletrocortical activity induced by the perfusion of 5-hydroxytryptamine into the nucleus of the solitary tract. Neuropharmacol. 16: 99-106, 1977.

Koe, K. and A. Weissman. p-Chlorophenylalanine: a specific depletor of brain serotonin. J. Pharmacol. Exp. Therap. 154: 499-516, 1966.

Komiskey, H.L. and T.A. Rudy. Serotonergic influences on brain stem thermoregulatory mechanisms in the cat. Brain Res. 134: 297-315, 1977.

Komissarov, I.V. and I.I. Abramets. Effect of monoamines on motorneurons of the isolated rat spinal cord. Neurophysiol. 12: 391-396, 1980.

Koob, G.F. and T.W. Robbins. The role of the mesolimbic dopamine system in locomotor activity, eating and drinking in the rat. In: Catecholamines: Basic and Clinical Frontiers, edited by E. Usdin, I.J. Kopin, and J. Barchas. New York: Pergamon Press, 1753-1755, 1979.

Kostowski, W., E. Giacalone, S. Garattinni, and L. Valzelli. Studies on behavioral arousal and biochemical changes in rats after lesion of midbrain raphe. Eur. J. Pharmacol. 4: 371-376, 1968.

Kostowski, W., E. Giacalone, S. Garattinni, and L. Valzelli. Electrical stimulation of midbrain raphe: Biochemical, behavioral and bioelectrical effects. Eur. J. Pharmacol. 7: 170-175, 1969.

Kostowski, W., R. Samanin, S.R. Baregge, V. Marc, S. Garattini, and L. Valzelli. Biochemical aspects of the interaction between midbrain raphe and locus coeruleus in the rat. Brain Res. 82: 178-182, 1974.

Kovacs, G.L., J. Kishonti, K. Lissak, and G. Telegdy. Inhibitory action of midbrain raphe stimulation on stress-induced elevation of plasma corticosterone level. Neurosci. Lett. 3/5-6: 305-310, 1976a.

Krueger. A.P., P.C. Andriese, and S. Kotaka. The effects of inhaling non-ionized or positively ionized air containing 2-4% CO2 on the blood levels of 5-hydroxytryptamine in mice. Int. J. Biometerol. 10/1: 17-28, 1966.

Krueger. A.P., and S. Kotaka. The effects of air ions on brain levels of serotonin in mice. Int. J. Biometerol. 13: 25-38, 1969.

Krueger, A.P. and R.F. Smith. The biological mechanisms of air ion action. J. Gen. Physiol. 44: 269-276, 1960.

Laventy, R. and K.M. Taylor. Effects of intraventricular 2,4,5-trihydroxphenylethylamine (6-hydroxydopamine) on rat behaviour and brain catecholamine metabolism. Brit. J. Pharmacol. 40: 839-846, 1970.

Leger, L. and L. Deacarries. Serotonin nerve terminals in the locus coeruleus of adult rat: a radioautographic study. Brain Res. 145: 1-13, 1978.

Lewis, B.D., B. Renaud, M. Buda, and J.-F. Pujol. Time-course variations in tryosine hydroxylase activity in the rat locus coeruleus after electrolytic destruction of the nuclei raphe dorsalis or raphe centralis. Brain Res. 108: 339-349, 1976.

Lidov, H.G.W., R. Grzanna, and M.E. Molliver. The serotonin innervation of the cerebral cortex in the rat-- An immunohistochemical analysis. Neurosci. 5/2: 207-227, 1980.

Loewy, A.D. and S. McKellar. Serotonergic projections from the ventral medulla to the intermediolateral cell column in the rat. Brain Res. 211: 146-152, 1981.

Lorens, S.A. Some behavioral effects of serotonin depletion depend on method: A comparison of 5,7-dihydroxytryptamine, p-chlorophenylalanine, p-chloroamphetamine, and electrolytic raphe lesions. In: Serotonin Neurotoxins, Annals of the N.Y. Acad. Sci. 305: 532-555, 1978.

Lorens, S.A. and H.C. Guldberg. Regional 5-hydroxytryptamine following selective midbrain raphe lesions on the cat. Brain Res. 78: 45-56, 1974.

Lorens, S.A., H.C. Guldberg, K. Hole, C. Kohler, and B. Srebro. Activity, avoidance learning and regional 5-hydroxytryptamine following intra-brain stem 5,7-dihydroxytryptamine and electrolytic midbrain raphe lesions in the rat. Brain Res. 108: 97-113, 1976.

Lyness, W.H. and K.E. Moore. Destruction of 5-hydroxytryptaminergic neurons and the dynamics of dopamine in nucleus accumbens septi and other forebrain regions of the rat. Neuropharmacology 20: 327-334, 1981.

McEwen, B.S., J.M. Weiss, and L.S. Schwartz. Uptake of corticosterone by rat brain and its concentration by certian limbic structures. Brain Res. 16: 227-241, 1969.

McRae-Degueurce, A., A. Berod, A. Mermet, A. Keller, G. Chouvet, T.H. Joh, and J.F. Pujol. Alterations in tyrosine hydroxylase activity elicited by raphe nuclei lesions in the rat locus coeruleus: evidence for the involvement of serotonin afferents. Brain Res. 235: 285-301, 1982.

Mabry, P.D. and B.A. Campbell. Serotonergic inhibition of catecholamine induced behavioral arousal. Brain Res. 49/2: 381-391, 1973.

Mackenzie, R.G., B.G. Hoebel, C. Norelli, and M.E. Trulson. Increased tilt-cage activity after serotonin depletion by 5,7-dihydroxytryptamine. Neuropharmacology 17: 957-963, 1978.

Magazanik, L.G., P. Illsch, and V.A. Snetkov. Effects of serotonin upon the voltage dependence of the end-plate current of muscle fibers. Doklady Biological Sciences 227: 163-166, 1976.

Matlina, E. Sh. Main phases of catecholamine metabolism under stress. In: Catecholamines and Stress, edited by E. Usdin, R. Kvetnansky, and I.J. Kopin. New York: Pergamon Press, 1976,p.353-365.

Matte, A.C. and H. Tornow. Parachlorophenylalanine produces dissociated effects on aggression, "emotionality" and motor behaviour. Neuropharmacology 17: 555-558, 1978.

Mayer, S. Regulation of cardiac and skeletal muscle glycogen metabolism by biogenic amines. In: Biogenic Amines as Physiological Regualtors, edited by J.J. Blum. Englewood Cliffs, New Jersy: Prentice-Hall, Inc., 139-159, 1970.

Mayer, S.E., D.H. Nammi, and J.P. Hickenbottom. Regulation of the phosphorylase activating pathway in intact cardiac and skeletal muscle. In: Advances in Enzyme Regulation, edited by G. Weber. Oxford: Pergamon Press, 8: 205-216, 1970.

Miller, F.P. and R.P. Maickel. The role of brain amines in the behavioural depression produced by a benzoquinolizine. Life Sci. 8 Part 1: 487-491, 1969.

Miller, M., R. Hasson, P.J. Morgane, and O. Resnick. Adrenalectomy: its effects on systemic tryptophan metabolism in normal and protein malnourished rats. Brain Res. 5: 451-459, 1980.

Moberg, G.P. and C.R. Clark. Effect of adrenalectomy and dexamethasone treatment on circadian running in the rat. Pharmacol. Biochem. Behav. 4: 617-619, 1976.

Monnier, M. and R. Tissot. Action de la reserpine et de ses mediateurs (5-hydroxytryptophan-serotonine et dopa-noradrenaline) sur le comportement et le cerveau du lapin.

Helv. Physiol. Pharmacol. Acta 16: 255-267, 1958.

Moore, R.Y., A.E. Haris, and B.E. Jones. Serotonin neurons of the midbrain raphe: ascending projections. J. Comp. Neurol. 180: 417-438,1978.

Morgane, P.J. and M.S. Jacobs. Raphe projections of the locus coeruleus in the rat. Brain Res. Bull. 4/4: 519-534, 1979.

Myslinski, N.R. and E.G. Anderson. The effect of serotonin precursors on α- and γ-motorneuron activity. J. Pharmacol. 204: 19-26, 1978.

Naftchi, N.E., M. Demeny, A. Ketesz, and E.W. Lowman. The CNS and adrenal tyrosine hydroxylase activity and norepinephrine, serotonin and histamine in the spinal cord after transection. Fed. Proc. 31: 832, 1972.

Nagatsu, T., M. Levitt, and S. Udenfriend. Tyrosine hydroxylase. J. Biol. Chem. 239: 2910-2917, 1964.

Neill, D.B., L.D. Grant, and S.P. Grossman. Selective potentiation of locomotor effects of amphetamine by midbrain raphe lesions. Physiol. Behav. 9: 655-657, 1972.

Newsholme, E.A. The role of the fructose 6-phosphate/fructose diphosphate cycle in metabolic regulation and heat generation. Biochem. Soc. Trans. 4/6: 978-984, 1976.

Newsholme, E.A. and C. Start. Regulation in Metabolism. London: John Wiley and Sons, 1973.

Nicolaou, N.M., M. Garcia-Munoz, G.W. Arbuthnott, and D. Eccleston. Interaction between serotonergic and dopaminergic systems in rat brain demonstrated by small unilateral lesions of the raphe nuclei. Eur. J. Pharmacol. 57: 295-305, 1979.

Oliveras, J.L., S. Bourgoin, F. Hery, J.M. Besson, and M. Hamon. The topographical distribution of serotonergic terminals in the spinal cord of the cat: Biochemical mapping by the combined use of microdissection and microassay procedures. Brain Res. 138: 393-406, 1977.

Olivereau, J.-M. Influence of variations of barometric pressure on the spontaneous activity in the rat (French). Z. Vergl. Physiol. 72/4: 435-441, 1971.

Olivereau, J.-M. Influence des ions atmospheriques negatifs sur l'adaptation a une situation anxiogene chez le rat. Int. J. Biometer. 17: 277-284, 1973.

Olpe, H.-R. The cortical projection of the dorsal raphe nucleus: Some electrophysiological and pharmacological properties. Brain Res. 216: 61-71, 1981.

Palkovits, M., M. Brownstein, and J.M. Saavedra. Serotonin content of the brain stem nuclei in the rat. Brain Res. 80: 237-249, 1974.

Palkovits, M., J.M. Saavedra, D.M. Jacobowitz, J.S. Koizer, L. Zaborszky, and M.J. Brownstein. Serotonergic innervation of the forebrain: effect of lesions on serotonin and tryptophan hydroxylase. Brain Res. 130/1: 121-134, 1977.

Parizek, J., R. Hassler, and I.J. Bak. Light and electron microscopic audioradiography of substantia nigra of rat after intraventricular administration of tritium labelled norepinephrine, dopamine, serotonin and precursors. Z. Zellforsch. 115: 137-148, 1971.

Pasquier, D.A. and F. Reinoso-Suarez. Differential efferent connections of the brain stem to the hippocampus in the cat. Brain Res. 120: 540-548, 1977.

Pataky, I. and A.K. Pfeifer. Physiological significance of the acetyocholine blocking agent in the central nervous system. Acta Physiol. Acad. Sci. Hung. 8: 221-229, 1955.

Patkina, N.A. and I.P. Lapin. Effect of serotoninergic drugs on positive and negative reinforcing systems in cats. Pharmacol. Biochem. Behav. 5: 241-245, 1976,

Pedersen-Bjergaard, K. and M. Tonnesen. The effects of steroid hormones on muscular activity in rats. Acta Endocrinologica 17: 329-337, 1954.

Pellegrino, L.J. and A.J. Cushman. A Stereotaxic Atlas of the Rat Brain. New York: Appleton-Century- Crofts, 1967.

Pfeifer, A.K. and I. Pataky. Acetylcholine blocking agent in the central nervous system. Acta Physiol. Acad. Sci. Hung. 8: 209-219, 1955.

Phillis, J.W., A.K. Tebecis, and D.H. York. Histamine and some other antihistamines: Their action on cerebral cortical neurones. Brit. J. Pharmacol. 33: 426-440, 1968a.

Phillis, J.W., A.K. Tebecis, and D.H. York. Depression of spinal motorneurones by noradrenaline, 5-hydroxytryptamine and histamine. Eur. J. Pharmacol. 4: 471-475, 1968b.

Pickel, V.M., T.H. Joh, and D.J. Reis. A serotonergic innervation of noradrenenergic neurones in the locus coeruleus: demonstration by immunocytochemical localization of the transmitter specific enzymes tyrosine and tryptophan hydroxylase. Brain Res. 131: 197-214, 1977.

Pijnenburg, A.J.J., W.M.M. Honig, J.A.M. Van der Heyden, and J.M. Van Rossum. Effects of chemical stimulation of the

mesolimbic dopamine system upon locomotor activity. Eur. J. Pharmacol. 35: 45-58, 1976.

Pope, S.G., P. Dean, and P. Redgrave. Dissociation of d-amphetamine-induced locomotor activity and stereotyped behaviour by lesions of the superior colliculus. Psychopharmacology 70: 297-302, 1980.

Proudfit, H.K. and E.G. Anderson. Blockade by serotonin antagonists of brain stem-evoked potentials recorded from spinal dorsal and ventral roots. Fed. Proc. 32: 303, 1973.

Pujol, J.-F., A. Buguet, J.-L. Froment, B. Jones, and M. Jouvet. The central metabolism of serotonin in the cat during insomnia. A Neurophysiological and biochemical study after administration of p-chlorophenylalanine or destruction of the raphe system. Brain Res. 29: 195-212, 1971.

Pujol, J.F., A. McRae- Degueurce, F. Crespi, P. Keane, B. Renaud, L. Leger, and M. Buda. Serotoninergic control of tyrosine hydroxlase (TH) and dopamine-b-hydroxylase (DBH) in the rat locus coeruleus (LC). In: Catecholamines: Basic and Clinical Frontiers, edited by E. Usdin, I.J. Kopin, and J. Barchas. New York: Pergamon Press, 1979, p.52-54.

Quirk, M. and T.L. Sourkes. Central dopaminergic and serotonergic systems in the regulation of adrenal tyrosine hydroxylase. J. Neurochem. 28: 137-147, 1977.

Raleigh, M.J., G.L. Brammer, A. Yuiviler, J.W. Flannery, M.T. McGuire, and E. Geller. Serotonergic influences on the social behavior of vervet monkeys (Ceropithecus aethiops sabaeus). Experimental Neurol. 68: 322-334, 1980.

Reader, T.A. Serotonin distribution in rat cerebral cortex: radioenzymatic assays with thin-layer chromatography. Brain Res. Bull. 5: 609-613, 1980.

Reader, T.A., A. Ferron, L. Descarries, and H.H. Jasper. Modulatory role for biogenic amines in the cerebral cortex. Microiontophoretic studies. Brain Res. 160: 217-229, 1979.

Renaud. B., M. Buda, B.D. Lewis, and J.-F. Pujol. Effects of 5,6-dihydroxytryptamine on tyrosine hydroxylase activity in central catecholaminergic neurons of the rat. Biochem. Pharmacol. 24: 1739-1742, 1975.

Richards, J.G., H.P. Lorez, and J.P. Tranzer Indolealkylamine nerve terminals in cerebral ventricles: identification by electron microscopy and fluorescence histochemistry. Brain Res. 57: 277-288, 1973.

Richardson, J.S. N. Cowan, R. Hartman, and D.J. Jacobowitz. On the behavioral and neurochemical actions of 6-hydroxydopa and 5,6-hydroxytryptamine in rats. Res. Commun. Chem.

Path. Pharmacol. 8: 29-44, 1974.

Richter, E.A., H. Galbo, and N.J. Christensen. Control of exercise-induced muscular glycogenolysis by adrenal medullary hormones in rats. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 50: 21-26, 1981.

Rinaldi, P., M. Sutko, J.H. Mahnke, and M. Verzeano. Serotonin in the lateral geniculate. Physiol. Behav. 14/1: 95-102, 1975.

Roberge, A.G. A morphological and biochemical dissociation between dopamine and serotonin in cat brain. In: Catecholamines: Basic and Clincal Frontiers, edited by E. Usdin, I.J. Kopin, J. Barchas. New York: Pergamon Press, 2: 1979, 1110-1112.

Romanes, G.J. The motor cell columns of the lumbo-sacral spinal cord of the cat. J. Comp. Neurol. 94: 313-363, 1951.

Romanowski, W. II. Studies on the inhibitory substance extracted from the brains of rats submitted to acute physical effort. Acta Physiol. Pol. 18/2: 225-232, 1967.

Romanowski, W. and S. Grabiec. The role of serotonin in the mechanism of central fatigue. Acta Physiol. Pol. 25/2: 127-134, 1974.

Romanowski, W. and J. Janota-Lukaszewka. I. Studies of the inhibitory substance extracted from the brains of rats submitted to acute physical effort. Acta Physiol. Pol. 18/2: 215-223, 1967.

Rommelspacher, H. and S. Strauss. Effect of lesions of raphe nuclei on the activity of catecholaminergic and serotonergic neurones in various brain regions of the rat in vivo. J. Neural Transmission 49: 51-62, 1980.

Saavedra, J.M., H. Grobecker, and J. Zivin. Catecholamines in the raphe nuclei of the rat. Brain Res. 114: 339-345, 1976.

Sakai, K., M. Touret, D. Salvert, L. Leger, and M. Jouvet. Afferent projections of the cat locus coeruleus as visualized by the horseradish peroxidase technique. Brain Res. 119: 21-41, 1976.

Sastry, B.S.R. and J.W. Phillis. Metergoline as a selective 5-hydroxytryptamine antagonist in the cerebral cortex. Can. J. Physiol. Pharmacol. 55: 130-133, 1977a.

Sastry, B.S.R. and J.W. Phillis. Inhibition of cerebral cortical neurones by a 5-hydroxytryptaminergic pathway from median raphe nucleus. Can. J. Physiol. Pharmacol. 55: 737-743, 1977b.

Satoh, K. The origin of reticulospinal fibers in the rat: A HRP study. J. Hirnforsch. 20: 313-332, 1979.

Schildkraut, J.J. and S.S. Kety. Biogenic amines and emotion. Science 156: 21-30, 1967.

Schimmel, R.J. The role of calcium ion in epinephrine activation of lipolysis. Horm. Metab. Res. 8: 195-201, 1976.

Schreiber, G.O.S. Space charge and atmospheric pressure. Int. J. Biometeor. 11 Suppl.3: 323, 1967.

Seeman, P., K. Westman, D. Cascina, and J.J. Warsh. Serotonin receptors in hippocampus and frontal cortex. Eur. J. Pharmacol. 66: 179-191, 1980.

Segal, M. Physiological amd pharmacological evidence for a serotonergic projection to the hippocampus. Brain Res. 94/1: 115-131, 1975.

Segal, M. The action of serotonin in the rat hippocampal slice preparation. J. Physiol. (London). 303: 423-439, 1980.

Segal, M. Regional differences in neuronal responses to 5-HT: Intracellular studies in hippocampal slices. J. Physiol. (Paris) 77: 373-375, 1981.

Segu, L. and A. Calas. The topographical distribution of serotonergic terminals in the spinal cord of the cat: quantitative radioautographic studies. Brain Res. 153: 449-464, 1978.

Semenova, T.P., V.A. Ivanov, and T.M. Tret'yak. Brain levels of noradrenalin, dopamine, and serotonin in rats with different levels of motor activity. Neurosci. Behav. Physiol. 11: 153-155, 1981.

Sharma, J.N. Microiontophoretic application of some monoamines and their antagonists to cortical neurones of the rat. Neuropharmacol. 16/2: 83-88, 1977.

Shimuzu, K., T. Yamamoto, and J. Ochi. Projection patterns of the brain stem serotonergic neurons in the central nervous system of the rat. Neuroscience Letters Supp. 6: S18, 1981.

Srebro, B. and S.A. Lorens. Behavioural effects of selective midbrain raphe lesions in the rat. Brain Res. 89: 303-325, 1975.

Stein, L and C.D. Wise. Serotonin and behavioural inhibition. In: Serotonin - New Vistas, Advances in Biochemical Pharmacology, edited by E. Costa, G.L. Gessa, and M. Sandler. 11: 281-291, 1974.

Stewart, R.M., J.H. Growdon, D. Cancian, and R.J. Baldessarini. 5-Hydroxytryptophan-induced myoclonus: increased sensitivity to serotonin after intracranial 5,7-dihydroxytryptamine in the adult rat. Neuropharmacol. 15: 449-455, 1976.

Svendgaard, N.A., A. Bjorklund, and U. Stenevi. Regenerative properties of central monoamine neurons. Advances in Anatomy, Embryology, and Cell Biology 51/(4): 1-77, 1975.

Svenson, T., B.S. Bunney, and G.K. Aghajanian. Inhibition of both noradrenergic and serotonergic neurons in brain by the α-agonist clonidine. Brain Res. 92: 291-306, 1975.

Szabadi, E., E.M. Bradshaw, and P. Bevan. Excitatory and depressant neuronal responses to noradrenaline and 5-hydroxytryptamine and mescaline: the role of the baseline firing rate. Brain Res. 126: 580-583, 1977.

Szafarczyk, A., G. Alonso, G. Ixart, F. Malaval, J. Nouguier-Soule, and I. Assenmacher. Serotonergic system and circadian rhythms of ACTH and cortcosterone in rats. Am. J. Physiol. 239: E482-E487, 1980.

Sze, P.Y. Glucocorticoid regulation of the serotonergic system of the brain. In: Advances in Biochemical Psychopharmacology, edited by E. Costa, E. Giacobini, and R. Paoletti. New York: Raven Press, 15: 251-265, 1976.

Takashi, K. and T. Kuga. Role of brain monamine systems in the jumping behavior induced in rats by the combination of harmine and apomorphine. Japan. J. Pharmacol. 31: 677-688, 1981.

Thierry, A.-M., M. Fekete, and J. Glowinski. Effects of stress on the metabolism of noradrenaline, dopamine and serotonin (5HT) in the central nervous system of the rat. (II) Modifications of serotonin metabolism. Eur. J. Pharmacol. 4: 384-389, 1968.

Tohyama, M., K. Sakai, M. Touret, D. Salvert, and M. Jouvet. Spinal projections from the lower brain stem in the cat as demonstrated by the horseradish peroxidase technique. II. Projections from the dorsolateral pontine tegmentum and raphe nuclei. Brain Res. 176: 215-231, 1979.

Torskaya, I.V. and V.N. Goloborod'ko. Relative amount of neurons with different transmitter metabolism in the motor nuclei of cat cervical spinal cord (Russ.). Neirofiziologiya 9/2: 191-197, 1977.

Trulson, M.E. and B.L. Jaocbs. Behavioral evidence for denervation supersensitivity after destruction of central serotonergic nerve terminals. In: Serotonin Neurotoxins N.Y. Acad. Sci. 305: 497-509, 1978.

Trulson, M.E. and B.L. Jacobs. Effects of 5-methoxy-N,N-dimethyltryptamine on behavior and raphe unit activity in freely moving cats. Eur. J. Phamacol. 54: 43-50, 1979a.

Trulson, M.E. and B.L. Jaocbs. Raphe unit activity in freely moving cats: correlation with level of behavioral arousal. Brain Res. 163: 135-150, 1979b.

Trulson, M.E. and B.L. Jacobs. Activity of serotonin-containing neurons in freely moving cats. In: Serotonin Neurotransmission and Behavior, edited by B.L. Jacobs and A. Gelperin. Cambridge, Massachusetts: MIT Press, 1981, 339-365.

Ungerstedt, U. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. Suppl. 367: 1-48, 1971.

Unvas, B. 2. The mechanism of histamine release from mast cells. In: Histamine II and Anti-Histamines. Handbook of Experimental Pharmacology, edited by M. Rocha e Silva. 18/2: 75-92, 1978.

Uzbekov, M.G., S. Murphy, and S.P.R. Rose. Ontogenesis of serotonin 'receptors' in different regions of rat brain. Brain Res. 168/1: 195-199, 1979.

Van de Kar, L.D. and S.A. Lorens. Differential serotonergic innervation of individual hypothalamic nuclei and other forebrain regions by the dorsal and median raphe nuclei. Brain Res. 162: 45-54, 1979.

Van Woert, M.H. and V.H. Sethy. Therapy of intention myoclonus with L-5-hydroxytryptophan and a peripheral decarboxylase inhibitor, MK 486. Neurology 25: 135-149, 1975.

Vermes, I., P.G. Smelik, and A.H. Mulder. Effects of hypophyectomy, adrenalectomy and corticosterone treatment on uptake and release of putative central neurotransmitters by rat hypothalamic tissue in vitro. Life Sci. 19/11: 1719-1726, 1976.

Waldmeier, P.C., R. Kam, and L. Maitre. Dopamine-serotonin interactions in the nigro-striatal feedback loop. In: Catecholamines: Basic and Clinical Frontiers, edited by E. Usdin, I.J. Kopin, and J. Barchas. New York: Pergamon Press, 2: 1979, p. 1104-1106.

Warbritton, J.D. III, R.M. Stewart, and R.J. Baldessarini. Decreased locomotor activity and attenuation of amphetamine hyperactivity with intraventricular infusion of serotonin in the rat. Brain Res. 143/2: 373-382, 1978.

Weiss, B.L. and G.K. Aghajanian. Activation of brain serotonin metabolism by heat: role of midbrain raphe

neurons. Brain Res. 26: 37-48, 1971.

Weiss, B. and V.G. Laties. Behavioural pharmacology and toxicology. Ann. Rev. Pharmacol. 9: 297-326, 1969.

Westermann, K.H., K. Funk, and L. Pawlowski. Effects of harmine and brain lesions on apomorphine induced motor activity. Pharmacol. Biochem. Behav. 4: 1-6, 1976.

White, S.R. and R.S. Neuman. Facilitation of spinal motorneurons excitability by 5-hydroxytryptamine and noradrenaline. Brain Res. 188: 119-127, 1980.

Wiklund, L., A. Bjorklund, and A. Nobin. Regeneration of serotonin neurons in the rat brain after 5,6-dihydroxytryptamine-induced axotomy. In: Serotonin Neurotoxins, N.Y. Acad. Sci., 305: p. 370-384, 1978.

Winsor, T., and J.C. Beckett. Biological effects of ionized air in man. Am. J. Physical Med. 37: 83-89, 1958.

Wong, D.T., F.P. Bymaster, J.S. Horng, and B.B. Malloy. A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: 3- (p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. J. Pharm. 193: 804-811, 1975.

Woolf, C.J., H.P. Laburn, G.H. Willies, and C. Rosendorf. Hypothalamic heating and cooling in monoamine depleted rats. Amer. J. Physiol. 228/2: 569-574, 1975.