THE ROLE OF DOPAMINE IN PREPARATORY AND CONSUMMATORY DEFENSIVE BEHAVIOURS

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Abstract

The effects of neuroleptic drugs on avoidance and freezing behaviours of rats were examined in a series of experiments. In Chapter I it was found that the acquisition of a one-way avoidance response was precluded by a dose of haloperidol (0.15 mg/kg) that did not prevent escape responses and that did not initially disrupt performance of a previously acquired response. The atypical neuroleptics thioridazine (10-50 mg/kg) and clozapine (1.25-10.0 mg/kg) did not preclude acquisition of the response and had non-specific effects on performance of an acquired response. In contrast, metoclopramide (5.0 mg/kg), like haloperidol, precluded acquisition of avoidance responding without initially disrupting performance. Given the clinical profiles of these drugs, these results suggest that disruption of avoidance responding by neuroleptic drugs may be more closely related to their capacity to produce extrapyramidal side effects than to their ability to relieve psychotic symptoms.

Chapter II examined the effect of metoclopramide on performance of avoidance responses after various training regimes. Metoclopramide effects were attenuated by a single training session of 10 trials, or, if the tone warning signal had previously been paired with shock, as few as 5 trials. No prophylactic effect of pretraining was observed if the rats were given noncontingent safety conditioning consisting of pairings of shock termination with the safe
side of the apparatus plus a light cue. However, metoclopramide had little impact if pretraining consisted of prior tone-shock pairings plus the opportunity to escape from unsignalled shock in the avoidance apparatus. These results exclude the possibility that attenuation of metoclopramide effects is due to overtraining of the avoidance response.

Chapter III established that freezing responses to shock are potentiated by metoclopramide, although the magnitude of freezing responses to a conditional stimulus signalling shock was not enhanced significantly. Following up on this discovery, Chapter IV determined that the disruptive effect of metoclopramide on avoidance responding was enhanced by the presence of additional shock or shock cues. It was concluded that the enhancement of freezing by metoclopramide contributes to the deficit in avoidance responding observed following metoclopramide treatment.

These results were interpreted as supporting a hypothesis that central dopamine systems are involved in the execution of preparatory responses directed towards distal stimuli, but not in consummatory responses directed towards diffuse local or internal cues.
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THE ROLE OF DOPAMINE IN PREPARATORY AND CONSUMMATORY DEFENSIVE BEHAVIOURS

Understanding the contribution of brain dopamine systems to behaviour has been the objective of a great deal of research in recent years. Although considerable progress has been achieved both theoretically and empirically, there is still little consensus on even the most basic issues. For example, it has been variously proposed that dopamine function is primarily involved in motor activity (Freed & Zec, 1982), attention (Solomon et al., 1981; Weiner & Feldon, 1988), motivational activation (Carli, Evenden, & Robbins, 1985; Salamone, 1988), learning (Beninger, 1988), reward (Wise, 1982), sensorimotor responsiveness (White, 1986), or response initiation (Fibiger, Zis, & Phillips, 1975; Posluns, 1962).

Recently, it has been proposed that central dopamine systems are preferentially involved in preparatory behaviours (Blackburn, 1985; Blackburn, Phillips, & Fibiger, 1987; Blackburn, Phillips, Jakubovic, & Fibiger, 1989a). Preparatory behaviours, such as foraging and hoarding, may be defined as responses that lead to and facilitate a separate class of consummatory behaviours (Craig, 1918; Konorski, 1967; Sherrington, 1906; Woodworth, 1918). Although the distinction between preparatory and consummatory behaviours is not always clear-cut, it has proven to be a useful concept in ethological (e.g., Eibl-Eibesfeldt, 1975; Tinbergen, 1951), neurobiological (e.g.,
Sherrington, 1906; Wilson & Soltysik, 1985) and theoretical (e.g., Konorski, 1967; Zernicki, 1968) analyses of behaviour. These two categories of motivated behaviour differ substantially along several important dimensions, and may be largely independent. Consummatory acts, such as chewing and swallowing, can typically be readily identified and described: They have rigidly defined topographies and clearly defined objectives. Most often they satisfy biological needs, thus their targets are primary reinforcers. They are typically controlled by proximal stimuli. In contrast, preparatory responses, such as foraging behaviours, are more flexible. They have less immediate objectives, and have more variable topographies. They do not directly satisfy biological needs, thus they are directed towards secondary reinforcers. They are typically controlled by distal stimuli. Several different preparatory patterns may lead to identical consummatory reactions.

Evidence indicates that dopamine-dependent systems in the forebrain may be involved in the potentiation of non-reflexive, topographically flexible, preparatory responses to distal, exteroceptive stimuli. For example, Blackburn et al. (1989a) analyzed the involvement of dopamine in

1. The autonomy of these two classes of behaviour is illustrated by the observation that each can occur in isolation from the other. Schallert, Pendergrass, & Farrar (1982) and Konorski (1967) have reported that sated animals remain responsive to feeding-related cues even after they have ceased ingesting freely-available food. In contrast, drugs can disrupt preparatory feeding responses in animals that will nonetheless consume undiminished quantities of food (Blackburn et al., 1987).
preparatory responses elicited by an incentive stimulus consisting of an extended conditional stimulus that had been paired repeatedly with the delivery of a meal. When rats were presented with this stimulus they responded by orienting to it, and by entering the feeding niche into which the meal was about to be delivered. Blackburn et al. (1989a) determined that these behaviours were accompanied by an increase in forebrain dopamine activity, as indexed by the ratio of the dopamine metabolite 3,4-dihydroxyphenylacetic acid to dopamine (DOPAC/DA ratio). DOPAC/DA ratios were significantly increased in the nucleus accumbens, and by a similar amount in the striatum.

Similarly, Schultz (1986) demonstrated that dopamine neurons in the midbrain are activated when monkeys are presented with incentive stimuli related to food. Neurons were identified as dopaminergic on the basis of their histological location, impulse form, spontaneous discharge rate, and response to systemic administration of low doses of the dopamine agonist apomorphine. When the monkeys were presented with auditory and visual cues that signalled a feeding trial, the majority (70) of the neurons increased their firing rate, and a few (11) became less active. When the monkeys reached for food, 40 neurons became more active and 22 became less active. However, when food was placed in the mouth, only 11 neurons showed activity above baseline levels, and 1 became less active. Thus, although many dopamine neurons increased their activity in response to the
incentive cue and during the performance of the preparatory response, very few were activated during the consummatory phase of the feeding trial. These data are consistent with the suggestion that dopamine systems are primarily involved in the preparatory phase of appetitive responding.

Further evidence suggests that the dopaminergic activation elicited by incentive stimuli potentiates forebrain systems critical for the execution of subsequent preparatory responses to appropriate exteroceptive stimuli. In the absence of such potentiation preparatory responses, but not consummatory responses, are diminished or abolished. For example, administration of the dopamine receptor antagonist pimozide was found to severely attenuate the overt preparatory responses elicited by presentation of a conditional stimulus that signalled the imminent delivery of a meal, yet did not disrupt the consumption of available food (Blackburn, 1985; Blackburn et al., 1987). These results were consistent with previous reports that the dopamine receptor antagonist chlorpromazine disrupts responding in the presence of conditional stimuli signalling food delivery by monkeys (Migler, 1975) and rats (Clody & Carlton, 1980).

Preparatory and consummatory defensive behaviours

Although the distinction between preparatory and consummatory responding has most often been discussed in the context of appetitive behaviours, the preparatory/
consummatory distinction may also apply to defensive behaviours. Indeed, Konorski (1967, chapter 6) proposed that the preparatory/consummatory distinction is orthogonal to the appetitive/defensive distinction. From this perspective the hypothesized role for dopamine in potentiating preparatory responses to distal exteroceptive stimuli should apply to defensive as well as to appetitive preparatory behaviours. Otherwise, it would be necessary to postulate a specific role in hedonic processing for dopamine function (e.g., Wise, 1982).

The distinction between preparatory and consummatory defensive behaviours may be operationalized by considering avoidance and escape responses. Escape, occurring in the presence of the primary reinforcer (in this case a negative reinforcer), may be considered as a consummatory response. Escape response patterns are relatively invariant and inflexible (Bolles & McGillis, 1968). In contrast, avoidance responding, with more a flexible topography, and elicited by a warning signal prior to delivery of the primary reinforcer, may be viewed as a preparatory response.

It has been demonstrated repeatedly that moderate doses of neuroleptic drugs preferentially disrupt conditioned avoidance responding without interfering with an animal's ability to execute an escape response (Arnt, 1982; Beninger, 1989; Cook & Weidley, 1957; Courvoisier, Fournel, Ducrot, Kolsky, & Koetschet, 1953; Davidson & Weidley, 1976; Herz, 1966). Although high doses of neuroleptic drugs will
disrupt escape responding, higher doses are required to disrupt escape than are required to disrupt avoidance, typically in the ratio of 3:1 or 5:1, sometimes higher (Arnt, 1982; van der Heyden & Bradford, 1988). Dopamine-depleting lesions in the brain, produced by appropriate administration of the neurotoxin 6-hydroxydopamine (6-OHDA), produce a similar preferential disruption of avoidance responding compared to their effects on escape (Cooper, Breese, Grant, & Howard, 1973; Cooper, Howard, Grant, Smith, & Breese, 1974; Delacour, Echavarria, Senault, & Houcine, 1977; Fibiger, Phillips, & Zis, 1974; Heybach, Coover, & Lints, 1978; Zis, Fibiger, & Phillips, 1974).

If we grant that avoidance responses are, by definition, preparatory responses, by virtue of occurring prior to the occurrence of the primary reinforcer, and escape responses are also, by definition, consummatory responses, then to a first approximation it follows that dopamine is in fact preferentially involved in preparatory defensive behaviours. However, despite the apparent surface validity of this analysis, a great many questions remain unanswered. Fundamentally, given the multidimensional, quantitative definitions of preparatory and consummatory responding that have been provided, it is not clear if those factors that separate avoidance from escape responding are those onto which an analysis of dopamine function might usefully be mapped. Accordingly, this dissertation shall investigate the contribution of dopamine to defensive
behaviour in greater detail in order to clarify the nature of dopamine's contribution to preparatory and consummatory responding. Central to this analysis shall be an attempt to interpret the role of dopamine in active avoidance behaviour. In order to do this it is first necessary to consider the nature of active avoidance responding.

Theoretical analyses of active avoidance responding

Despite an extensive history of research, and its central role in the evolution of learning theory, avoidance behaviour is still not well understood. The problem of what motivates avoidance behaviour has, by itself, been a central point of controversy for learning and motivation theorists for half a century. Consider a standard avoidance paradigm: An animal is exposed to a warning signal (WS) that signals the imminent onset of an unconditioned aversive stimulus (AS), usually a shock\(^2\). Should the animal perform the requisite response during the period in which the WS is presented, the WS is terminated and the AS is not presented (avoidance has occurred). If no response is performed, the AS is administered until an escape response is performed. Escape responding terminates both the AS and the WS.

---

2. The terms "aversive stimulus" and "warning signal" are used here because they are operationally defined and theoretically neutral. The more common designations of "unconditional stimulus" and "conditional stimulus" are historical artefacts of an era when avoidance responses were viewed as Pavlovian conditioned responses. (Bolles, 1972a).
The question that has so bedevilled learning theorists is why animals continue to respond in the presence of the WS. In simple S-R terms (Hull, 1937), performance of an escape response will terminate the AS and thereby reduce fear, a drive. This drive-reduction will be reinforcing, therefore an animal will be more likely to perform the response when it is in the same stimulus environment. The problem is why response acquisition is enhanced if the response cancels AS presentation (Brogden, Lipman, & Culler, 1938). A simple S-R model should predict that the response should extinguish rapidly when the animal regularly avoids the presentation of the AS and therefore fails to experience the reinforcement of AS termination.

The classic account of avoidance, still very influential, is the two-factor theory of Mowrer (1947). By this account, (a) the animal learns a Pavlovian association between the WS and the AS, which results in the elicitation of fear as a conditioned response by the WS, and (b) it then learns to perform an instrumental response that is reinforced by termination of the fear-eliciting WS (fear reduction being reinforcing).

Two-factor theory has considerable surface validity. Certainly the experimental contingencies of the typical avoidance paradigm are such as to permit Pavlovian learning to occur: The onset of the WS is regularly followed by the onset of the AS. And evidence indicates that the WS does acquire properties of a conditioned excitor of fear. For
example, Kamin, Brimer, & Black (1963) showed that after avoidance training the WS was able to elicit a conditioned emotional response. Other evidence attests to the motivating properties of the WS. First, if a stimulus is independently established as a conditioned stimulus for shock, then acquisition of avoidance responding is typically more rapidly acquired if that stimulus is subsequently used than if a neutral or novel stimulus is used as the WS (e.g. Anisman, Irwin, Zacharko, & Tombaugh, 1982; De Teledo & Black, 1967; Gallon, 1972). What is more, an excitatory Pavlovian conditional stimulus (CS+) associated with shock can substitute for the WS in an avoidance experiment with no deleterious impact on performance, but an inhibitory conditional stimulus (CS-) explicitly not associated with shock will not elicit avoidance responding in the same animals (Overmier & Leaf, 1965; Solomon & Turner, 1962). If these studies confirmed the sufficiency of fear to elicit avoidance responding, a study by Rescorla and LoLordo (1965) apparently confirmed the necessity of fear to motivate avoidance. Dogs were trained on a Sidman avoidance schedule. Response rates were increased if a conditioned excitor of fear was presented to the dogs, but response rates actually declined if a conditioned inhibitor of fear was presented (see also Jacobs & LoLordo, 1980; Weisman & Litner, 1969; Zielinski & Cotton, 1982).

The final contention of two-factor theory, namely that avoidance is reinforced by WS termination, was supported by
evidence that rats would learn a novel response, differing from the escape response, in order to terminate the WS and avoid shock (Mowrer & Lamoreaux, 1946). Other studies demonstrated that avoidance responding was most rapidly acquired if WS offset was contiguous with the avoidance response. Performance was impaired if the WS was a brief stimulus that terminated before the response occurred or if the WS persisted for some time after the response occurred (Kamin, 1957; Mowrer & Lamoreaux, 1942).

Despite these successes, two-factor theory has been challenged on a number of fronts. First, although it is clear that experimental animals do develop fear of the WS, the magnitude of this fear is not related to the vigour of the avoidance response in any straightforward manner. One observation, first made by Solomon and Wynne (1953), is that well-trained animals do not appear as frightened during WS presentation as do animals with only a small amount of training. Brady (1964) and Coover, Ursin, and Levine (1973a) reported that fear, as indexed by plasma levels of 17-hydroxycorticosteroid, declines over successive avoidance sessions. That this reflects a decline in fear of the WS is demonstrated by the decreasing effectiveness of an avoidance WS as a conditioned stimulus when tested in a classical conditioning paradigm, either the suppression of ongoing operant responding (the conditioned emotional response [CER] paradigm; Kamin et al., 1963; Linden, 1969; Mineka & Gino, 1980; Mineka, Miller, Gino, & Giencke, 1981; Starr & Mineka,
1977), or the induction of conditioned freezing (Cook, Mineka, & Trumble, 1987). As a further complication, it has been observed that decreases in fear need not accompany behavioural extinction of avoidance responding. Kamin et al. (1963) found little fear extinction in rats that were extinguished in avoidance to a criterion of five consecutive failures to respond. In the case of response extinction produced by flooding (exposing an animal to the WS in the absence of any opportunity to avoid) there may be no decrease in fear of the WS (Mineka & Gino, 1979; Shipley, Mock, & Levis, 1971) or fear may actually increase (Coulter, Riccio, & Page, 1969).

Another challenge to Mowrer's formulation of two-factor theory involves a re-evaluation of the role of WS offset. According to Mowrer (1947), termination of the WS serves as a reinforcing event by its drive-reducing properties. However, other evidence suggests that it acts primarily as a feedback stimulus that informs the animal that the avoidance response has been completed successfully.

Various lines of evidence indicate the power of feedback from safety signals in avoidance responding. First, if avoidance responding results in presentation of an explicit safety signal, avoidance responding is enhanced. This is true even if the response does not terminate the WS (Bolles & Grossen, 1969; Bower, Starr, & Lazarovitz, 1965; D'Amato, Fazzaro, & Etkin, 1968; Keehn & Nakkash, 1959). This finding is an embarrassment for two-factor theory,
which holds that WS termination motivates avoidance responding. Even more embarrassing is the finding that if explicit safety signals are presented when an animal executes an avoidance response, fear of the WS is subsequently decreased (Cook et al., 1987; Mineka, Cook, & Miller, 1984). Two factor theory, relying on fear of the WS to motivate avoidance, predicts that such a manipulation should decrease, rather than increase, avoidance responding.

A second demonstration of the power of safety signals is that if a signal is associated with the absence of shock, and that signal is then presented as a consequence of performing an avoidance response, performance of the response is subsequently enhanced (Rescorla, 1969; Weisman & Litner, 1969, 1972).

Third, rats will approach a cue that signals the non-occurrence of shock (Bartter & Masterson, 1980; Leclerc, 1985; Leclerc & Reberg, 1980). In fact, a rat can be trained to perform a novel operant response to obtain presentation of a cue established as a safety signal in the course of avoidance training (Moot, 1973, cited in Bolles, 1975; Morris, 1975). These observations are in line with the predictions of incentive motivational interpretations of avoidance responding, which hold that avoidance actually consists of running towards safety signals rather than running away from an aversive WS (e.g., Toates, 1982). This position accounts nicely for the persistence of avoidance in the absence of the primary motivator (shock)
because even when the animal is avoiding, and hence not receiving the WS, it still receives the safety signal which has acquired secondary reinforcing properties.

In light of the difficulties encountered by two-factor theory, it is not surprising that alternative accounts of avoidance have arisen in recent years. At one extreme is that of Herrnstein (1969), who has accounted for avoidance responding solely in terms of reinforcement contingencies: Rats perform responses that decrease the probability or frequency of their being shocked. In support of this analysis, Herrnstein and Hineline (1966) subjected rats to an avoidance procedure in which trials occurred randomly in time, but a response could reduce the overall rate of shock (e.g. from a probability of .3 in a 2 s period to a probability of .1). No other stimuli were presented, so no reinforcing or feedback events were contiguous with responding. Although this experiment demonstrated that a reduction in shock rate alone is sufficient to maintain avoidance responding, the fact that it took rats thousands of shocks to acquire the response, as opposed to a few (in the case of one-way avoidance) or a few dozen (in the case of shuttle avoidance), indicates that the role played by such contingencies in other avoidance paradigms may be marginal.

Other theories of avoidance have emerged from different theoretical perspectives. Several cognitive models have been developed, most notably by Seligman & Johnston (1973).
By these accounts, fear is conditioned to the WS. Gradually, however, the animal acquires two expectancies: First, that an avoidance response will be followed by an absence of shock; second, that the absence of an avoidance response will be followed by shock. Given a preference for no shock, these expectancies lead to a high probability of the response being executed.

Bolles (1970, 1975) begins his analysis of avoidance behaviour by postulating that in order to survive animals must have a repertoire of species-specific defence reactions (SSDRs) that occur when they are frightened. In the case of rats, these SSDRs are primarily running and freezing. In its strong form (Bolles, 1975), the SSDR hypothesis holds that in an avoidance experiment the animal quickly learns that some stimuli predict shock and other stimuli predict safety. Within the context of the stimulus environment, the behaviour of the frightened rat is held to consist entirely of SSDRs: "When the test situation looks like a good place to freeze, the animal will freeze if it expects shock; when the situation looks like a good place to run, the animal will run in it" (Bolles, 1975, p. 365). The development of a consistent response occurring through avoidance training is attributed to the punishment of all but one SSDR. In this hypothesis, Bolles has abandoned the notion of reinforcement. All responses are seen as respondent, rather than operant. That is, the response of the animal is a function of its level of fear and of the stimulus
environment in which it finds itself, rather than its history of reinforcement in the situation. In most cases any learning that occurs is stimulus learning, not response learning (Bolles, 1978). Thus, if the response that the experimenter has designated as the avoidance response in a given experiment is an appropriate SSDR for that environment (for example running to a safe place in a one-way avoidance experiment) then the animal will quickly reach a high level of performance. In contrast, if the designated responses is not an SSDR (such as a lever press) acquisition can be painfully slow - on the order of hundreds or thousands of trials. Thus the SSDR hypothesis, unlike any of its predecessors, can readily account for vast differences in avoidance acquisition that are seen when different responses are required.

Masterson and Crawford (1982) also make reference to the notion of SSDRs, but rather than respondents, they see these as reinforcers in a defence motivation system analysis of avoidance. By this account, avoidance behaviours are consummatory responses, motivated by fear and serving to reinforce the activities that led up to their execution. Thus, they demonstrated that rats could easily learn to press a lever to avoid shock, so long as the lever press permitted them to exit the shock compartment (Crawford & Masterson, 1978).

Jacobs and LoLordo (1980) suggest that the critical feature in determining avoidance responding is the presence
of appropriate supporting stimuli. They contend that apparent constraints on avoidance response repertoires may actually be constraints in the nature of the what those supporting stimuli can be. Specifically, Jacobs and LoLordo determined that some stimuli may be effective as warning signals but not as safety signals (e.g., tone onset), or effective as safety signals but not as warning signals (e.g., tone offset, light onset, or light offset).

Acquisition and maintenance of avoidance responding

Confronted with an unwieldy mass of conflicting data and theory, it seems reasonable to suspect that avoidance, operationally defined, may not be a unitary behavioural phenomenon with a single neurobiological substrate (Mineka, 1979). This hypothesis would permit the researcher to salvage remnants of strong theories that can account for portions, but not all, of the avoidance data. It is highly plausible that a behaviour so quickly acquired, so long retained, and so resistant to extinction as avoidance should be multiply represented in the nervous system.

One important distinction to be drawn with regard to avoidance behaviour is that between response acquisition and response maintenance. It is precisely here that many behavioural theories of avoidance have had the most trouble. Consider again a simple S-R account of avoidance responding. Presentation of an aversive stimulus (AS) such as shock produces a drive state. Responses that terminate the AS
will be reinforced by reducing this drive state, and will tend to occur sooner and sooner after onset of the AS. If the AS were consistently preceded by a warning signal (WS), simple reinforcement of the escape habit in the presence of the WS could account for responses in the presence of the WS alone, prior to AS presentation. Thus, an S-R theory of this sort can account for the acquisition of avoidance responding. However, responses occurring prior to AS presentation cannot be reinforced by AS termination, and thus should extinguish rapidly. This however, is not the case. For example, Solomon, Kamin, and Wynne (1953) reported that dogs may perform hundreds of successful avoidances after receiving only a few shocks during response acquisition. The same is true of rats (Seligman & Campbell, 1965). Thus, S-R theory cannot account satisfactorily for avoidance response maintenance.

In contrast to S-R theory, in Mowrer's (1947) two-factor theory WS presentation can independently produce a drive state, and thus WS termination can be reinforcing in the absence of AS termination. Thus, avoidance responding can be maintained even when no shocks are received. However, as we have seen, levels of fear decline over the course of extended training on the avoidance response. Partly on the basis of this observation Mineka (1979) and Seligman and Johnston (1973) have suggested that fear may play an important role in the acquisition of avoidance
responding, but a less critical role in response maintenance.

Other recent theories have treated the maintenance of avoidance as a primary datum for which they must account. Bolles' SSDR hypothesis holds that once an animal has learned that the avoidance apparatus and the stimuli in it are frightening, it will emit an SSDR whenever it is in the apparatus. Because the responses do not rely on reinforcement for their establishment, they will not extinguish so long as a certain level of fear is elicited by the environment.

Cognitive theories hold that avoidance is maintained by the expectancy that failure to emit the avoidance response will result in shock. As Seligman & Johnston (1973) and Toates (1982) point out, because there is no disconfirmation of this expectancy the cognitive theorist does not predict any change in the probability of avoidance responding.

Effects of neuroleptics on response acquisition

The distinction between the acquisition and maintenance of avoidance responding is particularly germane to the current discussion, as extensive evidence reveals that disruption of dopamine neurotransmission preferentially disrupts the acquisition of avoidance responding. If an animal has learned the avoidance response prior to the disruptive treatment, the avoidance response may be but little diminished. Under appropriate circumstances it is
possible to dissociate completely the effect of dopamine-depleting lesions or neuroleptic drugs on the acquisition of avoidance from their effects on performance of acquired responses (Anisman et al., 1982; Beninger, Phillips, & Fibiger, 1983; Carey & Kenney, 1987; Fibiger et al., 1974, 1975; Ray & Bivens, 1966). In general, the more slowly a given avoidance response is acquired the more severe the impact of neuroleptic treatment (Latz, Bain, & Kornetsky, 1969).

Initial protection from the effect of neuroleptic drugs has also been reported in cases of previously acquired appetitive operant responses (Gray & Wise, 1980; Mason, Beninger, Phillips, & Fibiger, 1980; Phillips & Fibiger, 1979; Singh, 1964; Tombaugh, Anisman, & Tombaugh, 1980; Wise, Spindler, de Wit, & Gerber, 1978). By themselves, these data could be taken to imply that dopamine disruption produces a deficit in learning: Following neuroleptic treatment an animal can perform a previously learned task but cannot learn to perform a new one (Beninger, 1988). However, a profound disruption was observed on the first trial on which pimozide was administered in the case of preparatory conditioned responding elicited by stimuli associated with meal delivery, even after 50-80 conditioning trials (Blackburn et al., 1987). Disruption of the same response was of approximately equal magnitude whether rats were administered haloperidol after 3, 6, 9, or 12 days of conditioning (unpublished observations). If deficits in
preparatory responding are to be attributed to altered responsiveness to exteroceptive stimuli, rather than to learning, this apparent discrepancy between the effects of neuroleptic drugs on avoidance and classically conditioned appetitive responding must be resolved.

Neural mechanisms in avoidance behaviour

An additional objective of this dissertation is to shed light on relations between various neural systems involved in defensive behaviour. In addition to neuroleptic treatment, alterations in avoidance behaviour have been found following administration of tranquilizing, anticholinergic, serotonergic, and other pharmacological agents (Barry & Miller, 1965; Cook & Weidley, 1957; Morpurgo, 1965; Ogren, 1986), as a result of changes in corticosteroid or ACTH level (Oei & King, 1980), and following sympathectomy (Wynne & Solomon, 1955; Di Giusto & King, 1972). Disruptive effects have also been reported following lesions of discrete brain regions including the caudate nucleus (Green, Beatty, & Schwartzbaum, 1967; Studelska & Beatty, 1978), the substantia nigra (Mitcham & Thomas, 1972), the cingulate cortex (Peretz, 1960; Thomas & Slotnick, 1962), the hippocampus (Rich & Thompson, 1965), the septum (Kenyon & Kreickhaus, 1965a,b), the amygdala (Goddard, 1964; Sarter & Markowitsch, 1985), the dorsomedial nucleus of the thalamus (Olton & Isaacson, 1967; Vanderwolf, 1962, 1963), the ansa lenticularis (Caruthers, 1968), and
the mammillothalamic tract (Krieckhaus, 1964). However, no single structure can be identified as the critical structure for avoidance behaviour, nor is there a coherent, inclusive, whole-brain model of avoidance. Mineka (1979) has suggested that avoidance, operationally defined, may not be a unitary behavioural phenomenon with a single neurobiological substrate. However, it is to be hoped that the understanding of avoidance in general would be enhanced if a substantial advance could be made in understanding the contribution of even a single critical neural system.

Although dopamine plays a critical role in the acquisition of avoidance responding, substantial doubt exists concerning which component or components of the widespread telencephalic dopamine projection is most important. There is a widely held belief that nigrostriatal dopamine is required for avoidance responding, in particular the dopaminergic projection to the ventral striatum, but the evidence supporting this hypothesis is actually very limited. Early studies with 6-OHDA often involved intraventricular or intracisternal infusion of the neurotoxin, leading to global depletion of dopamine (e.g., Cooper et al., 1973; Lenard & Beer, 1975). Other studies have found avoidance deficits after injecting 6-OHDA into the substantia nigra or the caudate nucleus but have failed to determine whether striatal dopamine was depleted (Delacour et al., 1977; Heybach et al., 1978; Neill, Boggan, & Grossman, 1974). Still others have determined that
striatal dopamine was depleted, but did not determine whether other dopamine terminal regions were also affected (Fibiger et al., 1974; Zis et al., 1974), or provided only crude anatomical detail of their histological analyses (Cooper et al., 1974).

Koob, Simon, Herman, and Le Moal (1984) did not observe avoidance acquisition deficits following single bilateral infusion of 6-OHDA into the prefrontal cortex, substantia nigra, nucleus accumbens or striatum, but abolished acquisition with joint infusion into the nucleus accumbens plus the striatum. This was interpreted as indicating that disruption of both the nucleus accumbens and the striatum is required to produce avoidance deficits. There are two problems with this interpretation. First, the double infusion resulted in more severe depletion of dopamine in each terminal region investigated than did any single infusion. Thus, a single site could be responsible for the avoidance deficit, but the deficit may require more extensive dopamine depletion than that achieved with any single lesion. Second, dopamine levels were only measured in the prefrontal cortex, nucleus accumbens, and the striatum. The possibility that some other brain regions might be involved was not considered, even though the area of depletion would have extended to other sites as well.

It should be noted that other evidence implicates the amygdala as the critical site of neuroleptic action in avoidance deficits. Ashford and Jones (1976) found that
administration of 6-OHDA to the amygdala substantially impaired acquisition of a two-way avoidance response, yet had only a slight impact on the performance of a previously acquired response. Similarly, infusion of neuroleptics drugs into the amygdala delayed acquisition of a one-way response (Petty, Mott, & Sherman, 1984; Sherman, Petty, & Sacquinte, 1982). This, along with a great deal of evidence implicating the amygdala as a critical structure in avoidance responding (Brady, Schreiner, Geller, & Kling, 1954; Coover, Ursin, & Levine, 1973b; Riolobos, 1986; Robinson, 1963; Werka, Skar, & Ursin, 1978; Werka & Zielinski, 1978), suggests that the effects of neuroleptic drugs on avoidance may be mediated at this site. Alternatively, the above evidence could be interpreted as indicating the significance of the anatomically rich connection between the amygdala and the ventral striatum (Sarter & Markowitsch, 1985).

Overview

In order to extend the analysis of dopamine function to the realm of preparatory and consummatory defensive behaviour in general, and to avoidance responding in particular, this dissertation shall examine the effects of dopamine antagonists (neuroleptic drugs) on various components of defensive behaviour. The research will fall into several broad areas, each focussing on a different
issue concerning the role of dopamine in defensive behaviour.

Chapter I will investigate the effects on avoidance behaviour of different neuroleptic drugs believed to act on different dopamine subsystems. This will accomplish several objectives. First, it may help to determine which neural systems are involved in avoidance behaviour. Second, given that neuroleptics have multiple behavioural actions in clinical settings, this study may indicate which of these effects is most closely related to the disruption of avoidance behaviour. Third, it will permit comparison with appetitive responses: If those neuroleptics that block anticipatory feeding responses are also those that block the acquisition of avoidance, it would help to validate generalizations concerning the larger class of preparatory responses. Finally, if it is possible to find a drug which acts only on a subset of dopamine terminal sites, yet disrupts avoidance behaviour in the same way as less specific antagonists, it would be preferable to use that drug in subsequent studies of defensive behaviour. For this final reason, these experiments will be presented at the outset of this dissertation.

The role that dopamine plays in the acquisition of avoidance behaviour will be examined in finer detail in Chapter II. This investigation will begin by determining how much training it takes rats before they are able to execute avoidance responses even under the influence of
neuroleptic drugs. This will lead into an attempt to define precisely what rats must learn in order to be protected from the disruptive effects of neuroleptic drugs. For example, does the dopamine receptor blockade interfere with the association between the warning signal and the aversive stimulus? Does dopamine play a particular role in learning the incentive value of safety signals in avoidance training? What is the relationship between learning to escape and learning to avoid? By examining the role of dopamine in the acquisition and maintenance of avoidance responding, it is hoped that we might not only clarify the contribution of dopamine to avoidance behaviour, but also shed light on the more general question of whether different psychological processes control avoidance at different stages of acquisition.

Chapter III will investigate the effect that dopamine receptor blockade has on defensive reactions other than avoidance. Freezing is an important component of the defensive repertoire of rats (Blanchard & Blanchard, 1969a), one that may conflict with avoidance responding. It would be illuminating to know whether neuroleptics alter unconditioned or conditioned responses to shock. Specifically, we shall determine whether neuroleptic treatment increases a rat's tendency to freeze in response to shock, or to conditional stimuli signalling shock.

Chapter IV will consider whether altered responses to shock can account in part for the observed deficits in
avoidance responding. Specifically, evidence shall be presented that enhanced consummatory freezing responses to shock and shock-related stimuli disrupt those preparatory responses to distal cues that would permit rats to avoid shock.

The general discussion will consider the capacity of several hypotheses of dopamine function to account for the results of the various studies, and shall develop the analysis of dopamine's contribution to preparatory behaviour in general.
EFFECTS OF DIFFERENT CLASSES OF NEUROLEPTIC DRUGS ON ONE-WAY AVOIDANCE BEHAVIOUR

A large variety of pharmacological substances may be classified as dopamine antagonists (neuroleptic drugs) on the basis of their ability to bind to dopamine receptors and to block effects of dopamine or dopamine agonists. However, not all neuroleptic drugs have the same pharmacological, behavioural, or clinical effects. The purpose of the experiments in this chapter is to determine the effect of markedly different neuroleptic compounds on the acquisition and performance of one-way avoidance behaviour. This shall accomplish four objectives. First, if valid parallels are to be drawn between defensive and appetitive behaviours, then both classes of behaviour should be affected similarly by different classes of neuroleptics. Otherwise, neuroleptic-induced disruption of these behaviours would appear to be under the control of independent dopamine systems. Second, we can determine which clinical effects of neuroleptics are most closely related to avoidance deficits. This will suggest whether it is reasonable to look for parallels between preparatory appetitive responses and avoidance behaviour, on one hand, and human neurological and neuropsychiatric disorders, on the other. As well, this approach may provide evidence relevant to the evaluation of avoidance responding as an animal model for testing the
potential clinical efficacy of novel neuroleptic compounds. Third, these pharmacological investigations may provide clues as to which anatomically identified dopamine subsystems are involved in avoidance, a question that has not been resolved clearly through studies employing selective brain lesions. Fourth, if it is possible to identify a neuroleptic drug which is more selective than compounds that have been used in the past, yet has a similar impact on avoidance responding, it would be preferable to use that drug in other studies of avoidance behaviour.

Experiment I.1: Effects of haloperidol

Haloperidol is a widely prescribed antipsychotic drug whose long-term use is often associated with undesirable extrapyramidal side effects (EPSEs). It has previously been shown to disrupt one-way (e.g., Fibiger et al., 1975) and two-way (e.g., Janssen, Niemegeers, & Schellekens, 1965), as well as discriminated and nondiscriminated lever press (e.g., Davidson & Weidley, 1976; Niemegeers, Verbruggen, & Janssen, 1969) avoidance behaviour. In the present experiment, the effects of haloperidol on one-way avoidance behaviour were examined again, in order to provide a basis of comparison for other neuroleptic drugs.

Method

Subjects: Male hooded rats obtained from Charles River Laboratories of Canada were used. All rats were experimentally naive, weighed 300 - 600 g at the start of
the experiment and were housed individually in a climatically-controlled colony room on a 12 h light-dark cycle in wire stainless steel cages. Each experimental session occurred between 0900 and 1300 h.

**Apparatus:** The avoidance apparatus consisted of a shuttlebox (25 cm x 78 cm x 33 cm deep) divided into two equal halves by a partition. Both halves were painted flat black. The partition could be opened by raising a 13-cm wide guillotine door. A grid floor on one side (the "shock" side) could be electrified by a scrambled 1.0 mA d.c. current (BRS/LVE shock generator). A 2900 Hz tone generator (Sonalert) was mounted below the grid floor at the end of the shock side, and a 3.3 ca cue light (not used in this experiment) was mounted above the tone generator, near the top of the same wall, centred 34 cm above the grid. Electromechanical relays and timers were used for stimulus control and data collection.

**Avoidance training:** Training sessions occurred at approximately the same time for six consecutive days. Each rat received 10 trials per session. Each session began by putting a rat into the "safe" (non-electrified) side of the shuttlebox. After 30 s the rat was placed on the shock side facing away from the guillotine door. The trial began with tone (WS) onset and the opening of the door. If the rat moved into the safe side during the 10-s tone period the tone was turned off, the door was lowered, and an avoidance response was recorded. If the rat failed to avoid during
the 10-s tone period, the offset of the tone was contiguous with the onset of the footshock (AS). Movement into the safe side was followed by lowering the door, and an escape response was recorded. If no response occurred within 10 s following shock onset, the rat was pushed gently into the safe side and was assigned a response latency of 20 s. Entry into the safe side always initiated the next 30-s intertrial interval.

**Statistical analysis:** The number of avoidances were analyzed using a two-way (Group x Day) Analysis of Variance (ANOVA). Latency scores were analyzed with a three-way (Group x Day x Trial) ANOVA. In each case significant effects were further analyzed using Newman-Keul's post hoc test at a .05 level of significance. Because the treatment of the groups changed between Phase A and Phase B, post hoc tests were only conducted on the Group x Day interaction.

**Haloperidol testing:** Drug effects on the acquisition of avoidance responding were investigated in Phase A (Days 1 - 3) of each experiment, in which groups of rats received injections of drug or vehicle. The vehicle-treated rats subsequently received an intermediate dose of drug in Phase B (Days 4 - 6) to determine effects on the performance of a previously acquired response. All other groups received vehicle injections in Phase B. All solutions were injected subcutaneously, 60 to 90 min prior to testing.

Haloperidol (McNeil Pharmaceutical, Stouffville, Ontario) was diluted to 0.075 or 0.150 mg/ml in distilled
water. Separate groups of rats, designated as .075-V and .150-V, received 0.075 and 0.150 mg/kg haloperidol, respectively, on each day of Phase A. Group V-.150 received water. In Phase B Groups .075-V and .150-V received water, and Group V-.150 received 0.150 mg/kg haloperidol. Each group consisted of 6 rats.

Results

The number of avoidances are illustrated in the top panel of Figure 1. Haloperidol, at a dose of 0.150 mg/kg, completely blocked the acquisition of avoidance responding in Phase A. Acquisition was also severely disrupted following treatment with the lower dose (.075 mg/kg), with this group attaining a mean of 3.3 avoidances in 10 trials on the third day. Rats that had acquired efficient avoidance behaviour in Phase A were only moderately affected by haloperidol (0.150 mg/kg) in the first session of Phase B (M = 7.2 avoidances). However, the disruptive effect became much more severe on the final two days of testing. The ANOVA indicated a significant effect of Day [F(5,75) = 45.84, p < .001], and a significant Group x Day interaction [F(10,75) = 60.88, p < .001], but not a significant effect of Group [F(2,15) = 3.30, p > .05]. Post hoc tests indicated that Group V-.150 made the most avoidance responses on Days 1 to 3. On Days 2 and 3 Group .075-V made more avoidances than Group .150-V. There were no between-group differences on Day 4. On Days 5 and 6 Groups .150-V and .075-V performed more avoidance responses than Group V-
Figure 1. Effects of haloperidol

Top panel indicates mean number of avoidances executed on each day by the rats of the various groups. Bottom panel indicates mean response latencies. In Phase A Groups .075-V and .150-V received 0.075 and 0.150 mg/kg haloperidol, respectively, and Group V-0.150 received vehicle. In Phase B Groups .075-V and .150-V received vehicle and Group V-.150 received 0.150 mg/kg haloperidol.
HALOPERIDOL

Phase A.  Phase B.

V - .150
.075 - V
.150 - V

AVOIDANCE RESPONSES

Phase A.  Phase B.

RESPONSE LATENCY

TEST DAY
.150. It is interesting to note that Groups .075-V and .150-V avoided significantly more often on Day 4, their first undrugged day, than Group V-.150 had on Day 1.

Additional information can be gleaned by considering the scores of individual groups across the six days of the experiment. Group V-.150 avoided significantly more often on Days 2 and 3 than on Day 1, as they acquired the response. On Day 4 their performance was significantly disrupted by administration of haloperidol, and their performance deteriorated further on Days 5 and 6. In contrast, the performance of Groups .150-V and .075-V did not change significantly from Day 1 to Days 2 and 3, as they did not acquire the response in Phase A. Group .150-V improved on Day 4, following the cessation of haloperidol treatment. Their performance improved further on Day 5. Group .075-V also improved on Day 4, relative to their drug test on Day 3, but their performance did not change significantly between Days 4 and 6.

A similar pattern of results held for response latencies (see bottom panel of Figure 1). The ANOVA indicated significant effects of Group \( F(2,15) = 5.24, p < .05 \) and Day \( F(5,885) = 101.34, p < .001 \), and a significant Group x Day interaction \( F(10,885) = 174.43, p < .001 \). Post hoc examination of the interaction indicated that throughout Phase A the latencies of Group V-.150 were shortest. Group .075-V had shorter latencies than Group .150-V on Day 2 and Day 3. On the first day of Phase B, the
latencies of Groups .150-V and .075-V did not differ from those of Group V-.150. On Days 5 and 6 Groups .150-V and .075-V had significantly lower latencies than Group V-.150. Note again that the latencies of Groups .075-V and .150-V were significantly lower on Day 4 than those of Group V-.150 had been on Day 1.

Considering the performance of individual groups across days in Phase A, the critical findings were (a) a significant improvement in the response latencies of Group V-.150, (b) no improvement by Group .075-V, and (c) a deterioration in the response latencies of Group .150-V from Day 1 to Day 2. In Phase B response latencies of Groups .150-V and .075-V decreased markedly, relative to Day 3. Group V-.150 response latencies were increased following 0.150 mg/kg haloperidol on Day 4, and response latencies increased substantially by Day 6.

Examination of the latency scores for individual groups across days reveals several interesting phenomena. As expected, the latencies for Group V-.150 decreased in Phase A while these rats acquired the response, while those of .075-V did not. Interestingly, the latencies of Group .150-V actually increased over the days of Phase A. In Phase B, as expected, the scores of Groups .150-V and .075-V decreased as they now acquired the response, while those of Group V-.150 increased significantly on each successive day.
Discussion

The present experiment confirmed that haloperidol can prevent acquisition of a one-way active avoidance response (Fibiger et al., 1975). The experiment also demonstrates several other previously described effects of neuroleptic drugs on avoidance behaviour.

First, although haloperidol prevented acquisition of the avoidance response, the drug had relatively little impact on the performance of escape responses occurring after the onset of shock (Arnt, 1982; Cook & Weidley, 1957; van der Heyden & Bradford, 1988). This was particularly evident on Day 1. On Days 2 and 3 the mean response latency increased. As responses were virtually always escape responses, this indicates that the impairment produced by 0.150 mg/kg haloperidol was so extreme that even escape latencies were increased.

Second, despite the high level of debilitation produced by 0.150 mg/kg during Phase A, the same dose had only a mild effect on the performance of Group V-.150 on Day 4, after these rats had received three days of drug-free training. Thus, there was a clear dissociation between the effects of haloperidol on the acquisition of avoidance responding and its sparing of a previously acquired response. This phenomenon has previously been noted with both haloperidol (e.g., Fibiger et al., 1975) and pimozide (e.g., Beninger et al., 1983).
Third, the protective effect of pre-training was not absolute. Administration of haloperidol to Group V-.150 on Day 4 produced a significant decrease in the number of avoidance responses executed (from 10.0/10 to 7.2/10). What is more, there was a progressive deterioration in performance by this group across the three days they received haloperidol in Phase B. Such progressive deterioration has previously been observed on consecutive days of neuroleptic testing (Beninger et al., 1983; Carey & Kenney, 1987) or on repeated testing following 6-OHDA lesions of central dopamine neurons (Beer & Lenard, 1975; Cooper et al., 1973; Lenard & Beer, 1975). The very rapid decline in performance over three days of testing in the present experiment was much more extreme than that observed by Beninger et al. (1983), and can again be attributed to the magnitude of the dose of neuroleptic used here. Coupled with the marked increase in response latencies observed for Group .150-V across Phase A, it seems probable that the dose may have been sufficiently high to have had non-specific as well as specific effects on avoidance responding.

A final feature of this set of data that warrants comment is the rapid acquisition of the avoidance response by those rats that were switched to vehicle in Phase B. Despite their abysmal performance on the third drug-test day of Phase A, the rats in Group .150-V had lower response latencies and more avoidance responses on Day 4 than Group V-.150 did on Day 1. Similar data have been reported
previously (Beninger, Mason, Phillips, & Fibiger, 1980b; Davidson & Weidley, 1976; Fibiger et al., 1975; Posluns, 1962; but see Beninger et al., 1980a). From this we can infer that (a) there are no serious deleterious effects from prior daily injections of haloperidol, thus the decline in performance over successive days by haloperidol-treated rats cannot be attributed to cumulative residual effects of the drug, and (b) although the rats of Group .150-V did not avoid at all on Day 3, they must have acquired knowledge relevant to the execution of the response during Phase A.

This experiment confirmed that the avoidance paradigm employed here is affected by neuroleptic drugs in the same manner as in other previously described research. The remainder of Chapter I shall examine the effects of other dopamine antagonists to determine whether the avoidance-disrupting properties of haloperidol are more closely related to its antipsychotic effects or to its ability to produce motoric side effects.

Experiment I.2a: Effects of thioridazine

So-called "atypical" neuroleptics are potent antipsychotic agents. However, compared to "classical" neuroleptic compounds, such as haloperidol or pimozide, their long-term use is infrequently associated with extrapyramidal side effects (EPSEs), such as tardive dyskinesia, at clinically effective doses (Snyder, Greenberg, & Yamamura, 1974; Tamminga, 1983). Thioridazine
is one widely-prescribed atypical neuroleptic. Thus, if it blocks the acquisition of avoidance behaviour, we might surmise that this effect of classical neuroleptic compounds is related to their antipsychotic properties, rather than to their ability to induce EPSEs. In contrast, if thioridazine does not block avoidance responding, it would seem unlikely that the blockade of avoidance is related to the antipsychotic properties of neuroleptics.

In work with appetitive behaviours, it has been demonstrated that preparatory behaviours are blocked by pimozide, a so-called "classical" neuroleptic drug (Blackburn, 1985; Blackburn et al., 1987). Similar effects have also been observed with haloperidol (unpublished observations). A recent study examined the effects of thioridazine on preparatory and consummatory feeding responses. Thioridazine (10 - 30 mg/kg) had no significant effect on any measure of preparatory or consummatory feeding behaviour (Blackburn, Phillips, & Fibiger, 1989b). Thus, if avoidance behaviour is blocked by thioridazine, avoidance and preparatory appetitive responding would appear to be under the control of distinct dopaminergic systems.

Method

Subjects, apparatus, procedure, and statistical analysis: Subjects similar to those of Experiment I.1 were used, and were tested in the same apparatus using the same procedure. Data were again analyzed using the ANOVA,
followed by Newman-Keul's post hoc test, as in Experiment I.1.

**Thioridazine testing:** Thioridazine (Sandoz Pharmaceuticals, E. Hanover, NJ) was dissolved as 30 mg of drug in 0.95 ml of 1% lactic acid. When dissolved, an additional 0.05 ml of 0.1 N NaOH was added to raise the pH to 5.75. Separate groups of rats, designated 10-V, 20-V, and 30-V, received 10, 20, and 30 mg/kg thioridazine, respectively, in Phase A. Group V-20 received vehicle. In Phase B Groups 10-V, 20-V, and 30-V received vehicle, while Group V-20 received 20 mg/kg thioridazine. Each group consisted of 9 rats. On Day 5 there was an equipment malfunction that precluded further testing of several rats, reducing group sizes to 7 on Day 5, and 6 on Day 6.

**Results**

Relative to control conditions the acquisition of avoidance responding was attenuated by 10 - 30 mg/kg thioridazine. Nonetheless, all groups made more avoidance responses over the three drug-treatment days of Phase A, relative to their scores on Day 1 (see top panel of Figure 2). As well, administration of 20 mg/kg thioridazine had little effect on the performance of previously acquired avoidance responding by Group V-20 in Phase B. These impressions were confirmed by the ANOVA. There were significant effects of Group \( F(3,32) = 3.28, p < .05 \) and Day \( F(5,140) = 81.29, p < .001 \), and a significant Group x Day interaction \( F(15,140) = 1.92, p < .05 \). Post hoc
Figure 2. Effects of thioridazine

Top panel indicates mean number of avoidances executed on each day. Bottom panel indicates mean response latencies. In Phase A Groups 10-V, 20-V, and 30-V received 10, 20 and 30 mg/kg thioridazine, respectively, and Group V-20 received vehicle. In Phase B Groups 10-V, 20-V, and 30-V received vehicle, and Group V-20 received 20 mg/kg thioridazine.
examination of the interaction indicated that Group V-20 made more avoidance responses than any other group on Day 1, more than Groups 20-V or 30-V on Day 2, and more than Group 30-V on Day 3. There were no between-group differences in Phase B.

A similar pattern held for the response latency scores (see bottom panel of Figure 2). The anova indicated a significant effect of Group \([F(3,32) = 4.74, p < .01]\), Day \([F(5,1685) = 188.10, p < .001]\), and a significant Group x Day interaction \([F(15,1685) = 18.99, p < .001]\). Post hoc tests indicated that Group V-20 had shorter latencies than any other on Days 1 to 3. When drug conditions changed on Day 4, Group 30-V still had longer latencies than any other group. However, on Days 5 and 6 Group 30-V was not significantly different from Group V-20. On these last two days, when Group V-20 was receiving 20 mg/kg thioridazine, it had significantly longer latencies than did Groups 10-V and 20-V.

In examining the progress of individual groups across days, each group improved on Days 2 and 3, relative to Day 1. Thus, thioridazine did not block acquisition of avoidance responding. In Phase B, when they received vehicle, Groups 10-V and 20-V performed better than at the end of Phase A. In contrast, Group V-20 had significantly longer response latencies in Phase B, when they received 20 mg/kg thioridazine, even though they still maintained a high number of avoidance responses.
Discussion

It seems improbable that the ineffectiveness of thioridazine in this experiment is due to the use of insufficient doses of the drug. A dose of 20 mg/kg is clinically equivalent to a dose of 0.5 mg/kg haloperidol (Baldessarini, 1985), a dose far in excess of that required to completely block the acquisition of avoidance responding in Experiment I.1 (see also Davidson & Weidley, 1976; Fibiger et al., 1975). Further, doses below this range have been shown previously to block dopamine- or amphetamine-induced locomotion (Costall & Naylor, 1976; Ljungberg & Ungerstedt, 1985) and to increase dopamine turnover and release in the nucleus accumbens (Crow, Deakin, & Longden, 1975; Lane & Blaha, 1987). Most importantly, even though 20 mg/kg thioridazine did not prevent acquisition of a high rate of avoidance responding, it was sufficient to increase the latency to perform a previously acquired response: Even though the number of avoidance responses executed by Group V-20 did not decrease from Day 3 to Day 4, their mean response latency increased significantly from 2.5 s to 4.1 s. Despite these considerations, it is still conceivable that some higher dose of thioridazine could block acquisition without disrupting performance of a previously acquired response as well. Accordingly, an additional experiment examined the effects of a higher dose of the drug.
Experiment I.2b: Effects of 50 mg/kg thioridazine

This experiment examined the effects of a higher dose of thioridazine than was used in Experiment I.2a.

Method

Subjects, apparatus, procedure, and statistical analysis: Subjects similar to those of Experiment I.1 were used, and were tested in the same apparatus using the same procedure. Data were again analyzed using the ANOVA, followed by Newman-Keul's post hoc test, as in Experiment I.1.

Thioridazine testing: Thioridazine (Sandoz Pharmaceuticals, E. Hanover, NJ) was dissolved by sonication in distilled water. Group 50-V (n = 6) received 50 mg/kg thioridazine in Phase A, and vehicle in Phase B. Group V-50 (n = 6) received vehicle in Phase A, and 50 mg/kg in Phase B.

Results

As shown in the top panel of Figure 3, rats receiving 50 mg/kg thioridazine attained a mean level of 5.2 avoidance responses in 10 trials by the end of Phase A. It is noteworthy that this level of performance was equivalent to that observed in Phase B for the group that had previously received 50 mg/kg in Phase A. The ANOVA indicated that there was a significant effect of Day \( F(5,50) = 16.17, p < .001 \) and a significant Group \( \times \) Day interaction \( F(5,50) = 27.43, p < .001 \), but no significant effect of Group \( F < \)
Figure 3. Effects of 50 mg/kg thioridazine

Top panel indicates mean number of avoidances executed on each day. Bottom panel indicates mean response latencies. In Phase A Group 50-V received 50 mg/kg thioridazine, and Group V-50 received vehicle. In Phase B Group 50-V received vehicle and Group V-50 received 50 mg/kg thioridazine.
Chapter I

THIORIDAZINE

Phase A.

Phase B.

AVOIDANCE RESPONSES

Phase A.

Phase B.

RESPONSE LATENCY

TEST DAY

V - 50
50 - V
Post hoc examination of the interaction indicated that Group V-50 made more avoidance responses than Group 50-V on Days 1 to 3, whereas Group 50-V made more responses than Group V-50 on Days 5 and 6. There was no between-group difference on Day 4. The performance of Group V-50 on Days 4 to 6 did not differ from that of Group 50-V on Days 2 and 3. That is, there was no dissociation between the effects of thioridazine on the acquisition and performance of avoidance responding.

The same pattern is seen for the response latencies (see bottom panel of Figure 3). The ANOVA indicated a significant effect of Day \( F(5,590) = 26.21, p < .001 \), and a significant Group x Day interaction \( F(5,590) = 75.79, p < .001 \), but no significant effect of Group \( F < 1 \). Post hoc tests indicated that the performance of Group V-50 was superior to that of Group 50-V on Days 1 to 3. When drug conditions were reversed, Group 50-V had shorter latencies than Group V-50 on Days 4 to 6. Again, analysis of response latencies indicated that the performance of Group V-50 on Days 4 to 6 did not differ from that of Group 50-V on Days 2 and 3.

**Discussion**

This experiment demonstrated that, in sufficiently high doses, thioridazine can significantly attenuate avoidance responding. However, in marked contrast to the effect of haloperidol, the disruptive effect of high-dose thioridazine was identical during acquisition of avoidance and during performance of a previously acquired response. This profile
of results suggests that thioridazine had a much less specific effect on avoidance than did haloperidol. As non-specific performance deficits are also observed with a wide variety of pharmacological agents, such as barbiturates, it is unlikely that such effects provide important clues concerning the specific role for dopamine in avoidance responding.

The inability of thioridazine to prevent the acquisition of avoidance responding parallels its lack of effect on appetitive responding. Thioridazine (10 - 30 mg/kg) had no significant effect on any measure of feeding behaviour (Blackburn, et al., 1989b). Thus, the present experiments do not indicate any pharmacological dissociation between the appetitive and defensive preparatory responding.

Experiment I.3: Effects of clozapine

Clozapine, like thioridazine, is an atypical neuroleptic compound. However, unlike thioridazine, a phenothiazine derivative, clozapine is a substituted piperidine. If the absence of a classical profile of neuroleptic drug action on avoidance observed with thioridazine is to hold for atypical neuroleptics in general, then it should also be found for clozapine.

Doses of clozapine in the range of 0.0625 to 15 mg/kg have been shown to attenuate amphetamine induced behaviours (Costall & Naylor, 1976; Ljungberg & Ungerstedt, 1985; Robertson & MacDonald, 1984). Higher doses (10 - 20 mg/kg)
have been used to show alterations in ventral tegmental area dopamine unit activity and increased release of dopamine in the nucleus accumbens (Blaha & Lane, 1987; Chiodo & Bunney, 1985; White & Wang, 1983). Preliminary testing of the compound in this laboratory indicated that doses of 20 or 30 mg/kg produced profound motor debilitation in rats. Accordingly, effects in a lower range (1.25 to 10.0 mg/kg) were examined.

Method

Subjects, apparatus, procedure, and statistical analysis: Subjects similar to those of Experiment I.1 were used, and were tested in the same apparatus using the same procedure. Data were again analyzed using the ANOVA, followed by Newman-Keul's post hoc test, as in Experiment I.1.

Clozapine testing: Clozapine (Sandoz Pharmaceuticals, E. Hanover, NJ) was dissolved as 10.0 mg of drug in 0.98 ml of 1% lactic acid. When dissolved, an additional 0.02 ml of 0.1 N NaOH was added to raise the pH to 5.0.

Separate groups received 1.25 (n = 6), 2.5 (n = 8), 5.0 (n = 8), 7.5 (n = 8), and 10.0 (n = 6) mg/kg clozapine in Phase A, and vehicle in Phase B. Group V-5.0 (n = 6) received vehicle in Phase A, and 5.0 mg/kg clozapine in Phase B. One rat, from Group 5.0-V, became ill after Day 2 and was excluded from further testing.
Results

As was the case with thioridazine, clozapine slowed but did not completely block the acquisition of avoidance responding (see top panel of Figure 4). The ANOVA indicated a significant effect of Day \( [F(5,176) = 115.15, p < .001] \), and a significant Group x Day interaction \( [F(25,176) = 4.44, p < .001] \), but not a significant effect of Group \( [F(5,36) = 1.45, p > .20] \). Post hoc tests showed that all groups improved from Day 1 to Day 3, indicating acquisition of the response. On Day 1 Group V-5.0 made significantly more avoidances than Groups 5.0-V or 7.5-V, whereas on Days 2 and 3 only Groups 2.5-V and 10-V were significantly worse than Group V-5.0. In Phase B there were no between-group differences on Days 4 or 6, but on Day 5 Group 7.5-V avoided significantly more often than group V-5.0.

Latencies for the clozapine tests are shown in the bottom panel of Figure 4. The ANOVA indicated a significant effect of Day \( [F(5,2084) = 368.23, p < .001] \), and a significant Group x Day interaction \( [F(25,2084) = 18.91, p < .001] \), but not a significant Group effect \( [F(5,36) = 1.37, p > .20] \). Examination of the interaction revealed that Group V-5.0 had the shortest latencies of any group throughout Phase A. Nonetheless, each group improved from Day 1 to Day 2. Thus, although clozapine had a disruptive effect, it did not prevent acquisition of the response. When Group V-5.0 received 5.0 mg/kg in Phase B they had the longest latencies of any group. Thus, there was no dissociation between the
Figure 4. Effects of clozapine

Top panel indicates mean number of avoidances executed on each day. Bottom panel indicates mean response latencies. In Phase A Groups 1.25-V, 2.5-V, 5.0-V, 7.5-V, and 10.0-V received 1.25, 2.5, 5.0, 7.5, and 10.0 mg/kg clozapine, respectively, and Group V-5.0 received vehicle. In Phase B Groups 1.25-V, 2.5-V, 5.0-V, 7.5-V, and 10-V received vehicle and Group V-5.0 received 5.0 mg/kg clozapine.
Chapter I

CLOZAPINE

Phase A.

Phase B.

AVOIDANCE RESPONSES

RESPONSE LATENCY

TEST DAY

TEST DAY

Phase A.

Phase B.

V - 5.0

1.25 - V

2.5 - V

5.0 - V

7.5 - V

10.0 - V
effects of clozapine on acquisition and performance. All groups that had received clozapine in Phase A showed further improvement when they were switched to vehicle on Day 4. In contrast, latencies were longer for Group V-5.0 on Day 4 (following injection of 5.0 mg/kg clozapine) than they had been on Day 3, indicating disruption of avoidance response performance by clozapine.

Discussion

The non-specific pattern of results observed following administration of thioridazine was even more pronounced in the case of clozapine. Doses that failed to block acquisition of avoidance responding interfered significantly with the performance of previously acquired responses. In fact, the mean latency (7.7 s) for Group V-5.0 on Day 4, following administration of 5.0 mg/kg clozapine, was similar to that for Group 5.0-V on Day 3 (6.7 s). Once again, this profile of results differs substantially from that observed with haloperidol, and suggests that the disruption of avoidance responding by this compound is not consistent with the primary impact of dopamine disruption observed with classical neuroleptics or 6-OHDA lesions of central dopamine neurons.

A lack of specific effects on preparatory responding was also observed in the case of appetitive responding. Clozapine (5.0 mg/kg) was found to have a serious impact on consummatory feeding behaviour, and so was not tested for
its effects on preparatory responding (unpublished observations).

Experiment I.4 Effects of metoclopramide

In contrast to the strong antipsychotic, weak EPSE profile of the atypical neuroleptics, the antipsychotic action of the substituted benzamide metoclopramide is disputed (Doongaji, Desai, & Satoskar, 1986; Nakra, Bond, & Lader, 1975; Stanley, Lautin, Rotrosen, Gershon, & Kleinberg, 1980) whereas its long term use is associated with severe EPSEs (Bateman, Rawlins, & Simpson, 1985; Harrington et al., 1983; Indo & Ando, 1982). Thus, the pharmacological profile of metoclopramide stands in direct contrast to the antipsychotic efficacy and mild EPSE profile of the atypical neuroleptics.

In an examination of its impact on preparatory and consummatory appetitive responses, it was found that metoclopramide (2.5 - 7.5 mg/kg) severely attenuated preparatory responses to a conditional stimulus signalling delivery of a meal. However, consummatory responding was only affected by the highest dose (Blackburn et al., 1989b). Thus, if metoclopramide is found to disrupt the acquisition of avoidance responding, we will have demonstrated its capacity to attenuate both appetitive and defensive preparatory behaviours.
Method

Subjects, apparatus, procedure, and statistical analysis: Subjects similar to those of Experiment I.1 were used, and were tested in the same apparatus using the same procedure. Data were again analyzed using the ANOVA, followed by Newman-Keul's post hoc test, as in Experiment I.1.

Metoclopramide testing: Metoclopramide-HCl (Sigma Chemical Co., St. Louis, MO) was dissolved as 7.5 mg of the salt weight in 1.0 ml of saline.

Separate groups received 2.5, 5.0, and 7.5 mg/kg metoclopramide in Phase A, and saline in Phase B. Group V-5.0 received saline in Phase A, and 5.0 mg/kg metoclopramide in Phase B. Each group consisted of 6 rats.

Results

Metoclopramide, at doses of 5.0 and 7.5 mg/kg, completely blocked the acquisition of avoidance responding in Phase A. In Phase B, the initial impact of 5.0 mg/kg on the performance of Group V-5.0 was negligible, but a significant disruption was observed over the three days of testing. The number of avoidances are illustrated in the top panel of Figure 5. The ANOVA indicated significant effects of Group \([F(3,20) = 22.68, p < .001]\) and Day \([F(5,100) = 69.29, p < .001]\), and a significant Group x Day interaction \([F(15,100) = 16.74, p < .001]\). Post hoc tests indicated that whereas Groups V-5.0 and 2.5-V improved across Phase A, Groups 5.0-V and 7.5-V showed no signs of
Figure 5. Effects of metoclopramide

Top panel indicates mean number of avoidances executed on each day. Bottom panel indicates mean response latencies. In Phase A Groups 2.5-V, 5.0-V, and 7.5-V received 2.5, 5.0, and 7.5 mg/kg metoclopramide, respectively, and Group V-5.0 received vehicle. In Phase B Groups 2.5-V, 5.0-V, and 7.5-V received vehicle and Group V-5.0 received 5.0 mg/kg metoclopramide.
acquiring the response. Group V-5.0 had the most avoidances on Day 1. On Days 2 and 3 Groups V-5.0 and 2.5-V made more avoidances than Groups 5.0-V or 7.5-V. This was also true on Day 4. There were no between-group differences on Day 5. On Day 6 Group V-5.0 performed fewer avoidances than any other group.

A similar pattern of results held for response latencies (see bottom panel of Figure 5). The ANOVA indicated significant effects of Group \(F(3,20) = 6.86, p < .01\) and Day \(F(5,1180) = 171.77, p < .001\), and a significant Group x Day interaction \(F(15,1180) = 54.07, p < .001\). Post hoc examination of the interaction indicated that throughout Phase A Group V-5.0 latencies were shortest, and Group 2.5-V had shorter latencies than Groups 5.0-V and 7.5-V. On the first day of Phase B, the latencies of Group 5.0-V and 7.5-V remained the longest. However, by Day 5 Groups 5.0-V and 7.5-V were significantly faster than Groups V-5.0 and 2.5-V. This was also the case on Day 6, when Group V-5.0 had the longest latencies. Looking at individual groups across days, the critical finding was that Groups 5.0-V and 7.5-V showed no sign of acquisition across Phase A, whereas the latencies of Groups V-5.0 and 2.5-V decreased substantially. In Phase B Groups 5.0-V and 7.5-V improved significantly, relative to Day 3. Although the behaviour of Group V-5.0 was only marginally disrupted by 5.0 mg/kg metoclopramide on Day 4, response latencies increased significantly by Day 6.
The results of these experiments indicate that although haloperidol, clozapine, thioridazine, and metoclopramide all impair avoidance responding, there are important qualitative differences in the way they do so. Even though the atypical neuroleptics thioridazine and clozapine slowed acquisition of avoidance responding, they did not completely block it. Critically, the deleterious effects they had on acquisition were also evident in rats that had received prior drug-free training. That is, there was no dissociation between the effects of these drugs on the acquisition of avoidance responding and their effects on the performance of an acquired response. Together, these results suggest that doses of thioridazine and clozapine high enough to disrupt avoidance responding had a general disruptive effect on motor performance. In marked contrast, haloperidol and metoclopramide completely blocked acquisition of avoidance responding at doses that had, initially, only a negligible impact on performance.

This pattern of results parallels that observed for appetitive responses (see Table I). Blackburn et al. (1989b) found that metoclopramide attenuated preparatory feeding responses at a dose as low as 2.5 mg/kg, but did not have any discernable impact on consummatory feeding behaviour at doses lower than 7.5 mg/kg. This is similar to the effects of metoclopramide observed here on defensive behaviour, where it abolished avoidance responding without
Table I
Summary of neuroleptic drug effects on preparatory and consummatory responses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Preparatory</th>
<th>Consummatory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Defen</td>
<td>Appet</td>
</tr>
<tr>
<td>Pimozide</td>
<td>classical</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>classical</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>atypical</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clozapine</td>
<td>atypical</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>atypical</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


Effects of pimozide on defensive behaviours from Beninger et al. (1983), on appetitive behaviours from Blackburn et al. (1987).

Effects of thioridazine and metoclopramide on appetitive behaviours, Blackburn et al., 1989b.

Effects of haloperidol and clozapine on appetitive behaviours, unpublished observations.

Other observations from present report.
preventing escape. In contrast, the atypical neuroleptic thioridazine had no significant effect on any measure of preparatory or consummatory feeding behaviour at doses from 10 to 30 mg/kg, just as it had negligible effects on defensive behaviours in that dose range. Clozapine, which had pronounced non-specific effects on defensive behaviour at 5.0 mg/kg, markedly disrupted consummatory feeding responses at 10.0 mg/kg, the lowest dose tested. The similarly of these patterns of results suggest that the process that is being disrupted by neuroleptics in the acquisition of avoidance behaviour may be equivalent to the dopamine-mediated process underlying preparatory appetitive responding.

Clinically, these findings are of interest in light of the widespread use of neuroleptic drugs to alleviate psychotic symptoms. Disruption of avoidance behaviour has been correlated with the antipsychotic potency of various neuroleptics (Davidson & Weidley 1976; Arnt 1982), and has been used as a screen for detecting drugs with potential antipsychotic activity (e.g., Iorio, Barnett, Leitz, Houser, & Korduba, 1983; Janssen et al., 1965). However, as noted by Arnt (1982), it has never been established whether the disruption of avoidance responding by neuroleptics is related to their anti-psychotic efficacy, their ability to induce EPS, or both.

The pattern of results observed in the current set of experiments suggests that the ability of classical
neuroleptics to block the acquisition of avoidance responding selectively may correlate more closely with their ability to induce EPSEs than with their ability to relieve psychotic symptoms. Classical neuroleptics like haloperidol are effective antipsychotic agents but, like metoclopramide, they can induce EPSEs with extended use. Unlike metoclopramide, atypical neuroleptics are effective antipsychotic agents that have a low probability of inducing EPSEs.

While it is clear that our understanding of the mechanisms by which neuroleptic drugs disrupt avoidance responding is far from complete, and that further studies will be required to elucidate the psychological and physiological mechanisms that underlie these behaviours, the present experiments suggest that caution should be exercised in using the disruption of avoidance responding as an animal model for assessing the antipsychotic potential of new pharmacological agents. In fact, these data suggest that avoidance disruption may be more appropriate as an animal model for EPSEs. At the same time, these data indicate that understanding the disruption of preparatory appetitive and defensive behaviours may be intimately related to an understanding of extrapyramidal pathology, such as parkinsonism (Fibiger et al., 1975).

One factor that may account for the different effects of these various drugs on avoidance responding is that although atypical neuroleptics are effective dopamine
antagonists, they are also potent anticholinergics (Snyder et al., 1974). Although controversial, earlier studies have suggested that normal basal forebrain function is maintained by a balance between cholinergic systems and nigrostriatal dopaminergic activity (Klawans, 1968).

An alternative hypothesis that may account for the differential effects of atypical neuroleptics and metoclopramide is that these compounds may act selectively on anatomically distinct sites in the forebrain. Evidence from receptor binding (Altar, Wasley, Neale, & Stone, 1986; Borison & Diamond, 1983; Howard, Large, Wedley, & Pullar, 1978), behavioural pharmacology (Ljungberg & Ungerstedt, 1985; Robertson & MacDonald, 1984, 1985), electrophysiology (Chiodo & Bunney, 1985; White & Wang, 1983), and in vivo electrochemistry (Blaha & Lane, 1987; Lane & Blaha, 1987) indicates that atypical neuroleptics may act preferentially at sites in the mesolimbic dopamine system, including the nucleus accumbens, whereas metoclopramide may have a selective action on dopamine function in the striatum.

Anatomically distinct sites of action for atypical neuroleptics and metoclopramide would be consistent with the hypothesis that the antipsychotic effects of neuroleptics are mediated by the mesolimbic dopamine system, including the nucleus accumbens, whereas EPSEs are induced by disruption of dopamine function in the striatum. By this line of reasoning, the present studies implicate the striatum as the critical site of neuroleptic action in
producing avoidance deficits. Although this is consistent with the conclusion of many previous researchers, it should be recalled from the introduction that the evidence supporting this conclusion has been very limited: Those studies that have examined the effects of 6-OHDA lesions in discrete terminal regions have either failed to confirm that striatal dopamine was in fact depleted, or did not determine whether other dopamine terminal regions were also affected. Evidence that the amygdala may be a critical site for dopaminergic modulation of avoidance (Ashford & Jones, 1976; Petty et al., 1984; Sherman et al., 1982) is impossible to impossible with the present results in the absence of data concerning the affinity of this site for atypical neuroleptics and metoclopramide. Thus, while the results of the present study are entirely consistent with the hypothesis that neuroleptic effects on avoidance behaviour and preparatory feeding responses are mediated by the nigrostriatal dopamine system, they cannot be taken as strong evidence on this point given the current state of knowledge concerning the actions of these drugs.

These results do permit us to identify metoclopramide as a pharmacological agent that has the full impact of classical neuroleptic drugs on defensive as well as preparatory responding. Because it appears to have only a subset of the clinical and neurobiological effects of these drugs, it appears to be an ideal agent for identifying more precisely the contribution of dopamine to preparatory
behaviours. For this reason, metoclopramide will be used exclusively throughout the remaining experiments of this dissertation.
WHAT MUST A RAT LEARN IN AVOIDANCE TRAINING IN ORDER TO BE PROTECTED FROM NEUROLEPTIC DRUG EFFECTS?

Both the performance and the acquisition of a wide range of avoidance behaviours can be disrupted by treatment with neuroleptic drugs. Most studies have used overtrained rats (Janssen et al., 1965, pretrained their rats for approximately 3000 multi-trial sessions before drug testing!) but testing has been conducted on naive animals as well. For example, acquisition of bar press avoidance was disrupted by chlorpromazine (Davidson & Weidley, 1976), and by haloperidol (Setler, Sarua, & McKenzie, 1976). Acquisition of one-way avoidance by rats has been disrupted by chlorpromazine (Posluns, 1962), haloperidol (Fibiger et al., 1975; Chapter 1), pimozide (Beninger et al., 1980a,b; Beninger et al., 1983), and metoclopramide (Chapter 1). Acquisition of a two-way response by mice was disrupted by pimozide (Anisman et al., 1982).

Despite the conspicuous ability of neuroleptic drugs to disrupt the performance of a previously acquired active avoidance response, there is strong evidence that they have a qualitatively greater effect on the acquisition of a new response: Simply showing a larger percentage decrease in responding among naive animals following administration of a given dose of drug could be an artefact of shifting a sharply rising acquisition curve to the right. However, several
studies have demonstrated that doses of neuroleptic drugs that can prevent acquisition of a new response over many days may have almost no effect on the performance of a previously acquired response (Anisman et al., 1982; Beninger et al., 1983; Carey & Kenney, 1987; Fibiger et al., 1975; Ray & Bivens, 1966). For example, in Experiment I.4 it was demonstrated that a dose of metoclopramide that limited avoidance to a mean of 0.2/10 responses on the third day of acquisition only decreased previously acquired responding from 9.8/10 successful responses on the third day of drug-free acquisition to 8.8/10 responses on the first drugged day.

Nonetheless, it is important to note that the performance of a previously acquired response may deteriorate over several sessions of neuroleptic testing (Hillegaart, Ahlenius, Magnusson, & Fowler, 1987; Niemegeers et al., 1969; Chapter 1). Beninger et al. (1983) observed progressive deterioration of previously acquired responding over repeated sessions of pimozide testing. The cumulative session-to-session disruption was reversed by interpolating two drug-free retraining sessions between each avoidance session with pimozide.

Acquisition of avoidance has also been studied following selective disruption of central dopamine neurotransmission by appropriate administration of 6-OHDA. The consistent outcome of all such studies has been the marked attenuation of acquisition of either one-way or two-way avoidance;
acquisition was abolished with more extreme levels of dopamine depletion (Cooper et al., 1973, 1974; Delacour et al., 1977; Fibiger et al., 1974; Heybach et al., 1978; Zis et al., 1974). Several studies have indicated that 6-OHDA lesions can also disrupt performance of a previously acquired response (Beer & Lenard, 1975; Cooper et al., 1973; Lenard & Beer, 1975; Neill et al., 1974). However, no deficit was observed when rats received extensive training prior to the lesion (Fibiger et al., 1975). As was the case with neuroleptic testing, when deficits have been observed following 6-OHDA lesions they have typically become more severe over successive test sessions (Beer & Lenard, 1975; Cooper et al., 1973; Lenard & Beer, 1975). This deterioration is not simply a function of progressive deterioration of dopamine neurons, as the effect is seen even when a delay is imposed between time of lesion and the onset of testing. If, however, the response is followed for an extended period of time there may be recovery (Beer & Lenard, 1975; Lenard & Beer, 1975). For these cases it has not been established whether the recovery is due to repeated testing or to neural compensation.

What is clear from both the pharmacological and the lesion studies is that if an animal has had sufficient avoidance training prior to disruption of dopamine neurotransmission, the impact of the treatment on performance is markedly attenuated. What is unclear is what constitutes sufficient training in this context.
Kimble and Perlmuter (1970) have suggested that when responses are well practiced they become "automatized", that is, they are automatically executed in the presence of the WS without regard to their consequences. It is conceivable that dopamine is involved in the production of "voluntary" responses, but is not required for an animal to execute such automatized responses.

Second, as reviewed in the Introduction, various theorists of avoidance responding have suggested that fear is required for the acquisition of avoidance responding, but may not be required for the maintenance of avoidance responding (Mineka, 1979; Seligman & Johnston, 1973). This is consistent with the finding that behavioural and physiological indices of fear may decline during extended avoidance training. Perhaps dopamine mediates fear, or the capacity for fear to effect responding. This hypothesis is related to a similar proposal that dopamine is involved in mediating reward, or the capacity for reward to effect behaviours (Beninger, 1988; Fibiger & Phillips, 1986; Phillips & Fibiger 1979; Wise, 1982, 1985).

These hypotheses, proposing that neuroleptics are ineffective against established avoidance responses because responding has become automatized or because fear has diminished, would be challenged by evidence that the disruptive effects of dopaminergic interference diminish before fear of the WS subsides.
Other potential roles for dopamine in the acquisition of avoidance responding have been excluded by earlier research. It has been clearly established that neuroleptic-treated animals are not deficient in associating the WS and the AS. Specifically, neuroleptic-treated rats that fail to avoid still show behavioural signs of fear during testing (Fibiger et al., 1975; Posluns, 1962). Further, if rats are trained in a drug-free state after having failed to acquire an avoidance response under the influence of a neuroleptic, they may show savings (Beninger et al., 1980b; Davidson & Weidley, 1976; Fibiger et al., 1975; Posluns, 1962; but see Beninger et al., 1980a). In fact, rats that fail to avoid while treated with neuroleptics can subsequently acquire an avoidance response or display other appropriate responses to shock-related stimuli even if no further shocks are presented (Beninger et al., 1980a,b; Beninger, MacLennan, & Pinel, 1980c). All these findings indicate that the rats must have learned the signal value of the WS even as they failed to acquire the avoidance response.

Further evidence that neuroleptic drugs do not interfere with the establishment of a WS-AS association comes from a study conducted by Anisman et al. (1982) who determined that (a) Pavlovian pairing of the WS and the AS prior to training facilitates the acquisition of avoidance responding, and that (b) when a dose of pimozide sufficient to block the acquisition of avoidance responding is administered at the time of WS-AS pairings it does not
disrupt the facilitatory effects of such pairings. Thus, neuroleptic drugs do not prevent the formation of a Pavlovian WS-AS association when administered during conditioning. On the other hand, Anisman et al. (1982) found, in an additional experiment, that if pimozide is administered at the time of avoidance training then no facilitatory effects of prior WS-AS pairings are observed. Apparently some process other than learning the WS-AS relationship must be disrupted on the acquisition day.

The experiments of Chapter 2 were aimed at identifying more precisely what the rats had to learn before neuroleptic drugs would not disrupt their performance of previously acquired avoidance responses. Characterizing the effects of neuroleptic drugs on avoidance acquisition more fully should rule out dopamine-dependence of certain factors that may be critical in avoidance response acquisition.

Experiment II.1 - Days of pretraining

Previous studies have examined the effects of various amounts of pretraining on the effects of haloperidol or pimozide on the performance of avoidance responding with inconsistent results. Fibiger et al. (1975) found that two days of pretraining did not prevent disruption of responding by 0.15 mg/kg haloperidol, although rats continued to perform flawlessly when given this dose after nine days of training. In contrast, Beninger et al. (1983) found protection from the effects of 0.5 or 1.0 mg/kg pimozide
following two days of training. This difference may be attributable to the very severe impact of 0.15 mg/kg haloperidol on avoidance acquisition. It would be interesting to determine the impact of low levels of pretraining on the effect of a dose of metoclopramide known to be sufficient to block acquisition, but which did not produce severe non-specific effects.

In addition to providing useful parametric data, the question of how little training is required to protect rats from the deleterious effects of neuroleptics is directly relevant to important theoretical issues discussed above. If protection from the disruptive effects of neuroleptics is observed within a few trials of the onset of training, it would appear implausible that the neuroleptics are ineffective because responding has become automatized or because fear has diminished.

As a first step toward determining the minimum amount of training rats need to become less susceptible to the effects of neuroleptic drugs, Experiment II.1 determined the effect of varying the numbers of days of pretraining on the impact of metoclopramide on avoidance.

Method

Subjects and apparatus: Subjects similar to those of Chapter 1 were used and were tested in the same apparatus.

Procedure: Rats were randomly assigned to one of four groups (n = 6 per group). Different groups received increasing numbers of daily drug-free sessions of avoidance
training in Phase A, each consisting of 10 trials, prior to three sessions in Phase B in which each received 5.0 mg/kg metoclopramide. Specifically, Group Zero received no days of pretraining, Group One received one day of pretraining, Group Two received two days of pretraining, and Group Three received three days of pretraining. Avoidance training was conducted in the same manner as in the experiments of Chapter 1, and metoclopramide was prepared and administered as in Experiment 1.4. Analysis of variance revealed that there were no differences between Groups One, Two, and Three on their respective first days of pretraining on either avoidance or latency scores ($F$s < 1).

**Statistical analysis:** The number of avoidances across the three days of metoclopramide testing in Phase B were analyzed using a two-way (Training x Day) ANOVA. Latency scores were analyzed with a three-way (Training x Day x Trial) ANOVA. In each case significant effects were further analyzed using Newman-Keul's post hoc test at a .05 level of significance.

**Results**

The number of avoidances are illustrated in the top panel of Figure 6. Over the three days of drug testing there was a marginally significant effect of Training [$F(3,20) = 2.75, p < .07$]. There was a significant main effect of Test Day [$F(2,40) = 5.60, p < .01$], and a significant Training x Day interaction [$F(6,40) = 4.84, p < .001$]. Post hoc tests indicated that on the first test day
Figure 6. Days of pretraining

Top panel indicates mean number of avoidances executed on each day. Bottom panel indicates mean response latencies. In Phase A groups were trained for zero to three days following saline injections. In Phase B all rats received 5.0 mg/kg metoclopramide on each test day.
DAYS OF PRETRAINING

Phase A.

Phase B.

Avoidance Responses

Response Latency

TEST DAY

1 2 3 4 5 6
(Day 4) Groups One, Two, and Three each avoided significantly more often than Group Zero, and that Group Three avoided significantly more often than Group One. On the second test day (Day 5) Group Two avoided more often than Group One. On the final test day there were no significant between-group differences. Looking across days, the number of avoidance responses in Phase B did not change significantly for Groups Zero, One, or Two. However, the performance of Group Three deteriorated through the course of Phase B: There were fewer avoidance responses on Days 5 and 6 than on Day 4.

Latency scores revealed further differences between groups in the drug tests (see bottom panel of Figure 6). There was a marginally significant effect of Training $[F(3,20) = 2.92, p < .06]$, a significant main effect of Test Day $[F(2,580) = 15.45, p < .001]$, and a significant Training x Day interaction $[F(6,580) = 7.47, p < .001]$. On the first drug day (Day 4) the latencies of each group differed from those of each other group. The latencies of Group Three were lowest, those of Group Two were next lowest, followed by those of Group One. Latencies of Group Zero were highest. On the second drug test day (Day 5) the latencies of Groups Two and Three were lowest, those of Groups Zero and One being higher. On Day 3 the latencies of Group Zero were again the highest. Looking across the days of Phase B, the latencies of Groups One and Three increased on Days 5
and 6, following the first drug test on Day 4, while the scores of Groups Zero and Two did not change across days.

**Discussion**

Considerable protection from the disruptive effects of metoclopramide was observed after only a single day of pretraining, and even greater protection was seen after two days of pretraining. A dose of metoclopramide that limited naive rats to 0.7/10 avoidance responses on Day 4 permitted rats with two days of pretraining to avoid 6.7/10 times. It is remarkable that after a single day of pretraining Group One was not only significantly superior to Group Zero, the rats of this group actually avoided more often on Day 4, while drugged, than they had while undrugged on Day 3 (4.2/10 vs. 1.7/10 avoidances). This result demonstrates that it was not necessary for rats to have achieved a substantial level of acquisition in order for the neuroleptic to have a substantially diminished impact on performance.

**Experiment II.2 - Effect of prior WS-AS pairings**

Acquisition of one-way avoidance responding has been reported to be facilitated by giving the animals WS-AS pairings prior to the commencement of training (De Toledo & Black, 1967). Acquisition of two-way avoidance may also be facilitated in this manner, though with less consistent results (Gallon, 1972; Overmier & Leaf, 1965; Weiss, Kriekhaus, & Conte, 1968). Anisman et al. (1982) found that
although prior WS-AS pairings could facilitate later acquisition of two-way responding by mice, such pairings were not in themselves sufficient to provide protection from the effects of neuroleptic treatment. Apparently Pavlovian association of the WS and the AS is a component of avoidance that an animal may use in the acquisition of avoidance responding, but this component is not in itself sufficient to permit avoidance responding to occur in the absence of dopaminergic neurotransmission, nor is it mediated by dopaminergic mechanisms. By instilling this association in rats prior to giving them avoidance training we might gain a more accurate view of the amount of avoidance training per se that the rats require before their performance will not be disrupted by neuroleptic treatment. By doing so, we improve our chances of isolating the dopamine-dependent component of avoidance acquisition.

Method

Subjects and apparatus: Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of testing, and were handled at least three times during that period. This procedure appeared to reduce the emotionality of the rats during handling and testing.

Avoidance training was conducted in the same apparatus as in the experiments described earlier. The pairings of tone and footshock were presented in a separate Plexiglas chamber, 26 cm x 30 cm x 40 cm high. The grid floor was
connected to the same shock generator as was the avoidance apparatus. The walls of this compartment were lined with brown shelf paper, making them translucent. A hinged Plexiglas ceiling remained transparent. A tone generator identical to that in the avoidance apparatus was centred 8 cm above the shock grid, and a 3.3 ca cue light (not used in this experiment) was mounted above the tone generator, near the top of the same wall, centred 37 cm above the grid.

Procedure: Rats were randomly assigned to one of four groups (n = 6 per group). The two Conditioned groups received 10 WS-AS pairings in the Plexiglas conditioning chamber. Each pairing consisted of a 10 s presentation of the tone, followed by a 1.5 s, 1.0 mA footshock. Two Control groups were simply put in the conditioning compartment and then removed. On the next day, all four groups received five avoidance training trials using the procedure described in Chapter 1. On these training trials the rats that had received the WS-AS pairings tended to avoid more often than those that had not (1.5/5 vs. 0.9/5 avoidances; p < .09). There were no differences between the groups that received metoclopramide or saline on the test day.

On the Test day, the third day, one Conditioned group and one Control group received 5.0 mg/kg metoclopramide 60 - 90 min prior to training, while the other Conditioned group and the other Control group received saline. All rats were tested for ten avoidance trials.
Statistical analysis: The data were analyzed using a two-way (Drug treatment x Conditioning) ANOVA. Latency scores were analyzed with a three-way (Drug x Conditioning x Trial) ANOVA. In each case significant effects were further analyzed using Newman-Keul's post hoc test at a .05 level of significance.

Results

Those rats that received saline performed very well on the test day regardless of whether or not tone-shock pairings had been administered prior to training. Of those rats that were injected with metoclopramide, those that had not received tone-shock pairings showed disruption of performance relative to saline controls. However, those rats that had received tone-shock pairings prior to training performed well during avoidance testing despite injection of the neuroleptic (compare Group Conditioned-Met to Group Control-Met).

Examination of the number of avoidance responses (see top panel of Figure 7) indicated that there was a significant effect of Drug [$F(1,20) = 19.10, p < .001$], a significant effect of prior Conditioning [$F(1,20) = 7.62, p < .05$], and a significant Drug x Conditioning interaction [$F(1,20) = 6.40, p < .05$]. Post hoc tests indicated that the Control group receiving metoclopramide avoided less frequently than any other group. There were no other significant between-group differences.
Figure 7. Effect of prior WS-AS conditioning

Top panel indicates mean number of avoidances on the test day. Bottom panel indicates mean response latencies. On Day 1 Conditioned Groups received 10 non-contingent pairings of tone and shock, while Control Groups did not. On Day 2 all groups received 5 avoidance training trials. On the test day all rats were tested for 10 trials. On the test day Met Groups received 5.0 mg/kg metoclopramide, and Sal Groups received saline.
EFFECT OF PRIOR WS-AS CONDITIONING

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control  Conditioned

SAL  MET
Analysis of the latency scores revealed a similar pattern of results (see bottom panel of Figure 7). There was a significant effect of Drug \[F(1,20) = 21.99, p < .001\], but not a significant effect of Conditioning \[F(1,20) = 2.41, p > .1\]. The Drug x Conditioning interaction was marginally significant \[F(1,20) = 4.27, p < .051\]. The post hoc tests indicated that Group Control-Sal had shorter avoidance latencies than did Group Control-Met, whereas there was no difference between the scores of the two Conditioned groups.

**Discussion**

These results confirm the finding of Anisman et al. (1982) that prior WS-AS pairings increased the amount of protection from the effects of neuroleptic drugs that animals receive from a small amount of avoidance training. Metoclopramide-treated rats that received only five avoidance training trials following a prior conditioning session consisting of 10 WS-AS pairings were able to execute almost twice as many avoidance responses as similarly drugged rats that had not received such pairings prior to the training session (8.2/10 vs. 4.3/10 successful avoidance responses).\(^1\) Unlike the study by Anisman et al., the present experiment does not determine whether such WS-AS

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1. The performance of the rats in several groups, particularly those in Group Conditioned-Met, are higher than may have been predicted from the results of Experiment II.1. This may be a result of the handling the rats received prior to conditioning or to other extraneous factors. These differences highlight the danger of drawing strong comparisons between the results of groups from different experiments.
pairings are sufficient for providing protection from neuroleptic effects, although Experiment II.5 shall confirm that they are not.

Together with the results of Experiment II.1, these results argue strongly against the notion that the protection from metoclopramide effects observed in Experiment 1.4 after three days of training was the result of overlearning through extensive response repetition. Indeed, the rats of Group Conditioned-Met managed only an average of 1.7 avoidance responses on the training day. One rat of this group avoided on every test trial despite having avoided only once on the training day. The ability of rats to become capable of withstanding neuroleptic effects in so few trials suggests that, rather than becoming a habit through incremental learning, the avoidance response is a problem that the rats have solved.

Experiment II.3 - Safety conditioning

During one-way avoidance training, an animal may learn not only that the location where the shock is to be delivered is to be avoided, but also that the alternative location is a safe place to be. Within the framework of incentive-motivation theory (e.g., Bindra, 1968; Bolles, 1972b; Toates, 1986), avoidance can thus be seen as approach to a place with acquired incentive value. The validity of this interpretation is supported by evidence that feedback cues potentiate avoidance acquisition (Bolles & Grossen,
If neuroleptic drugs interfere with learning the incentive value of cues, then such treatment could disrupt acquisition of avoidance responding. This interpretation is consistent with the hypothesis that central dopamine systems mediate incentive motivation (Blackburn et al., 1987, 1989a; Crow, 1973; Fibiger & Phillips, 1986; Mogenson & Phillips, 1976). If this is the case, then conditioning rats to associate the safe side of the box with the termination of shock should be sufficient to provide protection from the effects of metoclopramide.

An additional effect of pairing shock offset with salient cues is that fear of the WS is diminished, relative to levels in rats that do not receive such feedback (Cook et al., 1987; Mineka et al., 1984; Weisman & Litner, 1972). If dopamine blockade interfered with emotional processing of fear-related stimuli, while permitting information processing to continue, then performance could actually deteriorate as a result of such safety conditioning.

These hypotheses were tested in the following two experiments.

**Method**

**Subjects and apparatus:** Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of testing, and were handled at least three times during that
period. For this experiment an additional 3.3 cm cue light was mounted in the safe side of the box, at the top of the wall opposite the guillotine door leading to the shock side.

**Procedure:** Rats were randomly assigned to one of four groups. Each group of rats received 10 non-contingent WS-AS pairings in the shock side of the avoidance apparatus. Immediately following each WS-AS pairing the rats of the two "Safety" learning groups were removed manually to the safe side of the box. Beginning 3 s after shock termination the cue light in the safe side of the box was illuminated until 5 s before the onset of the next trial. This procedure was designed to give the non-shock side of the avoidance apparatus equal status as a safety signal as it would normally acquire in 10 escape trials. The cue light onset would have provided an additional salient safety signal towards which the rats could direct avoidance responses on the test day. Light onset paired with shock offset has previously been demonstrated to act as an efficient inhibitor of fear (Jacobs & LoLordo, 1980; Weisman & Litner, 1972).

The rats of the two Control groups were transferred manually to a Plexiglas carrying cage immediately after receiving the aversive footshock. This procedure gave all rats equal exposure to post-shock handling, and might have established either the handling or the Plexiglas compartment as a safety signal, but it would not have provided the
control rats with a cue towards which they could direct their responses on the test day.

On the test day rats of Group "Safety"-Met and Group Control-Met (each \( n = 8 \)) received 5.0 mg/kg metoclopramide, while rats of Groups "Safety"-Sal and Control-Sal (each \( n = 7 \)) received saline. On each trial illumination of the light in the safe side of the box was contiguous with onset of the WS. The cue light was extinguished 5 s prior to the start of the next trial.

**Statistical analysis:** The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment II.2.

**Results**

The performance of all groups was surprisingly uniform. Even the control group that received metoclopramide performed reasonably well on the test day. However, the experiment affords no evidence that putting the "Safety"-Met group into the safe side at the outset of the intertrial interval enhanced protection from metoclopramide's effects. The number of avoidances are shown in the top panel of Figure 8. The ANOVA indicated that there was a marginally significant effect of Drug \( [F(1,26) = 3.76, p < .07] \), no significant effect of Conditioning \( [F(1,26) = 1.12, p > .20] \), and no significant Drug x Conditioning interaction \( (F < 1) \).

The latency scores are shown in the bottom panel of Figure 8. The ANOVA indicated that there was a significant
Figure 8. Effect of "safety" conditioning

Top panel indicates mean number of avoidances executed on the test day. Bottom panel indicates mean response latencies. All groups initially received 10 non-contingent pairings of tone and shock in the shock side of the avoidance apparatus on the conditioning day. "Safety" Groups were placed in the safe side of the box and were presented with a cue light following each shock offset, while Control Groups were placed in a Plexiglas carrying cage. On the following day Met Groups were tested following administration of 5.0 mg/kg metoclopramide, while "Safety" Groups received saline.
EFFECT OF "SAFETY" CONDITIONING

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control  "Safety"

SAL MET
main effect of Drug \([F(1, 26) = 10.87, \ p < .01]\), but no significant effect of Conditioning \((F < 1)\), and no significant Drug \(\times\) Conditioning interaction \((F < 1)\).

**Discussion**

The results of this experiment failed to support the hypothesis that safety conditioning would enhance avoidance performance and would provide protection from the impact of metoclopramide on avoidance acquisition. In neither the case of undrugged or metoclopramide-treated rats did pairing shock-termination with placement into the safe side of the apparatus and exposure to the cue light enhance subsequent entry into the safe side, toward the illuminated cue light. This is consistent with the assertion of Bolles (1975) that one-way avoidance is learned too rapidly for safety learning to play a significant role in its acquisition.

Interpretation of this finding is complicated by the surprisingly good performance by the rats of the control groups, for whom shock termination was paired with placement into a neutral Plexiglas carrying cage that was not present on the test day. It is conceivable that the safety and control groups did not differ because the critical factor in the safety treatment was the pairing of shock termination with handling and removal from the shock side of the avoidance apparatus. Such treatment may have been sufficient to decrease fear conditioning to the WS and the shock side of the box, somehow leading to enhanced performance on the test day. Although intriguing, this
hypothesis is impossible to evaluate in the absence of a control group that received no shock termination-handling pairings. In the absence of such a control, it is equally reasonable to suggest that the surprisingly high level of performance by the rats not receiving safety conditioning was due to some unidentified extraneous factor. As a result, such a control was incorporated into the design of Experiment II.4.

Experiment II.4 - Amount of safety conditioning

The failure to see a significant enhancement of performance as a result of safety conditioning in the previous experiment could conceivably be a result of the use of an insufficient number of pairings. Accordingly, in the present experiment one group was tested after having received 20 pairings of shock termination and the safety cues over two days, in addition to groups receiving treatment identical to that of Groups "Safety"-Met and "Safety"-Sal from the previous experiment. The previous experiment also failed to compare the effects of such safety conditioning to a control condition in which rats did not receive pairings of shock termination and handling. Such a control was present in this experiment.

Method

Subjects and apparatus: Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of
testing, and were handled at least three times during that period.

**Procedure:** Rats were randomly assigned to one of four groups (n = 6 per group). On a first day of treatment, rats of each group were allowed to explore the avoidance apparatus with the guillotine door removed for 10 min. Subsequently, two groups of rats (10+Sal and 10+Met) each received 10 non-contingent WS-AS pairings in the shock side of the avoidance apparatus. Each shock termination was followed immediately by manual placement in the safe side of the avoidance apparatus and the onset of the safety light, as described in Experiment II.3. Thus, treatment of these two groups was equivalent to that of Groups "Safety"-Met and "Safety"-Sal from the previous experiment. Rats of a third group (0+Met) did not receive any pairings of the WS and the AS on this day, and remained in their home cages. Rats of a fourth group (20+Met) received 20 pairings of shock offset and safety signal over two days of conditioning prior to testing. On the test day, rats of the control group (0+Met), one of the 10 safety pairing groups (10+Met), and of the 20 pairing group (20+Met) each received an injection of 5.0 mg/kg metoclopramide. The other 10 safety pairing group (10+Sal) was administered saline.

**Statistical analysis:** The number of avoidances were analyzed using a one-way (Group) ANOVA. Latency scores were analyzed with a two-way (Group x Trial) ANOVA. In each case
significant effects were further analyzed using Newman-Keul's post hoc test at a .05 level of significance.

Results

In this experiment, a minimal amount of protection was observed following 10 safety conditioning trials, and no additional amount of protection was observed following 20 trials. The number of avoidances are shown in the top panel of Figure 9. The ANOVA indicated that there was a significant effect of Group \([F(3,20) = 8.58, p < .001]\). The post hoc test revealed that the 10+Sal group avoided more often than any group that received metoclopramide. There were no significant differences between the three metoclopramide groups.

Similar effects are observed in analysis of the latency scores (see bottom panel of Figure 9). There was a significant effect of Group \([F(3,20) = 10.52, p < .001]\). The post hoc test indicated that Group 10-Sal had shorter latencies than any of the three groups that received metoclopramide, which did not differ between themselves.

Discussion

As was the case in Experiment II.3, the present experiment failed to provide any evidence that pairing shock termination with the safe side of the compartment facilitated the development of protection from the disruptive effects of metoclopramide treatment. This was the case even though the safe compartment should have been readily distinguished on the basis of the cue light, and
Figure 9. 10 or 20 "safety" trials

Top panel indicates mean number of avoidances executed on the test day. Bottom panel indicates mean response latencies. Group 10+Sal and Group 10+Met received one conditioning session of 10 safety pairings, Group Safe+20 received two. Group 0+Met was placed in the shock side but received no other programmed events. Safety pairings consisted of non-contingent pairings of tone and shock in the shock side of the avoidance apparatus followed by placement of the rat in the safe side of the box and presentation of the cue light. On the test day Group 10+Sal received saline, while all other groups received 5.0 mg/kg metoclopramide.
10 or 20 "SAFETY" CONDITIONING TRIALS

Avoidance Responses

Response Latency

0+Met 10+Sal 10+Met 20+Met
Chapter II  

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despite the presence of the cue light as an additional salient safety cue. In contrast, in Experiment II.2 rats showed substantial protection from metoclopramide effects after only 10 tone-shock pairings and five avoidance training trials. This was less exposure to the tone-shock contingency, and substantially less exposure to the shock offset-safe compartment contingency than that obtained by Group 20+Met in the present experiment. In light of these findings it seems unlikely that learning of the incentive value of the safety cues could be the critical factor involved in obtaining protection from metoclopramide effects.

Experiment II.5 - Avoidance versus escape training

One curious observation made during the course of Experiment II.2 was that some rats were capable of avoiding on the test day despite the administration of metoclopramide even though they had executed as few as a single avoidance response on the avoidance acquisition day. This effect, if real, would exclude the possibility that protection from neuroleptic effects is due to the avoidance response becoming automatized through extensive overtraining. Nor could such protection be attributed to the incremental establishment of a neuroleptic-resistant expectation that the avoidance responses results in no shock being administered. Such an effect would also seem to exclude the possibility that neuroleptics disrupt acquisition of
avoidance responding by preventing the generalization of an escape response to an avoidance situation. In order to see if rats needed to avoid during WS presentation in order to acquire protection from metoclopramide effects, in Experiment II.5 rats receiving standard avoidance training were compared to rats for whom responding was prevented during WS presentation. Prior experience with escapable shock in the avoidance apparatus has previously been shown to enhance subsequent avoidance learning (De Teledo & Black, 1967; Radlow, 1958).

Method

*Subjects and apparatus:* Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of testing, and were handled at least three times during that period. Avoidance and escape were conducted in the standard avoidance apparatus, and the tone-shock pairings were administered in the Plexiglas boxes described in Experiment II.2.

*Procedure:* Rats were randomly assigned to one of six groups (n = 6 per group). On the first day each group of rats received 10 non-contingent tone-shock pairings in the Plexiglas compartment, as described in Experiment II.2. On the next day, the training day, the two Control groups received no treatment. The Avoidance groups both received five standard avoidance training trials. The number of avoidances and the response latencies did not differ between
these two groups ($F_s < 1$). The Escape Groups both received five training trials which were similar to avoidance trials in all respects except that the guillotine door remained shut during WS presentation, preventing avoidance. The door was only opened at the onset of the AS. The mean latency to escape following shock onset was 3.1 s for Group Escape-Sal and 3.5 s for Group Escape-Met ($F < 1$). On the test day (the third day) one of each pair of groups received saline, the other 5.0 mg/kg metoclopramide.

**Statistical analysis:** The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment II.2.

**Results**

The rats receiving prior avoidance training were able to avoid on the test day despite metoclopramide treatment, whereas those who received no prior training were not. Importantly, those receiving escape training were as good or better than those receiving avoidance training. The number of avoidance responses performed by each group are illustrated in the top panel of Figure 10. There was a significant effect of Training [$F(2,30) = 62.01, p < .001$], a significant effect of Drug [$F(1,30) = 20.19, p < .001$], and a significant Training x Drug interaction [$F(2,30) = 3.78, p < .05$]. The post hoc tests revealed that only in the case of the Control groups was the performance of the metoclopramide-treated group significantly worse than that of the saline-treated group. Following avoidance or escape
Figure 10. Avoidance or escape pretraining

Top panel indicates mean number of avoidances on the test day. Bottom panel indicates mean response latencies. Rats of all groups received 10 non-contingent pairings of tone and shock, while Control Groups did not. On the day prior to training Avoidance Groups received 5 avoidance training trials, Escape Groups received 5 escape training trials, and Control Groups were not trained. On the test day all rats were tested for 10 trials. Met Groups received 5.0 mg/kg metoclopramide while Sal Groups received saline.
AVOIDANCE OR ESCAPE PRETRAINING

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control  Avoidance  Escape

SAL  MET
training, rats were protected from the avoidance-disrupting effects of metoclopramide. A comparison of the performance of the two saline-treated groups revealed that naive rats displayed fewer avoidances than those that had received prior avoidance or escape pretraining.

The latency scores, illustrated in the bottom panel of Figure 10, reveal a similar pattern of results. However, in this case the effects can be attributed to significant main effects of Training \( [F(2,30) = 34.28, \ p < .001] \) and Drug \( [F(1,30) = 15.41, \ p < .001] \). There was no significant Training x Drug interaction \( (F < 1) \). It is interesting to note that post hoc examination of the Training effect revealed that those rats receiving escape training had shorter response latencies on the test day than rats that had received prior avoidance training.

**Discussion**

The results of this experiment indicate that rats can acquire the capacity to perform an avoidance response despite metoclopramide treatment in the absence of any prior opportunity to execute an avoidance response. Execution of five escape responses in the same apparatus, using the same WS, had an identical effect to that observed when rats were able to make avoidance responses. This is an important finding, as it rules out several possible hypotheses concerning the origin of the protection from neuroleptic effects. First, it excludes the possibility that the avoidance response becomes insensitive to neuroleptic
effects through overtraining of the avoidance response per se: Avoiding prior to shock onset was a novel response for the rats in Group Escape-Met on the test day. Second, the animals could not have had incrementally-established expectations that performing the avoidance response prior to shock onset would result in the non-occurrence of shock. This suggests that dopamine is interacting with cognitive mechanisms, as opposed to response reinforcement mechanisms, in the establishment of behaviour. Third, because the rats had only ever escaped from shock, dopamine blockade could not have disrupted the generalization of the escape response into an avoidance response.

In addition to the important comparison between the performance of rats that had previously received escape or avoidance pretraining, this experiment also indicates, in agreement with Anisman et al. (1982) that providing rats with 10 WS-AS pairings is not sufficient to provide protection from neuroleptic effects. Group Control-Met had received 10 such pairings, but unlike group Avoidance-Met it did not receive additional avoidance training prior to the test day. On the test day, the performance of Group Control-Met was substantially and significantly worse than that of Group Avoidance-Met (1.7 vs. 7.8 avoidance responses).
Experiment II.6 - Escape training following metoclopramide

It is apparent from Experiment II.5 that critical information regarding the avoidance task may be acquired during escape trials if dopamine function is normal, and that once this information is encoded it can subsequently influence the performance of rats treated with dopamine antagonists. If this is the case then metoclopramide treatment during escape training should attenuate the protective effects of training against disruption of avoidance acquisition by a neuroleptic. This hypothesis was tested in Experiment II.6.

Subjects and apparatus: Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of testing, and were handled at least three times during that period. Tone-shock pairings were presented in the same boxes as in Experiment II.2.

Procedure: Rats were randomly assigned to one of three groups (n = 8 per group). On the first day rats of each group received 10 non-contingent WS-AS pairings in the Plexiglas compartment, as described in Experiment II.2. On the next day the Control group received no treatment, whereas Groups Esc-Sal and Esc-Met received five escape training trials, as described in Experiment II.5. For Group Esc-Sal this escape training occurred following administration of saline, whereas for Group Esc-Met training occurred following administration of 5.0 mg/kg
metoclopramide. The escape latencies for these two groups did not differ on the training day ($F < 1$). On the test day (the third day) the rats of each group received 5.0 mg/kg metoclopramide and were tested for 10 avoidance trials.

**Statistical analysis:** The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment II.4.

**Results**

The rats receiving escape training following saline administration (Esc-Sal) were able to avoid successfully on the test day despite administration of metoclopramide. This replicates the major finding of Experiment II.5. However, rats that received identical escape training following metoclopramide administration (Group Esc-Met) were not protected from the effects of metoclopramide on the following day. The number of avoidances executed by these two groups, as well as by the control group that received no escape training, are illustrated in the top panel of Figure 11. The ANOVA indicated that there was a significant difference between the number of avoidance responses executed by rats of the three groups [$F(2,21) = 23.47, p < .001$]. Post hoc testing revealed that the group that received escape training following saline (Group Esc-Sal) avoided significantly more often than the other two groups on the test day.

The latency scores are shown in the bottom panel of Figure 11. Again, there was a significant effect of Group
Figure 11. Escape pretraining with metoclopramide

Top panel indicates mean number of avoidances on the test day. Bottom panel indicates mean response latencies. Rats of all groups initially received 10 non-contingent pairings of tone and shock. On the day prior to testing Group Cont-Sal was not trained and Esc Groups received 5 escape training trials. Group Esc-Met received 5.0 mg/kg metoclopramide, and Group Esc-Sal received saline on this day. On the test day all rats received 5.0 mg/kg metoclopramide.
ESCAPE PRETRAINING WITH METOCLOPRAMIDE

AVOIDANCE RESPONSES

RESPONSE LATENCY

Cont-Sal  Esc-Sal  Esc-Met
Post hoc tests indicated that the group trained under saline (Group Esc-Sal) had lower latencies than either of the other two groups.

**Discussion**

The performance of Group Esc-Met in this experiment confirmed the major finding of Experiment II.5, specifically that five escape trials were sufficient training to provide protection from the disruptive effects of metoclopramide on the performance of avoidance behaviours. In addition, they extend the previous findings to demonstrate that such escape training is not effective when given to neuroleptic-treated rats.

This latter finding is consistent with the finding that metoclopramide-treated rats are incapable of acquiring an avoidance response over several days of training (Experiment I.4). In each case the rats are exposed to the same warning and aversive stimuli, in each case they exit from the compartment after the onset of the shock. And in each case they experience these events under the influence of metoclopramide. What remains surprising is the ability of neuroleptic-treated rats to avoid on the day following escape training if they were not given metoclopramide prior to these trials. The two groups receiving escape training were exposed to identical experimental contingencies, and their responses were indistinguishable during the training trials. Yet on the test day only Group Esc-Sal was able to benefit from the experience of the training day.
It is conceivable that a critical factor for this outcome was the long delay between tone presentations and shock onset on escape training trials. The rats may have been attempting to avoid during this period, even though they were unable to enter the safe compartment because of the closed guillotine door. Experiment II.7 was conducted to exclude this possibility.

Experiment II.7 - Unsignalled escape training

Although the rats receiving escape training in the previous two experiments were unable to avoid shock, they were exposed to the WS for the standard 10 s period. It was noted that over the five training trials the rats typically came to stand by the closed guillotine door, sniffing and clawing at it. That is, they appeared to be attempting to avoid, even though they could not. Perhaps subsequent reinforcement of these attempts when escape ultimately occurred was the critical component of the procedure which required dopaminergic mediation. Accordingly, an additional experiment examined the effect of pretraining escape responses when no WS was present, and when the rats would not have time to orient to the door prior to shock onset.

Method

Subjects and apparatus: Subjects similar to those of previous experiments were used. All rats were housed in single cages at least one week prior to the beginning of testing, and were handled at least three times during that
period. Tone-shock pairings were presented in the same boxes as in Experiment II.2.

Procedure: Rats were randomly assigned to one of three groups (n = 6 per group). As described for Experiment II.6, each group of rats each received 10 non-contingent WS-AS pairings in the Plexiglas compartment on the first day of the experiment. On the next day Group Cont-Sal received no treatment, whereas Groups Esc-Sal and Esc-Met received five escape training trials. In the present experiment the escape training procedure was modified to limit the opportunity of the rats to perform any response prior to shock onset. First, the WS (tone) was not presented at all on the escape training day. Second, the interval between placing the rat in the shock side of the compartment and the onset of shock was reduced from 10 s to 1 s. As in Experiments II.5 and II.6, shock onset was synchronous with the opening of the guillotine door. Those rats that received saline prior to escape training (Group Esc-Sal) had a mean response latency of 2.1 s, those that received metoclopramide (Group Esc-Met) had a mean latency of 3.3 s [F(1,10) = 5.64, p < .05]. On the test day all rats received 5.0 mg/kg metoclopramide and were tested for 10 standard avoidance trials.

Statistical analysis: The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment II.4.
Results

As shown in the top portion of Figure 12, rats that had received the reduced form of escape training while undrugged were able to avoid on 7.3/10 trials on the test day despite metoclopramide treatment. In contrast, those that received the escape training under the influence of metoclopramide were only able to avoid 1.5/10 times, no more than untrained controls (1.5/10 trials).

The ANOVA indicated that there was a significant difference between the number of avoidance responses executed by rats of the three groups on the test day as a function of their training \[F(2,15) = 12.71, p < .001\]. Post hoc tests revealed that the group that received escape training following metoclopramide treatment avoided significantly more often than either of the other two groups.

The latency scores are shown in the bottom panel of Figure 12. Again, there was a significant effect of Training \[F(2,15) = 7.26, p < .01\]. Post hoc tests indicated that the group trained under saline (Group Esc-Sal) had lower response latencies than the other two groups.

Discussion

Once again, as in Experiment II.6, we observe that if rats are trained for five escape trials prior to being tested on avoidance, they show remarkable resilience to the effects of metoclopramide treatment, but only if they received the escape training in the absence of the drug. If
Figure 12. Escape pretraining without WS

Top panel indicates mean number of avoidances on the test day. Bottom panel indicates mean response latencies. Rats of all groups initially received 10 non-contingent pairings of tone and shock. On the day prior to testing Group Cont-Sal was not trained and Esc Groups received 5 escape training trials with the WS absent, and a delay of only 1 s between placement in the shock side of the box and shock onset. On the training day Group Esc-Met received 5.0 mg/kg metoclopramide, and Group Esc-Sal received saline. On the test day all rats received 5.0 mg/kg metoclopramide.
ESCAPE PRETRAINING WITHOUT WS

Avoidance Responses

Response Latency

Cont-Sal  Esc-Sal  Esc-Met
rats receive identical training in a session where they have been administered metoclopramide their performance is indistinguishable from that of rats who have received no prior training.

In this case, escape training amounted to little more than dumping the rats into the shock side of the compartment, turning on the shock, and letting them run out again. Yet something that happened during those five trials gave the rats the knowledge or experience they needed to perform avoidance responses while drugged on the following day.

Discussion of Chapter II

The experiments in this chapter demonstrate just how little training is required to attenuate the effects of metoclopramide on avoidance behaviour dramatically. Following administration of metoclopramide a rat with no prior training will not respond to the WS by avoiding. It remains in the compartment until the shock comes on and elicits an escape response. In contrast, rats that have executed as few as five escape responses, even in the absence of the stimulus that normally signals shock, are subsequently able to initiate avoidance responses successfully despite administration of the same dose of metoclopramide.

The results of Experiments II.6 and II.7 indicate that the animals are failing to learn something while drugged. After all, the escape groups in those experiments were treated identically on the test day, and on the training day
the only difference in the treatment of the two groups was that one received metoclopramide while the other received saline. Yet the performance of the two groups differed markedly during the test, when they were treated identically.

Although this suggests that the metoclopramide produces a learning deficit, the drugged rats do not seem unaware of where to go. They can, after all, perform successful escape responses reliably and with short latencies. Similarly, neither neuroleptic-treatment nor 6-OHDA lesions of the substantia nigra disrupt the ability of rodents to learn the appropriate cues towards which they should direct responses in a discriminated escape procedure (Corradini, Tombaugh, & Anisman, 1984; Price & Fibiger, 1975; but see Ranje & Ungerstedt, 1977). Yet this knowledge is not sufficient to allow them to execute the response while drugged. Indeed, conditioning them on the association between shock termination and the place where they are supposed to go does nothing to enhance their subsequent ability to avoid. It may further be argued that neuroleptic treatment is unlikely to disrupt avoidance acquisition by preventing learning of the incentive value of safety cues on the grounds that safety learning typically takes dozens or hundreds of trials, not five as in several experiments here.

There is a variant of the incentive learning deficit that is not ruled out by the results of Experiments II.3 and II.4. This is Beninger's recent proposal that dopamine is involved in transferring the incentive motivational
properties of the reward to the safety related signal.
According to Beninger (1989) "animals can learn where safety
is but cannot learn to go there when dopaminergic
neurotransmission is blocked" (p. 275).

Although this formulation contradicts the assertion of
Bolles (1975) that safety learning is not necessary for one-
way avoidance acquisition, Beninger's hypothesis is not
refuted by the observation that escape training is sufficient
to establish avoidance responding only if it occurs when
animals are undrugged. However, the assertion that the
effects of dopaminergic blockade are primarily on learning,
rather than performance (Beninger, 1988, 1989), does
contradict the finding that well-acquired appetitive
preparatory responses are disrupted by an initial
administration of neuroleptic (Blackburn et al., 1987,
1989b). Either Beninger's analysis applies only to defensive
behaviours, or else we must also look for effects of
neuroleptics on performance.

If the metoclopramide-treated rats are leaving the
escape training session with deficient knowledge, perhaps the
failure is in response learning, as opposed to stimulus
learning (see Bolles, 1978). Even a retardation of learning
could have had disruptive effects in this situation where
rats had only five learning trials. It is still possible,
following Experiment II.7, to argue that the escape responses
emitted by the drugged and undrugged rats were not the same
responses, given the differences in response latencies
between the two groups during training. It might be argued that the saline-treated rats had the opportunity to associate a voluntary response with safety, but that the escape responses of drugged rats were involuntary, and thus they could not acquire this association. It is difficult to see what advantage that kind of analysis provides us with.

Perhaps we are approaching this question from the wrong direction. Instead of asking why drugged rats do not execute avoidance responses when the WS is presented, perhaps we should ask how in fact they do respond to the WS. In order to do this we shall leave avoidance responding for a while and take a closer look at how metoclopramide-treated rats do in fact respond to shock and to shock-related stimuli. We shall return to avoidance in Chapter 4 with this newly acquired knowledge.
III

DO NEUROLEPTIC DRUGS ALTER CONSUMMATORY DEFENSIVE REACTIONS?

In examination of the effects of neuroleptic drugs on appetitive behaviour it was possible to dissociate profound disruption of preparatory responding from minimal disruption of consummatory feeding behaviour. This has been established for metoclopramide (Blackburn et al., 1989b) as well as for pimozide (Blackburn et al., 1987). Similarly, in the case of defensive behaviour it has often been reported that neuroleptic drugs can block preparatory avoidance responses at doses that do not disrupt consummatory escape responses. Studies of the effects of neuroleptics on other consummatory defensive responses to conditional or unconditional fear-related stimuli have been negligible.

One of the primary responses of rodents to fear-related stimuli is freezing. Freezing was described by Konorski (1967) as a "passive fear reflex" of small animals that are subject to predation. A similar notion is conveyed in the description of freezing as a species-specific defense reaction, or SSDR (Bolles, 1970, 1975; Masterson & Crawford, 1982). In both cases the suggestion is that freezing is an adaptive response that has evolved to limit the visibility of animals to nearby predators. This hypothesis is supported by findings that freezing is reliably elicited in rats by the presence of a threatening predator. Blanchard, Mast, and Blanchard (1975) have shown that the presence of a moving dog
or cat can rapidly induce virtually complete immobility. Even the movement of an otherwise neutral stimulus (i.e., a circular white card) elicits substantial freezing behaviour.

Freezing can be reliably elicited by shock. Even a single 1-s, 1.3 mA footshock can increase levels of freezing (or "crouching") over a 3-hr period (Blanchard, Dielman, & Blanchard, 1968),¹ and the amount of freezing is an increasing monotonic function of shock intensity (Blanchard & Blanchard, 1969a; Fanselow & Bolles, 1979).

The following experiments examined the effect of metoclopramide on the freezing reactions of rats. Experiment III.1 examines the reactions of rats following footshocks, and Experiment III.2 extends this study to freezing elicited by conditional stimuli paired with shock.

Experiment III.1 - Shock-induced freezing

Freezing has been identified as a response by rats to a single footshock (e.g. Blanchard et al., 1968; Blanchard & Blanchard, 1969a; Blanchard, Fukunaga, & Blanchard, 1976; Fanselow, 1980; Fanselow & Bolles, 1979), as well as after a

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¹ "Crouching", as defined by Blanchard & Blanchard, 1969a, is not identical to "freezing", as defined by Bolles & Collier (1976), Fanselow (1980), or in the experiments presented below. It is a more inclusive term that includes periods designated as "inactivity" by Bolles & Collier and here. Although this results in considerably higher baseline levels of "crouching" than "freezing", it appears that the two definitions lead to similar experimental findings.
series of shocks (Blanchard & Blanchard, 1969a; Bolles & Riley, 1973; Fanselow & Bolles, 1979). The present study examined the freezing responses of rats after they had received 1, 2, and a series of 7 footshocks.

Method

Subjects and apparatus: Subjects similar to those of the experiments of Chapters I and II were used. All testing was conducted in the Plexiglas shock compartment described in Experiment II.2. The brown shelf paper was removed from one wall to permit viewing of the rats. A video camera, stationed approximately 50 cm from the Plexiglas compartment, recorded the behaviour of the rats during test sessions. A title generator affixed to the video camera presented trial time to an accuracy of 0.1 s.

Procedure: Rats were assigned randomly to one of two groups (n = 7 per group). Rats of Group Sal were administered saline, rats of Group Met were administered 5.0 mg/kg metoclopramide. Sixty to ninety minutes after injection, a single rat was placed in the Plexiglas compartment. No shocks or other events occurred in the first 10 min that the rat was in the compartment. At the end of this habituation period the rat received a 1.0-s, 1.0-mA footshock. A second shock was presented 2 min after the first. A series of five additional shocks began 2 min after the second, on a variable-time (VT) 60 s schedule. Rats remained in the compartment for 40 min following the final shock.
Reactions to shock were scored from the videotape using a time sampling technique adapted from Bolles and Collier (1976). The experimenter scored rat behaviours (a) in a baseline period comprising the two minutes prior to the first shock, (b) in the two minutes following the first shock, (c) in the two minutes following the second shock, and (d) in the two minutes after the rat had experienced the final shock. Every 5 s, timed from shock onset (or from 2 min prior to the first shock), the behaviour of the rat was classified into one of four exhaustive categories: Freezing (immobile except for breathing and movements related to heartbeat, typically accompanied by conspicuous muscle rigidity and laying back of the ears), Active (locomoting, moving the body axis or limbs, or sniffing accompanied by head movements), Grooming (stereotyped face washing or self-directed oral actions), or Inactive (absence of marked body axis or head movements, but presence of sniffing or oral activity, with the ears in their normal, upright position. Transitory periods of immobility between actions were classified as Inactive.)

Data analysis: Only the freezing responses were analyzed statistically. In order to maximize the relevance of the analysis to the reactions of rats to shock during avoidance training the analysis was restricted to responses of the rats beginning 30 s after the onset of each of the four 2-min periods and for the 1 min thereafter, even though behaviour was scored over the entire 2-min period. The
pattern of results was substantially the same during this middle minute as it was over the entire 2-min period.

The number of freezing scores the rats received during the periods before the first shock (baseline), after the first shock, after the second shock, and after the final shock were analyzed using a two-way (Group x Period) ANOVA. Significant effects were further examined using Newman-Keul's post hoc test at a .05 level of significance.

Results

The number of freezing responses recorded in each of the four observation periods are illustrated in Figure 13. Note that in each 1 min period recorded there were 12 observations that occurred at 5-s intervals. The ANOVA conducted on the freezing scores indicated that there was a significant main effect of Group \( [F(1,12) = 7.59, p < .05] \), a significant effect of Period \( [F(3,36) = 33.26, p < .001] \), and a significant Group x Period interaction \( [F(3,36) = 2.83, p < .05] \).

Post hoc analysis of the interaction revealed that the number of freezing responses by Group Met increased significantly in the first post-shock interval, relative to the baseline scores of zero freezing responses. Further increases occurring after subsequent shocks were not significant. In contrast, the freezing responses of Group Sal did not differ significantly from the Baseline period until after the second shock. Comparing the two groups, Group Met had significantly higher freezing scores than
Figure 13. Freezing 30 – 90 s after shock

Number of freezing responses by rats 30 to 90 s after footshock. Behaviours were scored every 5 s, for a total of 12 observations per period, during the baseline period, in the period after the first shock, in the period after the second shock, and after a series of five additional shocks. Prior to testing Group Sal was injected with saline, Group Met was injected with 5.0 mg/kg metoclopramide.
FREEZING 30 - 90 sec AFTER SHOCK

% FREEZING RESPONSES

Base    First    Second    Seventh
Group Sal after the first and second shocks, but scores did not differ significantly after the final shock.

Discussion

This experiment demonstrated that the freezing responses of rats increased from a baseline of zero to a high level over the course of 1, 2, and then 7 brief footshocks. A moderate dose of metoclopramide enhanced the onset of freezing so that significant freezing occurred after the first shock, whereas in undrugged rats significant freezing was not observed until after the second shock. It should be noted that the lack of significant freezing by saline-treated rats following the first shock was probably an artefact of the short observation time employed. Post-shock freezing responses have been observed following a single footshock similar to that used in the present experiment, up to 3 hr after the shock (Blanchard & Blanchard, 1969a). However, it should be noted that the number of freezing responses by saline-treated rats did show a small increase, not statistically significant, from the baseline of zero responses.

The increase in freezing produced by metoclopramide was not limited to the first shock. Freezing responses were significantly more frequent by drugged rats after the second shock as well. After the seventh shock metoclopramide-treated rats were freezing in a mean of 11.6 of 12 observation periods. If this group was experiencing a facilitation in freezing responses during this final
observation period, this would have been masked by ceiling effects.

There are no grounds for attributing the enhancement of freezing by metoclopramide to changes in pain thresholds or to changes in the activity of pain systems. Metoclopramide did not disrupt escape responses elicited by shock presentation in Experiment I.4 or in the experiments of Chapter II.

The result of this experiment is important in that it provides another instance of a substantial effect of a neuroleptic compound on its first administration. As such, it provides strong evidence against the possibility that neuroleptic effects on aversively motivated behaviours are mediated exclusively by some form of learning deficit (Beninger, 1988).

Experiment III.2 - Conditional stimulus-induced freezing

Freezing is a response of rats not only to aversive stimuli such as shock and predators, but also to conditional stimuli that have previously been paired with aversive events. For example, Blanchard and Blanchard (1969a), Bolles and Collier (1976), and Fanselow (1980) have all reported that if rats are shocked in one shock chamber their freezing responses are greater if they are subsequently observed in the same chamber than if they are observed in a discriminably different chamber. Apparently the
environmental cues are acting as conditioned stimuli for shock presentation.

Conditioned freezing may also be observed when rats are presented with more discrete conditional stimuli. For example, Bouton and Bolles (1980) demonstrated conditioned freezing when rats were presented with a tone that had previously been paired with shock: Levels of freezing were much higher when the tone had been paired with shock in a forward-conditioning procedure than when they had been paired in a backward-conditioning procedure. Similarly, Sigmundi, Bouton, and Bolles (1980) observed conditioned freezing when white noise or a light was used as the conditional stimulus, relative to a pseudoconditioning control. Interestingly, the amount of freezing observed increased with unconditional stimulus intensity only if the conditional stimulus was the white noise. Subsequent to these reports freezing has been used as a sensitive index of conditioned fear in a number of studies (e.g., Cook et al., 1987; Fanselow & Helmstetter, 1988; Iwata, Ledoux, Meely, Arneric, & Reis, 1986; Ledoux, Iwata, Pearl, & Reiss, 1986; Mineka et al., 1984).

Having determined that freezing responses following shock presentation are enhanced by metoclopramide in Experiment II.1, the present experiment investigates whether a similar effect is to be found when rats are presented with a conditional stimulus previously paired with shock delivery. In addition to a group receiving saline prior to
the test for conditioned freezing, additional control groups included a Sensitization group which received only pre-exposure to the conditional stimulus, and a Pseudoconditioning group which received exposure to only the unconditional footshock.

Method

Subjects and apparatus: Rats similar to those of previous experiments were tested using the same Plexiglas chamber, and video recording equipment as in Experiment III.1. The Pseudoconditioning group received shock presentations in the shock side of the one-way avoidance apparatus.

Procedure: The experiment was conducted across a two day period, a Conditioning Day and a Test Day. Rats were assigned randomly to one of four groups. On the conditioning day rats of the two conditioning groups (Groups Cond-Met and Cond-Sal, each n = 7) were placed in the Plexiglas chamber. After a 10-min acclimatization period they were presented with five tone-shock pairings. Each pairing consisted of a 10-s tone period followed by a 0.5-s, 1.0 mA footshock during which the tone remained on. (A pilot experiment indicated that all shocked rats, even saline-treated controls, would freeze for virtually all of the observation period if they had been given 10 pairings of tone with 1.0-s, 1.0-mA footshock) The intertrial interval was 2 min. Following the final shock each rat remained in the chamber for an additional 10 min. Rats of the
Sensitization group ($n = 7$) received exactly the same pattern of tone presentations as the Conditioning Groups, but did not receive any footshocks. Rats of the Pseudoconditioning group ($n = 6$) received five shocks on the same schedule as the Conditioning groups, but did not receive any tone presentations. To minimize associations between the chamber and the shocks, shocks were presented to the Pseudoconditioning group in the shock side of the one-way avoidance apparatus.

On the test day, rats in Group Cond-Met were administered 5.0 mg/kg metoclopramide, as were rats of the Sensitization and Pseudoconditioning groups. Rats in Group Cond-Sal were administered saline. Sixty to ninety minutes after injection, a single rat was placed in the Plexiglas compartment. No scheduled events occurred in the first 10 min that the rat was in the compartment. At the end of this 10-min period the rat received five 10-s presentations of the tone, with an intertrial interval of 2 min. After the fifth tone the rat remained in the chamber for an additional 10 min.

Reactions to the five tones were scored from the videotape using the same sampling technique used in Experiment III.1. During the tones themselves, behaviour was sampled every 2 s, timed from tone onset (or from 2 min prior to the first tone for the baseline score). Following the tone, behaviour was sampled every 5 s for the next 2 min.
Data analysis: As in Experiment III.1, an ANOVA was conducted on freezing response occurring during the 1 min period beginning 30 s after the offset of each tone, as well as for a baseline period prior to the onset of the first tone. In addition, a separate ANOVA was conducted on freezing responses that occurred during the 10-s CS period, and during a 10-s baseline period commencing 2 min prior to the onset of the first tone. During these 10-s periods, behaviours were scored every 2 s, for a total of five observations. For both tone and post-tone intervals, data was analyzed using a two-way (Group x Trial) ANOVA. In each case significant effects were further analyzed using Newman-Keul's post hoc test at a .05 level of significance.

Results

The number of freezing responses during the tone periods are illustrated in the top panel of Figure 14. Note that in the 10-s tone period there were five observations that occurred at 2-s intervals. There was a significant effect of Trial \(F(5,115) = 3.22, p < .01\), but there was no significant effect of Group \(F(3,23) = 1.80, p > .10\), and no significant Group x Trial interaction \(F < 1\). The post hoc test indicated that the only significant comparison between trials was between the baseline period and Trial 4.

Freezing responses during the intervals from 30 to 90 s following tone offset are illustrated in the bottom panel of Figure 14. Note that in this 60-s period there were 12
Top panel shows number of freezing responses by rats during the 10 s periods in which the conditional stimulus (tone) was being presented, as well as during the baseline period 2 min prior to the first tone. Behaviours were scored every 2 s from tone onset for a total of five observations per period. Bottom panel shows number of freezing responses by rats in the period from 30 to 90 s after tone presentation, as well as during the baseline period 90 to 30 s prior to the first CS+. Behaviours were scored every 5 s in baseline period and after each CS+, for a total of 12 observations per period. On the day prior to testing rats of Group Cond-Sal and Cond-Met received five pairings of CS+ and shock, Group Sensitization received only CS+ presentations, and Group Pseudoconditioning was shocked five times in a separate compartment. On test day Groups Cond-Met, Sensitization, and Pseudoconditioning received 5.0 mg/kg metoclopramide, Group Cond-Sal received saline.
Chapter III

FREEZING DURING CS+ PRESENTATION

FREEZING 30 - 90 s AFTER CS+

FREEZING RESPONSES

FREEZING RESPONSES

Cond-Sal
Cond-Met
Sensitization
Pseudocond
observations that occurred at 5-s intervals. There was a significant effect of Trial \[F(5,115) = 11.12, p < .001\], but there was no significant effect of Group \[F(3,23) = 1.52, p > .20\], and no significant Group x Trial interaction \[F(15,115) = 1.38, p > .10\]. Post hoc examination of the Trial effect indicated that there were more freezing responses after each conditional stimulus presentation than during the baseline period. There were no significant differences between the five trials.

**Discussion**

The data from the present experiment do not support the hypothesis that metoclopramide increases the amount of freezing induced by a conditional stimulus that has been paired with shock. Such a conclusion would have required a significant difference between Groups Cond-Met and Cond-Sal, and further demonstration that the magnitude of freezing was higher in Group Cond-Met than in the Sensitization and Pseudoconditioning controls. In the absence of saline-treated sensitization and pseudoconditioning controls it is not even possible to determine if the freezing seen in all groups following tone presentations is due to Pavlovian associations, as previously reported (Blanchard & Blanchard, 1969a; Bolles & Collier, 1976; Bouton & Bolles 1980; Cook et al., 1987; Fanselow 1980; Mineka et al., 1984; Sigmundi et al., 1980).

Examination of Figure 14 suggests that it would be inappropriate to dismiss the notion that metoclopramide
enhances conditioned freezing out of hand. In the 1-min
observation intervals following the first three tone
presentations the rats of Group Conditioned-Met were frozen
during 86% of the behavioural samples observed, compared to
40% for Group Conditioned-Sal, 49% for the Sensitization
group and 62% for the Pseudoconditioning group. These data
suggest that with a more sensitive measuring technique
substantial differences might have been found between the
groups.

A surprising outcome of this experiment was the high
level of freezing observed in the rats of the Sensitization
and Pseudoconditioning groups. That this freezing was not a
primary effect of metoclopramide treatment is attested to by
the low level of freezing by these groups during the baseline
period and by the absence of freezing by Group Met in the
baseline period of Experiment III.1. Instead, such freezing
might be attributed to the generalization of apparatus cues
on the part of the Pseudoconditioning group. In the case of
the Sensitization group it appears that fear must have been
elicited directly by the tone, or possibly by a combination
of the cue and unconditioned fear-eliciting properties of the
test box (bright overhead light, probable presence of fear
pheromones). In this context, it is interesting to note that
various experimenters have reported occasionally that
avoidance responses can be potentiated by presentation of a
supposedly neutral signal (e.g., Jacobs & LoLordo, 1980;
Discussion of Chapter III

The first experiment in this chapter clearly indicated that metoclopramide enhances freezing responses following shock presentation. It is less obvious that metoclopramide increases freezing responses elicited by conditional stimuli. The results of Experiment III.2 fail to support such a conclusion. However, the results of Experiment III.1 may be interpreted in just this way.

It may seem surprising that the freezing responses observed in the interval following shock presentation should be regarded as a conditioned response to shock-related cues. However, consider the alternatives. Is freezing an instrumental response that is reinforced by somehow modifying the shock's delivery or impact? Arguing against this proposal is the fact that the probability of freezing decreases, rather than increases, through the duration of an extended footshock (Blanchard & Blanchard, 1969a).

There is another argument against viewing freezing as an instrumental response. Indeed, freezing as an avoidance response has been reported to be acquired rapidly by rats (Bindra & Anchel, 1963; Brener & Goesling, 1970). But consider an important paper in which Bolles and Riley (1973) examined freezing responses reinforced by shock avoidance on a Sidman schedule. In this experiment the animals were shocked every 5 s as long as they were active, but shock was withheld as soon as freezing occurred. The shock series was reinstated if the animals quit freezing and were active for a
period of 15 s. A complementary group was punished for freezing. That is, the series of shocks occurred after the rats froze for 15 s and continued as long as the freezing continued. Freezing was apparently acquired rapidly as an instrumental response, whereas the punishment contingency resulted in lower levels of freezing. However, comparison of the experimental rats with yoked controls, with rats in extinction, and with rat punished for freezing for even 1 s all showed that the avoidance and punishment contingencies affected freezing only to the extent that they produced different frequencies of shock. Bolles and Riley concluded that freezing was neither strengthened by the avoidance procedure nor weakened by the punishment procedure, and on the strength of this finding Bolles (1975) argued that freezing must always be a respondent, not subject to learning as an operant response.

The other obvious interpretation of freezing following shock administration is that it is an unconditional response to shock. However, as Fanselow (1980) points out

This idea would require some adjustment of the usual view of the UR [unconditional response] as an immediate, short-lived reflex, because freezing is not like the usual sudden jerk UR that is invariably elicited by shock. The occurrence of freezing is probabilistic, freezing has a delayed onset, and it occurs in prolonged bouts lasting several minutes...These probabilistic and temporal properties set the freezing response somewhat apart from the usual UR. (p. 177).

Beyond these considerations, empirical evidence argues that freezing following shock is a conditioned, rather than an unconditional, response. Blanchard and Blanchard (1969a)
and Bolles and Collier (1976) found much less freezing following shock treatment if they moved rats into a novel compartment than if they handled them and returned them to the shock compartment. In the study by Blanchard and Blanchard freezing (or "crouching") was reduced to the level of nonshocked controls, but interpretation of their findings is complicated by their failure to counterbalance compartments. In the study by Bolles and Collier freezing was reduced to an intermediate level, higher than that of nonshocked controls. To determine if post-shock freezing constituted a conditioned response or an unconditional response Fanselow (1980) not only changed compartments for half of his rats, he also delayed testing of half the rats by 24 hr in a factorial design. Greater freezing was observed if the rats were tested in the same compartment that they were shocked in, and the magnitude of this effect was just as great if a 24-hr delay was imposed between shock and test. If there was an unconditional component to the freezing, it is only reasonable to expect that it would at least have diminished after this delay. As it did not, it was concluded that all freezing observed in the compartment in which the shocked rats had not been shocked was due to generalization with the shock apparatus.

This conclusion receives further support from reports that no freezing is observed in the five minutes following shock if rats are shocked immediately upon being placed in the compartment (Blanchard et al., 1976; Fanselow 1986).
This demonstrates that freezing is not simply a reaction to shock, but rather a response conditioned to cues in the environment. If the rat does not have sufficient exposure to the environment prior to shock onset, no crouching occurs.

Together, these considerations lead to the conclusion that freezing responses observed after shock administration are conditioned responses elicited by environmental stimuli that the rat has come to associate with shock after as few as a single unconditional shock presentation. Accordingly, it is concluded from Experiment III.1 that metoclopramide does indeed increase conditioned freezing responses of rats to shock-related stimuli. In light of this demonstration, we must re-evaluate the avoidance acquisition deficit produced by metoclopramide.
IV

CAN FEAR DISRUPT AVOIDANCE RESPONDING?

If an animal freezes, it cannot perform an avoidance response. It follows that manipulations that enhance freezing can disrupt avoidance responding. For example, Weiss et al. (1968) found that when they gave rats eight pairings of a tone conditional stimulus with 10-s footshock, acquisition of avoidance, using the tone as the WS, was subsequently inhibited. This finding, in contrast to those of Experiment II.2 and those of several other investigators (Anisman et al., 1982; Gallon, 1972; Overmier & Leaf, 1965), appears to be the result of the very long shocks administered by Weiss et al. Such severe shock experience would be expected to lead to intense freezing, and, indeed, analysis of the rats' behaviour during avoidance trials indicated that they were freezing, rather than avoiding. In fact, avoidance responding was improved if fear levels (and hence, freezing) were reduced by giving fear extinction. These results are consistent with other reports that responding may decline if excessively strong shocks are used as the AS (e.g., Moyer & Korn, 1964). An inverse relationship between freezing and avoidance has also been demonstrated in situations not involving intense shock levels. Blanchard & Blanchard (1969b) found a negative correlation between discriminated avoidance of a moving prod and freezing following a single shock.
Lenard and Beer (1975) proposed that inappropriate reactions to shock lead to impaired avoidance response maintenance following central application of 6-OHDA. According to them,

during the first few sessions after treatment with [6-OHDA] there was an increase in the frequency of a new series of responses, including freezing, that was incompatible with the avoidance response and was correlated with the decline in the frequency of avoidance behaviour. It is possible that the rats had learned to suppress avoidance responses (p. 177).

Although no quantitative data on these incompatible responses were provided, Beer and Lenard (1975) supported this hypothesis by demonstrating that administration of diazepam, which apparently attenuated freezing during avoidance sessions, alleviated the 6-OHDA-induced deficit, even though this anxiolytic had no effect on avoidance by itself.

This hypothesis gains credence by virtue of the fact that parallel arguments have been advanced to account for avoidance deficits observed following lesions of the amygdala or the dorsomedial nucleus of the thalamus (DMN). For example, Robinson (1963) found elevated levels of crouching in amygdala-lesioned rats, and a strong correlation ($r = 0.83$) between crouching and log response latency for amygdalectomized rats, but not for controls. Robinson (1963) suggested that the amygdalectomized rats were over-responsive to aversive stimuli. Similarly, Campenot (1969) proposed "that amygdaloid lesions increase an animal's tendency to suppress responding as a reaction to being shocked" (p. 496).
Disruption of avoidance responding by inappropriate reactions to shock could also account for the curious findings of Olton and Isaacson (1967) concerning the effects of DMN lesions. Deficits were observed in the retention of avoidance responding only if rats were tested in reacquisition, when the rats received footshock as a result of failures to respond. The rats were perfectly capable of performing avoidance responses, as demonstrated by their undiminished capacity to execute responses if they were tested in extinction, yet somehow the presence of shock disrupted performance. This interpretation is supported by the observation that the deficit was not so pronounced in one-way as in two-way avoidance, in which both control and lesioned rats received more shocks.

Can a similar analysis be applied to the avoidance deficits observed after administration of neuroleptic drugs? As reviewed in Chapter II, it is clear that such drugs do not disrupt learning about the aversive nature of shock. On the other hand, it was demonstrated in Chapter III that neuroleptics do in fact alter freezing responses in a fearful environment. Thus, it is reasonable to hypothesize that the enhanced freezing observed in Chapter III should interfere with avoidance responding. The experiments of the present chapter test this hypothesis.
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Experiment IV.1 - Effect of non-contingent shock

If shock-induced freezing following metoclopramide treatment contributes to the avoidance deficit observed in Experiment I.4 and throughout Chapter II, then presenting the rats with additional uncontrollable footshocks throughout the avoidance session should act synergistically with a dose of metoclopramide to disrupt avoidance responding.

Method

Subjects and apparatus: Subjects similar to those of the experiments of Chapters I to III were used. All testing was conducted in the one-way avoidance apparatus used in Chapter I, and preliminary tone-shock pairings were delivered in the Plexiglas compartment described in Experiment II.2.

Procedure: Rats were assigned randomly to one of four groups (n = 6 per group). Each rat received 10 non-contingent WS-AS pairings in the shock side of the avoidance apparatus. On the next day rats of all groups received an initial avoidance training session consisting of five standard avoidance trials. This amount of training was selected to provide the rats with a moderate amount of protection from the effects of metoclopramide (see Experiment II.2). There were no significant differences between groups on the training day (all Fs < 1).

On the following day, the test day, rats of each group were tested on 10 avoidance trials. Two groups of rats, the
non-contingent footshock (NCF) groups, received a 3.0-s footshock in the shock side of the avoidance apparatus prior to the first trial. In addition, these rats received a 1.0-s footshock on each trial after being placed in the shock side of the compartment, prior to the onset of the WS. Rats of the two Control groups did not receive the non-contingent footshock. One NCF group (NCF-Met) and one control group (Control-Met) received 5.0 mg/kg metoclopramide prior to testing, while the other two groups (NCF-Sal and Control-Sal) received saline injections.

Statistical analysis: The number of avoidances were analyzed using a two-way (Drug treatment x Shock treatment) ANOVA. Latency scores were analyzed with a three-way (Drug x Shock x Trial) ANOVA. In each case significant effects were further analyzed using Newman-Keuls post hoc test at a .05 level of significance.

Results

The number of avoidances are illustrated in the top panel of Figure 15. As can be seen in the figure, non-contingent footshock disrupted the performance of the rats that had received metoclopramide, but it did not disrupt the performance of the rats that had received saline. Drug administration alone produced a minor deficit (6.9/10 correct responses vs. 9.0/10 for Control rats). This deficit was markedly exacerbated by administering non-contingent shocks to the drug-treated rats prior to each
Figure 15. Effect of pretrial shock

Top panel indicates mean number of avoidances executed on the test day. Bottom panel indicates mean response latencies. All rats received 10 tone-shock pairings on Day 1 and 5 avoidance training trials on Day 2. On the test day NCF Groups received non-contingent shock prior to each trial, Control Groups did not. Sal Groups received saline on the test day, Met Groups received 5.0 mg/kg metoclopramide.
NON-CONTINGENT FOOTSHOCK

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control  NCF

SAL  MET
trial (reducing Group NCF-Met to 3.8/10), a procedure that had no effect on undrugged rats (9.2/10 for Group NCF-Sal). This impression is confirmed by the ANOVA. There was a significant effect of Drug [$F(1,20) = 43.83$, $p < .001$], a significant effect of Shock [$F(1,20) = 6.26$, $p < .05$], and a significant Drug x Shock interaction [$F(1,20) = 7.81$, $p < .05$]. Post hoc testing indicated that of the two groups that received metoclopramide, the one that received non-contingent shocks (NCF-Met) performed worse than the group that did not receive shock (Control-Met). In contrast, the performance of the two groups that received saline did not differ. Thus, there was a synergistic effect of metoclopramide and non-contingent shock.

Examination of the latency scores (bottom panel of Figure 15) suggests a similar pattern of results. However, because of greater within-group variability, the interaction was not significant. There was a significant effect of drug [$F(1,20) = 19.74$, $p < .001$], but not a significant effect of Shock [$F(1,20) = 1.49$, $p > .20$], nor a significant Drug x Shock interaction [$F(1,20) = 1.73$, $p > .20$].

**Discussion**

The results of this experiment support the hypothesis that rats treated with neuroleptic drugs freeze in response to shock, thereby suppressing avoidance responding. However, an alternative interpretation of these results is possible. Rather than disrupting the performance of metoclopramide-treated rats by interfering with their
response capabilities, the non-contingent footshocks may have interfered with their avoidance performance by disrupting their representations of response-outcome contingencies. This is a variant of the "learned helplessness" hypothesis of Overmier and Seligman (1967), in which they suggest that subjects may learn that their responses are independent of shock termination. There is no obvious reason why the drug should have produced such a confusion in metoclopramide-treated rats when the undrugged rats were not disrupted. Nonetheless, Experiment IV.2 was conducted to exclude this possibility.

Experiment IV.2 - Effect of shock in a different context

It is possible that rather than eliciting inappropriate, incompatible responses, the noncontingent shocks administered to the rats in Experiment IV.1 interfered with avoidance performance by disrupting their representations of response-outcome contingencies. This interpretation could be discounted by showing that shock administered in a separate compartment, prior to testing, has a similar deleterious effect.

Method

Subjects and apparatus: Subjects similar to those of the experiments of Chapters I to III were used. Avoidance testing was conducted in the one-way avoidance apparatus described in Chapter I, and additional tone and shock
presentations were delivered in the Plexiglas compartment described in Experiment II.2.

Procedure: The design of the experiment was identical to that of Experiment IV.1 except for the manner in which non-contingent footshocks were administered. Rats were assigned randomly to one of four groups (n = 8 per group). On the first day of the experiment each rat received 10 WS-AS pairings in the Plexiglas compartment. On the next day rats of all groups received an initial avoidance training session consisting of five standard avoidance trials. This amount of training was selected to provide rats with a moderate amount of protection from the effects of metoclopramide, as in Experiment IV.1. There were no differences between groups in number of avoidances or response latencies on this training day (Fs < 1). On the following day, the test day, rats of each group received 10 avoidance trials. Immediately prior to the commencement of these test trials the rats of two groups, the Shock groups, received three non-contingent, 1.5-s, 1.0-mA footshocks in the Plexiglas apparatus, with an intershock interval of 30 s. Rats of the two Control groups did not receive such non-contingent footshock. Rats of one Shock group (Shock-Met) and one Control group (Control-Met) received injections of 5.0 mg/kg metoclopramide prior to testing, while the other two groups (Shock-Sal and Control-Sal) received saline injections.
Statistical Analysis: The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment IV.1.

Results

The number of avoidances are illustrated in the top panel of Figure 16. As can be seen in this figure, footshock disrupted the performance of the rats that had received metoclopramide, but did not disrupt the performance of the rats that had received saline. This impression is confirmed by the ANOVA. There was a significant effect of Drug \[ F(1,28) = 14.24, p < .001 \], a significant effect of Shock treatment \[ F(1,28) = 6.33, p < .05 \], and a significant Drug x Shock treatment interaction \[ F(1,28) = 14.24, p < .001 \]. Post hoc tests indicated that Group Shock-Met avoided less often than any other group on the test day.

Examination of the latency scores (bottom panel of Figure 16) revealed a similar pattern of results. There was a significant effect of Drug \[ F(1,28) = 8.15, p < .01 \], a significant effect of Shock treatment \[ F(1,28) = 4.37, p < .05 \], and a significant Drug x Shock treatment interaction \[ F(1,28) = 8.81, p < .01 \]. Post hoc tests indicated that the response latencies of Group Shock-Met were longer than those of any other group on the test day.

Discussion

In conjunction with Experiment IV.1, the present results indicate unambiguously that additional presentations of shock disrupt the avoidance responding behaviour of
Figure 16. Out of context pretrial shock

Top panel indicates mean number of avoidances executed on the test day. Bottom panel indicates mean response latencies. All rats received 10 tone-shock pairings on Day 1 and 5 avoidance training trials on Day 2. On the test day the Shock Groups received three 1.5 s footshocks in a separate compartment prior to the first avoidance trial. Sal Groups received saline and Met Groups received 5.0 mg/kg metoclopramide prior to testing.
OUT-OF-CONTEXT PRETRIAL SHOCK

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control  Shock

SAL  MET
metoclopramide-treated rats. Unlike Experiment IV.1, where shock presentations occurred on each trial and in the same compartment in which the rat was about to receive an avoidance trial, circumstances that could have disrupted avoidance responding by distorting the rat's representations of the stimulus-environment-response contingencies, the shocks in the present experiment were all administered prior to the onset of the trial and in a separate compartment. In neither the previous experiment nor this was there any indication that the additional shocks had a disruptive effect on the avoidance responding of undrugged rats. But in each case shocks clearly disrupted avoidance responding by rats that had been administered 5.0 mg/kg metoclopramide.

The observed disruption of avoidance responding by shock treatment in drugged rats is consistent with the finding of Experiment III.1 that metoclopramide-treated rats have an exaggerated freezing response to shock. It is also consistent with the proposal of Lenard and Beer (1975) that dopamine disruption causes inappropriate reactions to shock that lead to impaired avoidance responding and with Robinson's (1963) finding that there is a strong correlation between avoidance disruption and freezing following avoidance-disrupting brain lesions. Together, these findings suggest that at least some portion of the disruptive effect of neuroleptic drugs on avoidance can be attributed to the enhancement of incompatible freezing responses following shock.
As described in the discussion of Chapter III, post-shock freezing may best be interpreted as a conditional response to environmental cues. In this perspective the results of the present experiment may seem somewhat surprising: Transferring the rats to a new environment should have decreased the magnitude of such conditioned freezing. However, Bolles and Collier (1976) and Faneslow (1980) reported considerable freezing when rats were moved to a novel compartment following shock, freezing that Faneslow (1980) attributed to inter-compartment generalization. That such generalization was evident in the present experiment is not surprising, given that the Plexiglas box in which the noncontingent shocks were administered had a grid floor like that of the avoidance apparatus, the two boxes were in the same room, and both had high, flat walls. Further, the rats had received shock in both the Plexiglas compartment and in the avoidance apparatus before the test day.

Experiment IV.3 - Effect of a conditional stimulus

The previous experiments demonstrated that shock can disrupt the avoidance behaviour of neuroleptic-treated rats, apparently by increasing incompatible freezing responses. Evidence described above indicates that freezing responses following non-contingent shock are conditioned responses (Fanselow, 1980, 1986). Thus, it appears that conditioned responses to shock-related stimuli disrupt avoidance
responding by metoclopramide-treated rats. The present experiment was designed to establish this point unequivocally by demonstrating that a stimulus previously paired with shock could interfere with avoidance responding. In order that a tone could be used as the additional conditional stimulus, the usual tone WS was replaced by illumination of a cue light for this experiment.

**Method**

**Subjects and apparatus:** Subjects similar to those of the other experiments were used. The one-way avoidance apparatus was described in Chapter I, and additional stimuli were presented in the Plexiglas compartment described in Experiment II.2.

**Procedure:** Rats were assigned randomly to one of four groups. Two groups of rats (CS+ groups) received 10 non-contingent tone-shock pairings in the Plexiglas compartment on each of the first two days of the experiment. Rats of the other groups (Control groups) were simply placed in the Plexiglas compartment and then removed, without having experienced any programmed events in the box. On the following day rats of all groups received an initial avoidance training session consisting of five avoidance trials. In this training session the WS consisted of illumination of the cue light mounted on the end wall of the shock side of the box. The ceiling lights in the test room were not illuminated on this day, the only ambient lighting
being provided by two dim red incandescent bulbs. Prior testing indicated that this amount of training would provide rats with a moderate amount of protection from the effects of metoclopramide, as in Experiments IV.1 and IV.2. There were no differences between groups on number of avoidances or response latencies on this training day (Fs < 1). On the following day rats of each group were tested on 10 avoidance trials. On the test day the two Control groups were tested using only the cue light WS. However, for the two CS+ groups the tone was activated at the same time as the light WS. One CS+ group (CS+-Met, n = 9) and one Control group (Control-Met, n = 9) received 5.0 mg/kg metoclopramide prior to testing, while Groups CS+-Sal (n = 10) and Control-Sal (n = 10) received saline injections.

**Statistical Analysis:** The data were analyzed using the ANOVA and Newman-Keul's post hoc test, as described in Experiment IV.1.

**Results**

The number of avoidances are illustrated in the top panel of Figure 17. It is apparent that the conditional stimulus disrupted the performance of the metoclopramide-treated rats. This impression is confirmed by the ANOVA. There was a significant effect of Drug [F(1,34) = 23.33 p < .001], and a significant Drug x Conditioning interaction [F(1,34) = 11.46, p < .005], but there was no significant effect of Conditioning (F < 1). Post hoc tests indicated
Figure 17. Effect of additional shock CS+

Top panel indicates mean number of avoidances executed on the test day. Bottom panel indicates mean response latencies. CS+ rats received 10 tone-shock pairings on Days 1 and 2. All rats received 5 avoidance training trials with a light WS on Day 3. On the test day the WS was a tone-light compound for the CS+ Groups and was a light for the Control Groups. Sal Groups received saline on the test day, while Met Groups received 5.0 mg/kg metoclopramide.
EFFECT OF ADDITIONAL SHOCK CS+

AVOIDANCE RESPONSES

RESPONSE LATENCY

Control
CS+

SAL
MET
that Group Control-Sal did not differ from either Group Control-Met or Group CS+-Met, but that Group CS+-Met performed significantly worse than any other group. Thus, the presence of the additional tone CS+ did not have an adverse effect on the performance of the saline treated rats (in fact Group CS+-Sal performed non-significantly better than Group Control-Sal), but the conditional stimulus had an adverse impact on the performance of metoclopramide-treated rats.

Examination of the latency scores (bottom panel of Figure 17) suggests a similar pattern of results. However, the statistical analysis indicated a slightly different pattern of effects. There was a significant effect of Drug \( F(1,34) = 20.12 \ p < .001 \), and a significant Drug x Conditioning interaction \( F(1,34) = 9.47, \ p < .005 \), but there was no significant effect of Conditioning (\( F < 1 \)). The post hoc tests again indicated that there was no difference between the performance of the saline- and metoclopramide-treated rats that were not exposed to the tone. However, Group CS+-Met did not have significantly longer latencies than did Group Control-Met. Instead, interestingly, Group CS+-Sal had significantly lower latencies than did Group Control-Sal. Thus, the additional conditional stimulus potentiated performance for undrugged rats, as indexed by the latency scores, whereas for drugged rats there was a non-significant disruption of performance.
Discussion

The presence of an additional tone conditional stimulus did not have an adverse effect on the performance of saline-treated rats (compare Group CS+-Sal with Group Control-Sal). In fact, the response latencies of the rats that were presented with the conditional stimulus were actually lower with than those of control rats. This finding is consistent with numerous reports that presentation of a classically conditioned stimulus associated with shock can lead to enhanced avoidance responding (e.g., Jacobs & LoLordo, 1980; Overmier & Leaf, 1965; Rescorla & LoLordo, 1965; Scobie, 1972; Solomon & Turner, 1962; Weisman & Litner, 1969, 1972; Zielinski & Cotton, 1982).

Yet the conditional stimulus decreased, rather than increased, the number of avoidances successfully executed by the metoclopramide-treated rats. Metoclopramide by itself had only a minor effect on the performance of control rats, but in combination with the conditional stimulus it produced a substantial disruption in performance. Thus, the disruptive effects of shock and metoclopramide in combination that were observed in Experiments IV.1 and IV.2 were also observed using a conditional stimulus in place of footshock. These observations lend support to the proposal that, for present purposes, freezing responses following shock are conditioned responses to fear-eliciting stimuli.
Together, the experiments of this chapter clearly indicate that the avoidance performance of metoclopramide-treated rats is adversely influenced by the non-contingent presentation of aversive footshock or conditioned stimuli associated with footshock. In combination with the findings of Chapter III, and the observations of Weiss et al. (1968) and Blanchard & Blanchard (1969b) that freezing elicited by fear can disrupt avoidance responding, it appears that increased freezing by metoclopramide-treated rats can account for this deficit.

These findings are extremely important for the evaluation of deficits in avoidance acquisition observed following neuroleptic treatment. During acquisition all rats will normally experience several shocks before becoming proficient one-way avoiders. However, whereas these shocks will potentiate the subsequent avoidance responding of undrugged rats, they will disrupt the responding of metoclopramide treated rats. In subsequent sessions, back in the shock-related environment, the neuroleptic-treated rats will freeze more and avoid less than controls.

This line of reasoning may also account in part for the gradual onset of disruption of avoidance responding seen after neuroleptic treatment in rats who have previously acquired the response. Although a drugged rat may respond well at first, environmental cues may eventually lead to an increase in freezing and consequent response inhibition, or
else the rat may eventually get a shock, and is more likely to freeze in response to that shock than a non-drugged rat. Thus, it is not surprising that doses of neuroleptic drugs required to impair performance on bar press or shuttle avoidance are lower than those required to disrupt performance of a simpler response (Latz et al., 1969).

Although these considerations support the suggestion that metoclopramide enhances freezing in the avoidance situation, thereby disrupting avoidance responding, confidence in this conclusion must be tempered by two factors. First, there is no independent evidence that neuroleptic-treated rats actually freeze in the avoidance situation. However Posluns (1962), examining the effects of chlorpromazine on one-way avoidance, made just such an observation. He found that under chlorpromazine there was a highly significant correlation between the time it took a drugged rat to initiate locomotion and the number of shocks it received in the session (r = .94). From Posluns' systematic observation and description of the response pattern of his rats, it is apparent that the rats' failure to initiate locomotion was equivalent to freezing. Thus, freezing was associated with failure to avoid on the part of the neuroleptic-treated rats. It should be noted, however, that not all avoidance response failures can be attributed to freezing at the commencement of the trial. Posluns observed that rats frequently paused just before entering the safe compartment. In the present series of experiments
metoclopramide-treated rats were frequently observed running to the divider separating the two portions of the avoidance apparatus, often freezing in front of the divider or rearing and freezing while leaning against it, but failing to pass though the open guillotine door.

A second, more subtle consideration is the problem of inferring a causal relationship in the correlation between freezing and impairment in avoidance responding. Such a correlation has been noted in the case of rats' failure to acquire a bar press avoidance. But, as Bolles (1975) has pointed out, rather than failing to avoid because it is freezing, a rat may freeze because it is unable to avoid. Certainly, the rats of Experiment III.1 were unable to avoid, so freezing was an appropriate response. How can we be certain that the metoclopramide-treated rats of the experiments presented in this chapter were not reacting similarly? If this is the case we must ask yet again why neuroleptic-treated rats are unable to avoid. This question will be addressed, yet again, in the general discussion.
GENERAL DISCUSSION

The preceding sections have presented a variety of data that replicate and extend earlier findings concerning the effects of neuroleptic drugs on the defensive behaviours of rats. This final section begins by summarizing the major findings of the research and the conclusions that may be drawn from them. The numbers in parentheses refer to specific experiments.

First, the acquisition of one-way avoidance behaviour by naive rats is abolished by administration of a moderate dose of haloperidol (I.1). This effect of haloperidol is also observed with metoclopramide (I.4, II.1).

Second, haloperidol does not initially have a strong effect on the performance of a previously acquired response, but the effect increases over repeated drug tests (I.1). This is also observed following metoclopramide administration (I.4, II.1).

Third, complete and selective disruption of avoidance acquisition was not observed with thioridazine (I.2a, I.2b) or clozapine (I.3). Thioridazine and clozapine are atypical neuroleptics, potent antipsychotic agents infrequently associated with extrapyramidal side effects (EPSEs), whereas metoclopramide is not well established as an antipsychotic agent, but it is strongly associated with EPSEs.

Accordingly, these findings suggest that disruption of avoidance acquisition is more closely related to the EPSE-inducing properties of neuroleptics than to their
antipsychotic effects. This in turn suggests that disruption of avoidance acquisition may not be an appropriate model for detecting drugs that will alleviate psychoses. Because EPSEs are associated with nigrostriatal dopamine dysfunction, and in light of the evidence reviewed on pp. 64, these pharmacological studies are consistent with the suggestion that avoidance acquisition is primarily dependent on nigrostriatal dopamine activity.

Fourth, in order to be protected from the effect of metoclopramide treatment, the one-way avoidance response need only have been performed a few times (II.1, II.2). In fact, the rat need never have actually avoided the shock: Escape training was as effective as avoidance training (II.5). This is consistent with the notion that the development of resistance to neuroleptic effects is more a matter of "problem-solving" than a case of "habit-formation".

Fifth, exposing rats to prior pairings of the tone WS and footshock facilitated the development of resistance to metoclopramide effects (II.2) but was not sufficient for this purpose (II.5).

Sixth, giving rats prior "safety" conditioning while they were undrugged did not attenuate metoclopramide's effects on avoidance acquisition (II.3, II.4). This argues against the possibility that neuroleptic drugs specifically disrupt learning about the incentive value of safety signals.

Seventh, a strict performance deficit interpretation is ruled out by the finding that if metoclopramide was
administered during escape training the prophylactic effect of such training was eliminated, even though both drugged and undrugged rats escaped the shocks (II.5, II.6, II.7).

Eighth, metoclopramide enhanced freezing responses following shock administration (III.1). Even though no conclusive evidence of enhanced freezing to a tone conditional stimulus was found (III.2), previous studies indicate that freezing observed following shock administration is a conditioned response to the presence of shock-related environmental stimuli (Fanselow, 1980, 1986).

Finally, shock (IV.1, IV.2) and cues for shock (IV.3) disrupted the avoidance responding of metoclopramide-treated rats, whereas the performance of saline-treated rats was not disrupted (IV.1, IV.2). In fact, performance of control rats was actually enhanced by presentation of a shock-related conditional stimulus (IV.3).

These findings, plus the many previously reported phenomena concerning dopamine systems and avoidance behaviour, must be addressed by any theoretical account of the effects of neuroleptic drugs and of the role of dopamine in behaviour.

Theoretical interpretation of dopamine involvement in avoidance behaviour

In the 35 years since Courvoisier et al. (1953) found that a neuroleptic drug (chlorpromazine) would attenuate avoidance responding, various theoretical interpretations of
the effect have been put forward. At the same time, several hypotheses of dopamine function have arisen from analysis of dopaminergic involvement in appetitive behaviour. The following sections will examine the capacity of these various hypotheses to account for the data at hand.

**Neuroleptic drugs as major tranquilizers**

One early hypothesis developed to account for neuroleptic effects on avoidance behaviour suggested that they acted by decreasing fear or anxiety (Ader & Clink, 1957; Miller, Murphy, & Mirsky, 1957). This hypothesis ran into trouble when it was shown that neuroleptic-treated rats could acquire a conditioned emotional response (Hunt, 1956; see also Beninger et al., 1980b), and even more seriously, that neuroleptic-treated rats which had failed to acquire an avoidance response while drugged nonetheless showed considerable savings when later tested in an undrugged state (Posluns, 1962; see also Beninger et al., 1980b; Davidson & Weidley, 1976; Fibiger et al., 1975). The ability of rats to acquire, or manifest, other shock-related learning while drugged also challenged this notion (Beninger et al., 1980c; Corradini et al., 1984). In the present experiments, the increased amount of freezing observed in metoclopramide-treated rats provides further evidence against the possibility that fear is decreased by neuroleptics.

**Motor impairment or response bias**

It has often been suggested that neuroleptic effects on behaviour primarily reflect a motor deficit. In the case of
the avoidance deficit this could be interpreted as an inability to execute an active avoidance response. This possibility is excluded by the high level of performance seen in previously trained rats on their initial treatment with neuroleptics. An alternative hypothesis could be that neuroleptics predispose rats to freeze, rather than to perform active responses. Such an analysis would lead to the prediction that immobility as an avoidance response would be enhanced universally by neuroleptics. This is not the case. In fact, several studies have reported neuroleptic-treated rats displayed reduced response latencies in passive avoidance situations, while others have reported no changes (see Bammer, 1982, for review). These conflicting results are difficult to interpret, given great divergences in test procedure and drug administration between the tests. Step through passive avoidance was disrupted by chlorpromazine (Iwahara, Iwaski, & Hasegawa, 1968; Johnson, 1970), and by very low doses of haloperidol (Kovacs & De Weid, 1978). No effects were seen using doses of haloperidol or pimozide that typically disrupt active avoidance (Bammer, 1982). The results of the passive avoidance study of Iwahara et al. (1968) are interesting in that examination of their data indicates that chlorpromazine-treated rats spent a majority of the test time in the to-be-avoided small compartment, where shocks had been administered, rather than in an adjacent large compartment. It is conceivable that the rats were indeed freezing, but in their fright first ran into the
smaller compartment, which might have served as an unconditional safety signal. Whatever the reason for the shorter latencies sometimes reported in passive avoidance, the critical point is that neuroleptic-treated rats do not simply become immobile, cataleptic, or slower to initiate movements as a result of drug treatment. Therefore the increased freezing observed following metoclopramide treatment in Experiment III.1 must be dependent upon environmental stimuli.

**Anhedonia**

One influential account of neuroleptic effects, developed in the context of appetitive behaviour, is the "anhedonia" hypothesis of Wise (1982, 1985). It originated from the observation that the operant responding of neuroleptic-treated animals declines over the course of a test session when any of a variety of reinforcers are used (e.g., Ettenberg & Carlisle, 1985; Fouriezos & Wise, 1976; Wise et al., 1978). In its original form the anhedonia hypothesis attributed these deficits to an ability of neuroleptics to blunt the hedonic impact of positive reinforcers, thereby leading to extinction of the response. Later the hypothesis was extended to recognize the ability of neuroleptics to blunt the motivational impact of incentive stimuli (Gray & Wise, 1980; Wise, 1985).

If the anhedonia hypothesis were to be extended to the case of avoidance behaviour, it might contend that the reward value of safety stimuli are blunted by neuroleptic treatment.
Although such an approach could account for the gradual deterioration in performance seen with successive metoclopramide treatments, it does not account for the ability of drugged rats to learn an escape response, nor the ineffectiveness of explicit safety conditioning to overcome neuroleptic-induced deficits. Nor, more critically, can any apparent variation on the hypothesis account for increased freezing responses or the negative impact of shock and shock cues on avoidance performance observed following metoclopramide treatment. The anhedonia hypothesis is silent with respect to performance, therefore it cannot account for these alterations in performance.

**Incentive motivational learning**

Beninger (1988, 1989) has recently developed a proposal that incorporates elements of the anhedonia hypothesis but which focuses on the involvement of dopamine systems in learning. He proposes that disruption of dopaminergic function does not interfere with learning associations between shock offset and safety-related stimuli. However, he suggests that following neuroleptic treatment the incentive motivational properties of the reward (shock offset) may not be transferred to the safety-related stimuli, and hence the animals can learn where safety is but cannot learn to go there. This formulation can account for the findings of Experiments II.3 and II.4: Even though the rats learn the significance of the safety cues on the conditioning day they are unable, when drugged, to learn to direct their responses
towards them. This analysis is consistent with other reports that dopamine activity, if not necessary for learning, can play a facilitatory role in the acquisition of stimulus-stimulus learning (Carr & White, 1984; White & Major, 1978).

However, Beninger's hypothesis runs into serious trouble in accounting for the data of Chapters III and IV. In the case of Experiment III.1, there are no incentive stimuli present towards which drugged or undrugged rats can direct their responses. Why should the metoclopramide-treated rats freeze more in response to the shock? Nor can the hypothesis account for the outcome of Experiment IV.2. Why should the rats' avoidance responses be altered by the presentation of shock before the session? A learning-based hypothesis cannot account for alterations in responding that occur outside of the context of the avoidance contingencies. Drugged and undrugged, shocked and unshocked, the rats of all groups in Experiment IV.2 had identical training in the avoidance apparatus prior to the test. Nor is any analysis based entirely on learning able to account for the ability of neuroleptics to suppress a previously conditioned appetitive response (Blackburn et al., 1987; 1989b).

Response initiation deficit

Posluns (1962) and Fibiger et al. (1975) have proposed that neuroleptics impair avoidance responding by selectively blocking the initiation of voluntary or operant motor responses. Posluns (1962) observed that during initial training the avoidance responses of naive rats consisted of a
number of discrete component acts and hypothesized that each component was under voluntary control. With additional training the initiation latencies of the components were hypothesized to decrease until avoidance became a smooth integrated response. Neuroleptics were held to disrupt the dopamine-mediated process by which the WS triggered the initial components of the avoidance response. Fibiger et al. (1975) proposed that the ineffectiveness of neuroleptics at disrupting the behaviour of "well-trained animals could reflect a progression of the [avoidance] response from a series of voluntarily initiated component behaviors in naive rats to a more reflexive, automatic, synthesized type of behavior in trained animals" (p. 313).

By ascribing the attenuated impact of the drugs on previously acquired responses to the progressive automatization of avoidance responding, the response initiation deficit hypothesis is now challenged by the finding that a rat may be protected from neuroleptic effects after having successfully executed only a single avoidance response (Experiment II.2), or having been trained only with escape contingencies (Experiments II.5, II.6, II.7). Further, although this formulation, like that of Beninger (1989), can account for some of the phenomena concerning neuroleptic effects on avoidance behaviour, it is unable to account for the effects of neuroleptic drugs that are observed following the presentation of shock (Experiment III.1), or the interaction of shock and neuroleptic
treatments in the disruption of an acquired avoidance response (Chapter IV).

Sensorimotor deficit

Ungerstedt (1971), in the paper first describing the behavioural effects of 6-OHDA lesions of the nigrostriatal bundle, reported that rats with unilateral lesions show a chronic tendency to turn in the direction of the lesioned side of the brain. Marshall, Richardson, and Teitelbaum (1974) observed that such rats display difficulty using the limbs contralateral to the lesion for righting, climbing and resisting gravitational pull. Extrapolating from earlier work they had conducted on rats with unilateral lesions of the lateral hypothalamus (Marshall, Turner, & Teitelbaum, 1971) they proposed that this postural asymmetry reflects a state of "sensory neglect". That such lesions do not reflect a motor deficit was shown by the finding that lesioned rats have increased latencies to remove small pieces of adhesive paper that are applied to various parts of the limbs or the snout, if those objects are applied contralaterally to the lesion. This deficit was observed even though removal of the adhesive paper did not require body movements or postural adjustments (Schallert, Upchurch, Lobaugh, Farrar, Spirduso, Gilliam, Vaughn, & Wilcox, 1982). That this affliction does not reflect a primary sensory deficit was shown by the capacity of stimuli to evoke relatively normal responses on first presentation. For example, if the whiskers of a lesioned rat are touched it may turn toward the stimulus, but
if they are brushed again soon afterward the rat will not orient (Marshall et al., 1974). Thus, it appears that deficits observed following nigrostriatal bundle damage are neither wholly motoric nor wholly sensory, but rather appear to reflect disruption of a higher level of sensorimotor integration.

White (1986) has developed the sensorimotor hypothesis further to account for the aphagia observed after damage to the nigrostriatal bundle. White (1986) proposed that intense environmental stimuli can elicit responses despite severely reduced levels of dopamine activity, but that high levels of neuronal activity are required for responses to weak stimuli. Thus, he proposed that the aphagia of lesioned animals results largely from an inability of food-related cues to elicit approach responses that would bring them into contact with the food. In a similar vein Dews and Morse (1961) and Clody and Carlton (1980) have suggested that neuroleptics preferentially disrupt responses elicited by less efficacious stimuli, but still permit responses immediately related to primary reinforcement. Although many data are compatible with this interpretation of dopamine function in ingestive behaviour, Blackburn et al. (1989a) have pointed out that it is incomplete in that it fails to acknowledge the ability of food-related stimuli to influence the activity of dopaminergic neurons, which in turn could influence the initiation and vigour of approach behaviours.
No attempt has been made to account for avoidance deficits in terms of the sensorimotor hypothesis. However, the outline of such an approach can readily be sketched. When a naive rat is treated with a neuroleptic drug, shock is capable of eliciting responses from it, but the weaker, less efficacious WS is not. Thus, the rat is unable to acquire the avoidance response. A previously trained rat may experience a conditioned release of dopamine following presentation of shock or shock-related stimuli (Herman et al., 1982) which is able, in part, to compensate for postsynaptic receptor blockade\(^1\). Nonetheless, this interpretation is unable to account for enhanced freezing observed following metoclopramide treatment, and for the adverse effects of shock on the avoidance performance of metoclopramide-treated rats.

As pointed out by Carli et al., (1985) the notion of a sensorimotor deficit can be interpreted in terms of either an attentional failure, where the appropriate stimuli are not available centrally for triggering responses, or an activational failure, in which actions may be selected but cannot be initiated. The experiments of Carli et al. (1985) provided evidence favouring an activational deficit: Animals were capable of responding to a stimulus presented contralateral to their lesioned side so long as the response

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\(^1\) In a similar vein Fowler (1989; Skjoldager & Fowler, 1988) has suggested that the relatively mild impact of neuroleptics at the beginning of a test session may be due to elevated dopamine release as a result of neuroleptic actions at presynaptic autoreceptors.
was to be directed ipsilaterally, but were deficient in responding contralaterally regardless of the position of the cue. The data of Carli et al. led them to support a version of the sensorimotor deficit hypothesis that was similar to the response initiation deficit hypothesis described above, namely that dopamine-depleted rats have no deficit in knowing which environmental stimuli to respond to, but cannot respond to them (see Salmone, 1988, for a similar activational hypothesis of dopamine function).

**Attentional deficit**

It may be unwise to dismiss out of hand the possibility that dopaminergic disruption interferes with attentional mechanisms. The term "attention" is used by different researchers to denote different concepts, and it is unlikely these will ever be reduced to a single construct. Thus, the relationship of attention to dopamine function cannot be determined with a single experiment. The definition of attention used in the experiment of Carli et al. (1985) is equivalent to enhancement of signal detection. Their evidence indicates that this is not a function mediated by dopamine. However, other studies indicate that dopamine may play a role in distinct attentional phenomena.

One line of evidence implicating dopamine in attention comes from a recent study by Brown (1988). Rats were placed in a restraining harness and their forelimbs were stimulated with a nylon bristle. Monitoring of metabolic activity, indexed by $^{14}$C-deoxyglucose analysis, indicated that such
stimulation produced a minor focus of activation in the portion of the striatum topographically related to the forelimb, and that this focus was ringed by an inhibitory surround. 6-OHDA treatment, depleting the dopamine input to the striatum, removed the inhibitory surround. These data were interpreted as indicating that dopamine serves to enhance the signal-to-noise ratio of sensory stimuli, which is often considered to be a function of attentional mechanisms. It is important to note that such changes were independent of learning or any opportunity to respond on the part of the animals.

There is an additional experimental literature, still in its infancy, indicating that dopamine systems may be involved in selective attention mechanisms. This work has relied primarily upon the phenomenon of latent inhibition. In the latent inhibition paradigm, subjects given nonreinforced preexposures to a stimulus are much slower to learn, subsequently, when that stimulus is paired with a reinforcer. For example, rats will exhibit a greatly attenuated conditioned response to a tone following tone-shock pairings if they received 10 or 100 tone presentations prior to the beginning of conditioning. Latent inhibition is disrupted in rats given chronic amphetamine treatment (Hellman, Crider, & Solomon, 1983; Solomon & Staton, 1982; Solomon et al., 1981; Weiner, Lubow, & Feldon, 1984) and in rats that have had dopamine receptor supersensitivity induced by chronic haloperidol treatment (Solomon et al., 1981), but is enhanced
when testing is conducted with neuroleptic-treated rats (Christison, Atwater, Dunn, & Kilts, 1988; Weiner & Feldon, 1987; Weiner, Feldon, & Katz, 1987).

A recent study by Baruch, Hemsley and Gray (1988) examined latent inhibition in schizophrenics. Schizophrenia is believed to be related to a hyperactivity of dopamine systems involving an increase in postsynaptic dopamine receptors (Swerdelow & Koob, 1987). It has been suggested that a diminished ability to screen out irrelevant stimuli may underlie psychotic symptoms (see Clark, Geffen, & Geffen, 1987; Nuechterlein & Dawson, 1984, for reviews). Consistent with this notion is the finding that antipsychotic drugs improve the ability of psychotic patients to attend to relevant stimuli (Spohn, 1977). In their study Baruch et al. (1988) found that acute schizophrenics, but not chronic schizophrenics, showed impairment in a latent inhibition task, relative to normal controls.

Another behavioural test purported to test for selective attention is the blocking paradigm (Mackintosh, 1975). "Blocking" refers to the phenomenon by which the amount of conditioning accruing to one element of a compound conditional stimulus is attenuated by prior conditioning of the other element alone. For example, if rats are conditioned to asymptotic levels of responding using a tone as the conditional stimulus, and then receive as many reinforced tone-light presentations as are normally required for robust conditioning, they will subsequently fail to
exhibit a conditioned response to the light if it is presented alone. The second stimulus (e.g., light) is treated as irrelevant by an intact animal. Blocking, like latent inhibition, was found to be attenuated by chronic amphetamine treatment (Crider, Solomon, & McMahon, 1982) or by dopamine receptor supersensitivity (Crider, Blockel, & Solomon, 1986).

It is tempting to view the alterations in latent inhibition and blocking as alterations in the animals' ability to learn that a given stimulus is irrelevant. However, things are not so simple. The effects on latent inhibition are not seen if the drugs are only administered during pre-exposure to the stimulus, they must also be applied during the conditioning phase (Weiner et al., 1984, 1987). Interestingly, blocking effects are diminished if amphetamine is only administered during initial conditioning or compound conditioning, not if it is administered during both (Ohad, Lubow, Weiner, & Feldon, 1987). These findings were interpreted as indicating that

the drug does not disrupt animals' ability to learn that a given stimulus is irrelevant, but, instead, disrupts their ability to respond to a stimulus as irrelevant under changed contingencies of reinforcement...It points in all cases to a failure in applying previous experience under changed environmental conditions and to an exaggerated control of the prevailing situational demands (Ohad et al., 1987, p. 141).

It is difficult to incorporate these findings within the established bounds of learning theory, and more difficult to extrapolate from them to make strong predictions concerning
effects in behavioural paradigms not explicitly incorporating irrelevant stimuli. Nonetheless, these data are of great importance. What the findings concerning latent inhibition and blocking tell us is that animals with altered dopamine function may learn different things about environmental stimuli than do control animals. What is more, this alteration can occur in a context in which the animals need not actually respond to those stimuli. These data exclude any interpretation of dopamine function based exclusively on hedonic, motivational, or responses initiation processes. Instead, analysis must refer to changes in which stimuli control responses, and to the criteria by which those stimuli gain or lose control.

Using a stimulus-based approach, we might try to consider enhancement of freezing observed after metoclopramide treatment in the light of additional studies conducted by Blanchard and Blanchard (1969b, 1970a,b). They found that rats were more likely to perform an active avoidance response if the eliciting stimulus was salient and discrete (such as a moving prod or an aluminum box), but were more likely to freeze if the eliciting stimulus was less distinct (such as an unmarked portion of an otherwise safe grid floor). Might a neuroleptic-treated rat respond to different stimuli in the box than an undrugged rat? The data from the selective attention studies provide little guidance on this point. If anything, the latent inhibition studies
suggest that neuroleptics should heighten rats' ability to ignore irrelevant background stimuli.

Nonetheless, the studies of Blanchard and Blanchard remind us that changes in defensive response strategies need not rely on concepts such as feedback cues or incentive learning. Instead we can fall back on Bolles' analysis, that "when the test situation looks like a good place to freeze, the animal will freeze if it expects shock; when the situation looks like a good place to run, the animal will run in it" (Bolles, 1975, p. 365). The neuroleptics only need to change what makes a situation look like a good place to freeze.

Preparatory Responding

Examination of preparatory appetitive behaviours led to the suggestion that dopamine-dependent systems in the forebrain may be involved in the potentiation of non-reflexive, topographically flexible, preparatory responses to distal, exteroceptive stimuli (Blackburn, 1985; Blackburn et al., 1989a). Similarly, we may hypothesize that there are certain forebrain systems that mediate the elicitation of active avoidance behaviours by distal cues that signal aversive events. These are flight systems. There are other neural systems responsible for autonomic responses and freezing to shock and shock-related stimuli. We would

2. LeDoux, Iwata, Cicchetti, and Reis (1988) have recently demonstrated that conditioned changes in blood pressure and freezing involve projections of the central amygdaloid nucleus to, respectively, the lateral hypothalamus and the caudal portion of the central gray region.
expect a well-adapted nervous system to establish mutual inhibition between such incompatible responses (Konorski, 1967). Thus, flight systems should inhibit freezing responses, and it seems reasonable to expect that freezing should inhibit flight systems, perhaps at a central level as well as in terms of behavioural competition.

Within this framework we can speculate that dopamine activity facilitates or primes flight systems in the presence of appropriate environmental stimuli, but does not potentiate freezing. In the absence of regular levels of effective dopamine neurotransmission, flight systems are still capable of functioning, but they have lost a facilitatory input. The dopamine systems that promote preparatory behaviours in response to distal stimuli are disabled. This leads to high levels of freezing in anticipation of shock. As a result, the animal experiences additional shock which further enhances the probability of freezing at the expense of flight responses.

Once they have established an expectation that flight, or approach toward certain stimuli, will lead to safety, rats are capable of performing avoidance responses despite neuroleptic treatment. That is, potentiation by dopamine is not required for the flight systems to operate. In the case of one-way avoidance this expectation can be established extremely rapidly, perhaps in the course of a single successful avoidance response. Neuroleptics evidently disrupt the establishment of this expectation. There may be
two mechanisms by which this happens. First, because of treatment with the neuroleptic drug, previously untrained rats are incapable of initiating a first successful response that would provide them with the information that certain responses or stimuli are related to the absence of shock. However, an expectation sufficient to permit avoidance to occur in drugged rats can also be established in the context of escape training. The finding that such training does not have a prophylactic effect if it is conducted while the rat is treated with metoclopramide indicates that the neuroleptic is disrupting the formation of the expectation through an additional mechanism. That is, in addition to disrupting preparatory responding while the animal is drugged, neuroleptic drugs also appear to disrupt some learning process. Conceivably, dopamine plays a role in learning about those stimuli that come to evoke preparatory responses, or in associating responses with those stimuli.

It is important to note that in the absence of effective dopaminergic neurotransmission, animals may still recognize stimuli in their capacity as cues signalling important events. Thus even though a rat's ability to direct a preparatory skeletal responses towards appropriate stimuli may be diminished by neuroleptics, it will still recognize a tone as a signal for shock, and will therefore freeze. This analysis is consistent with the observed effect of neuroleptic drugs on appetitive behaviours. Neuroleptic-treated rats were observed to orient to conditioned meal
cues, but did not engage in vigourous approach responses. Nonetheless, food was still capable of eliciting appropriate consummatory responses from neuroleptic-treated rats (Blackburn et al., 1987, 1989b). Similarly, the freezing of frightened rats may be viewed as a locally-directed consummatory response controlled by the fear-eliciting properties of the WS and the shock-related environment.

If we grant that flight and freezing systems are likely to be mutually inhibitory we can account readily for the findings of Chapter IV. By exposing a rat to shock, or to a cue for a previously inescapable shock, at the same time as we damp its flight system by administering metoclopramide, we may expect an increase in freezing and a decrease in avoidance.

Summary and conclusions

The analysis offered here recognizes that frightened rats usually have a behavioural repertoire that is limited to a few species-typical defence reactions, some of which are compatible with one-way avoidance responding, some of which are incompatible. The current hypothesis contends that neuroleptics bias the selection of which SSDR is elicited towards freezing by impairing the ability of drugged rats to respond to distal cues by fleeing. To this extent the analysis is consistent with the assertion of Jacobs and LoLordo (1980) that the critical feature in determining avoidance responding is the presence of appropriate
supporting stimuli, and with a sensorimotor analysis that views dopamine as potentiating the ability of stimuli to elicit responses (Clody & Carlton, 1980; Marshall et al., 1974; White, 1986). That the effect of the drugs is not primarily on learning is indicated by the ability of neuroleptics to alter freezing responses to a single shock. That the effect is not directly on response mechanisms is indicated by the differential effects of drugged and undrugged escape pretraining, as well as by the observation that neuroleptics do not enhance passive avoidance responding.

This analysis has emerged from the joint consideration of how appetitive and defensive behaviours are influenced by neuroleptic drugs. The data reviewed above indicate that these drugs alter fundamental psychological processes by which environmental stimuli come to exert control over preparatory behaviours. In the future, research will have to integrate findings from the emerging literature indicating a role for dopamine in cognitive mechanisms with more traditional analyses based on motivational approaches. It is hoped that the ideas presented in this dissertation will advance the understanding of those processes an additional step.
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