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10 The Role of Serotonin and Dopamine in Learning to Avoid Aversive Stimuli

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INTRODUCTION

In psychopharmacological research concerned with the possible role played by various neurotransmitter systems in learning, the use of aversive stimuli is extensive. Some researchers may be interested in this class of stimuli per se, they may for example be interested in neurotransmitter systems mediating nociception, but many researchers employ aversive stimuli in learning experiments for convenience. Aversive stimuli such as electrical footshock are easy to deliver in discrete episodes and can easily be quantified. Furthermore, they have unconditioned effects that are less influenced by the animals' state by comparison to many appetitive stimuli such as food, for example, that is most effective in appropriately deprived animals. The effects of aversive stimuli on learning are also relatively free of satiation effects unlike those of food which weaken as the animal eats more.

Operant learning tasks involving the acquisition of responses to escape or avoid electrical footshock are frequently employed. One way to classify these tasks is as passive or active avoidance. Passive avoidance tasks usually involve a learning phase in which particular environmental stimuli are associated with an unconditioned aversive stimulus such as footshock. Testing is done in the absence of shock and the animals' latency to approach the shock-associated stimuli is taken as an index of the strength of original learning. Variations of this task have been employed in an extensive number of studies concerned with the possible role played by neurotransmitter systems in learning and/or memory. A typical approach is to present animals with pairings of environmental stimuli and shock followed by administration of centrally active pharmacological compounds.

The effects of these treatments are assessed in test trials at a later time (cf., McGaugh, Liang, Bennett and Sternberg, 1984). Although studies employing passive avoidance procedures have provided valuable information concerning the involvement of various neurotransmitters in memory (McGaugh, this volume), they will not be discussed here. The present chapter will focus on active avoidance procedures which provide an explicit reward (offset of unconditioned or conditioned aversive stimuli) for an explicit operant response, usually running to a particular place.

Active avoidance tasks can be subdivided into one-way and two-way. Both types of tasks typically involve the use of a long narrow box. In one-way active avoidance, the animal is placed into one side of the box and after a delay (e.g., 10 sec) receives electrical footshock. The shock can be escaped by running to the other (safe) side of the box. The animal is then removed from the safe side and after an intertrial interval, placed again into the side associated with shock and shock again is delivered at the end of the delay period. The latency to make the running response can be taken as an index of learning. Running responses that occur after the delay period when shock has been turned on are termed escape responses; those that eventually occur before shock onset are termed avoidance responses. Running latencies typically show a learning curve, getting shorter from trial to trial as responses shift from escape to avoidance. Theoretically, animals are learning the association between stimuli identifying the shock side of the box and shock itself and the association between stimuli identifying the safe side of the box and safety itself. Reward would be occurring at the time of offset of shock or shock-associated stimuli.

Two-way avoidance training is similar to one-way with one important distinction. After the first trial the animal is not removed from the apparatus. Instead, the animal remains in the original safe side and after a delay a signal (e.g., tone) indicates that shock will occur there. The required response now is to run to the original shock side. This task, although convenient for experimenters because it can be automated and therefore does not require the continuous presence of the experimenter as in one-way avoidance, is difficult for rats to learn because it requires their returning to a place where they previously received shock (cf., Bolles, 1970). In addition, pharmacological treatments that lead to increased locomotor activity (e.g., scopolamine, Bauer, 1982) generally lead to improved performance of two-way avoidance. This may not reflect improved learning, however, as increased activity may simply lead to the occurrence of more shuttle responses. For these reasons, two-way avoidance will not be considered further here.

This chapter will focus on the role of the neurotransmitters serotonin and dopamine in one-way avoidance learning. It will be argued that serotonin may play a role in the modulation of perceptual input and possibly in the modulation of the strength of synapses mediating the learning of associations between stimuli. It will be suggested that the reported effects of dopamine receptor blockers make it possible to identify some of the elements of learning in avoidance tasks and to better understand the effects of reward on learning.

SEROTONIN AND ONE-WAY AVOIDANCE LEARNING

The brain and spinal cord are extensively innervated by serotonergic fibers originating in raphe nuclei of the brainstem (for detailed anatomy see Steinbusch and Nieuwenhuys, 1983). There has been considerable interest in the contribution of these systems to learning (for a review see Ögren, 1982a). Many data suggest that increases in serotonergic neurotransmission lead to impairments in the acquisition and retention of one-way avoidance responding whereas decreases lead to enhanced acquisition.

Perhaps the most thorough psychopharmacological study of the role of serotonin in avoidance behaviour has been carried out by Ögren and his colleagues. Employing acute systemic treatments with p-chloroamphetamine (PCA), a compound that increases the presynaptic release of serotonin, these investigators found that one-way avoidance acquisition and retention was impaired in a dose-dependent manner (Ögren, 1986). This effect was likely due to the effects of PCA on the brain. Thus, animals receiving intrathecal injections of the neurotoxin 5,6-dihydroxytryptamine, that significantly reduced the number of serotonergic synapses in the spinal cord, while showing no change in avoidance acquisition following saline injections, were still seen to be impaired when injected with PCA (Ögren, Berge and Johansson, 1985).

The PCA disruption of avoidance learning seemed to be specific to its action at serotonergic synapses in the brain. Thus, the effect of PCA was blocked by zimeldine or fluoxetine, drugs that prevent serotonin uptake but also inhibit the ability of PCA to stimulate the release of serotonin (Ögren, 1982b; Ögren and Johansson, 1985; Ögren, Johansson, Johansson and Archer, 1982). Furthermore, pretreatment with a large dose of PCA, known to be toxic to serotonergic terminals, blocked the acute effects of PCA on avoidance acquisition (Ögren, 1982b; Ögren and Johansson, 1985; Ögren, et al. 1982). The tryptophan hydroxylase inhibitor parachlorophenylalanine (PCPA) or the serotonin receptor blocker methergoline also blocked the effects of PCA on avoidance learning (Ögren, 1982b, 1985; Ögren and Johansson, 1985). On the other hand, the norepinephrine uptake blocker desipramine failed to mitigate the effects of PCA on avoidance (Ögren, 1982b; Ögren et al. 1982), nor did treatments with the selective norepinephrine neurotoxin DSP4 (Ögren, 1985; Ögren and Johansson, 1985; Ögren et al. 1982). Tyrosine hydroxylase inhibition also failed to influence the effects of PCA on avoidance, nor did the opiate receptor blocker naloxone have any effect (Ögren, 1985; Ögren and Johansson, 1985). Further studies showed that the effect of PCA was related to an increase in serotonin release but not to changes in catecholamine content (Ögren, 1985). Behavioural studies showed that the effect of PCA on avoidance was independent of changes in nociception or locomotor activity (Ögren and Johansson, 1985).

The effect of PCA on avoidance may be due at least in part to its action on serotonergic synapses in the hippocampus and frontal cortex. Intraforebrain injections of 5,7-dihydroxytryptamine produced decreases

prefrontal cortex and hippocampal, but not striatal, serotonin and attenuated the effect of PCA on avoidance learning (Ögren, Johansson and Magnusson, 1985). These excellent and thorough studies of Ögren and his coworkers argue strongly for a role for the brain's serotonergic systems in avoidance learning.

The results of a number of previous studies from other laboratories support those of Ögren and his colleagues. Thus, whereas PCA-induced increases in serotonin release led to deficits in avoidance learning, PCPA-induced decreases in serotonergic neurotransmission led to enhanced acquisition of one-way avoidance responding (Brody, 1970; Schlesinger, Schreiber and Pryor, 1968; Tenen, 1967). Tenen (1967) also found that PCPA-treated rats had increased sensitivity to nociceptive stimuli and hypothesized that this may have led to increased rates of avoidance learning. To examine this possibility, Tenen (1967) conducted further avoidance tests using a higher shock intensity that was highly aversive to both groups. In this study control and PCPA-treated rats did not differ significantly.

Investigators using forebrain serotonin-depleting electrolytic lesions of the dorsal raphe and/or central superior nucleus have found an impairment in one-way avoidance learning (Lorens, Guldberg, Hole, Kohler and Srebro, 1976; Srebro and Lorens, 1975) although one report of increased acquisition has appeared (Plaznik, Kostowski, Bidzinski and Hauptmann, 1980). If these lesions had a selective effect on serotonergic neurons, they would be expected to lead to an enhancement of avoidance learning like that seen following PCPA. Unfortunately, electrolytic lesions are relatively nondiscriminating and would lead to damage to nonserotonergic cells and fibers as well as serotonergic ones. An alternative approach would be to use the selective neurotoxin 5,7-dihydroxytryptamine to place a lesion in the serotonergic cell bodies. When this approach was used, no effect on avoidance learning was seen in spite of substantial depletions of forebrain serotonin (Hole, Fuxe and Jonsson, 1976; Lorens et al. 1976). One possibility suggested by Lorens et al. (1976) is that a compensatory change in brainstem monoamine metabolism may have masked possible effects of the neurotoxic lesion on avoidance learning.

In summary, it appears that increases in forebrain serotonergic neurotransmission lead to deficits in avoidance learning whereas decreases may enhance learning. It may be possible to interpret these results in the context of the hypothesis that serotonin is involved in learning to decrease responding to nonrewarded or irrelevant stimuli. This "tuning-out" hypothesis is supported by the results of a number of studies. Thus, it was found that animals treated with the serotonin synthesis inhibitor PCPA failed to show latent inhibition. This paradigm involves preexposure to a stimulus that subsequently is used as a conditioned stimulus. Animals nondrugged during preexposures in comparison to rats without preexposures showed impaired acquisition during conditioning trials possibly because during preexposure they learned to ignore or tune out the apparently irrelevant stimulus. When serotonergic neurotransmission was blocked during preexposure, this putative tuning out process may have

failed to occur and subsequent conditioning was seen to be similar to that without preexposure. One interpretation is that serotonin normally is involved in the tuning out process (Solomon, Kiney and Scott, 1978). Further support for this hypothesis is provided by the observation that animals treated with PCPA during extinction of a food-rewarded operant response or a punished stepdown response showed slower rates of extinction. Possibly, during extinction animals must learn to tune out stimuli that previously signalled reward (Beninger and Phillips, 1978). Also consistent with this hypothesis is the finding that PCPA treatment retarded the rate of habituation (Carlton and Advokat, 1973; Connor, Stolk, Barchas and Levine, 1970) and led to an increased reactivity to novel stimuli (Connor et al. 1970).

The tuning out hypothesis also provides a useful framework for interpreting the results of a series of studies by Archer and his colleagues. These investigators employed a conditioning procedure involving the delivery of inescapable shock in one compartment of a two-compartment chamber. During retention tests the strength of original conditioning was assessed by measuring the activity level of the animal, presumably longer durations of immobility indicating stronger conditioning. Results showed that rats treated with a low dose of PCA during conditioning showed less immobility than untreated controls during retention tests (Archer, 1982; Archer, Ögren and Johansson, 1981; Archer, Ögren and Ross, 1982). The authors argued that their results could not be attributed to state dependent learning. A number of pharmacological manipulations confirmed that the PCA effect was probably a consequence of elevated release of serotonin. Thus, the effects of PCA were blocked by zimeldine and fluoxetine but not desipramine, pretreatment with a large dose of PCA but not DSP4 blocked the PCA effect and methergoline but not the dopamine receptor blocker pimozide blocked the PCA effect (Archer, 1982; Archer et al. 1981, 1982). According to the tuning out hypothesis, during conditioning trials elevated levels of serotonin produced by PCA may have led the rats to ignore or tune out environmental stimuli associated with shock. When subsequently exposed to those stimuli in retention tests, the rats may have failed to remain immobile because they had failed to learn the association of those stimuli with shock.

The effects of manipulations of central serotonergic neurotransmission on one-way avoidance learning may also be interpreted by the tuning out hypothesis. Animals undergoing avoidance training while levels of serotonergic neurotransmission are elevated may show impaired acquisition because excessive tuning out of environmental stimuli leads to poorer learning of the association between stimuli associated with shock and shock itself and between stimuli associated with safety and safety itself. This poorer learning is also reflected in retention tests conducted a day later when the animals are no longer drugged. Conversely, animals undergoing avoidance training while levels of serotonergic neurotransmission are decreased may show enhanced rates of acquisition because of more effective learning of associations. The mechanism by which serotonin influences the formation of associations between stimuli remains to be worked out. These results, however, suggest that serotonin

may be involved in the modulation of perceptual input and possibly in the modulation of the strength of synapses mediating the learning of associations between stimuli.

DOPAMINE AND ONE-WAY AVOIDANCE LEARNING

The brain's dopaminergic systems, originating in nuclei of the ventral midbrain have been mapped in detail (see Lindvall and Bjorklund, 1983). There has been much interest in the possible behavioural function of these systems including, for example, their role in the control of locomotor activity (Costall and Naylor, 1979; Ungerstedt, 1979), hedonic processes (Wise, 1982), learning (Beninger, 1983, 1987) and eating and drinking (White, 1986). Many data suggest that manipulations that decrease central dopaminergic neurotransmission impair the acquisition of one-way avoidance learning. Given that dopamine may participate in a number of different behavioural functions, interpretation of the effects of decreased dopaminergic transmission in behavioural situations must be made with caution. It will be argued here that dopamine, unlike serotonin, is not involved in the learning of associations between environmental stimuli in avoidance tasks. Rather, dopamine may be involved in mediating the learning that results from the presentation of reward.

When experimentally naive animals were given treatments that decreased neurotransmission at central dopaminergic synapses and then underwent one-way avoidance training, they were seen to be impaired in acquisition and often never made any avoidance responses. This was observed following treatments with dopamine receptor blockers including chlorpromazine (Posluns, 1962), haloperidol (Fibiger, Zis and Phillips, 1975), pimozide (Anisman, Corradini, Tombaugh and Zacharko, 1982a; Anisman, Irwin, Zacharko and Tombaugh, 1982b; Beninger, Mason, Phillips and Fibiger, 1980a,b; Beninger, Phillips and Fibiger, 1983) and *cis*-flupenthixol (Koob, Simon, Herman and LeMoal, 1984). Similar results were reported following bilateral destruction of dopaminergic systems with the neurotoxin, 6-hydroxydopamine (6-OHDA). Sites of injection included the substantia nigra or the nigrostriatal bundle (Zis, Fibiger and Phillips, 1974). It is noteworthy that the deficit seen following bilateral destruction of the dopaminergic nigrostriatal bundle was reversed by treatment with the dopamine precursor 3,4-dihydroxy-L-phenylalanine suggesting that the effect was due to destruction of dopaminergic neurons (Zis et al. 1974). Using small injections of 6-OHDA into dopamine terminal regions Koob et al. (1984) found that combined lesions of the caudate nucleus and nucleus accumbens but not lesions of either alone nor lesions of dopaminergic terminals in the frontal cortex impaired acquisition of one-way avoidance.

When animals were pretrained in a one-way avoidance paradigm and then tested while treated with a drug that disrupted dopaminergic neurotransmission, responding was also seen to be impaired. This was reported following treatments with chlorpromazine (Posluns, 1962) and

pimozide (Beninger et al. 1983). However, responding did not cease immediately but showed a gradual decline with repeated testing, as illustrated in figure 10.1. Two groups (n=48) of rats were pretrained for

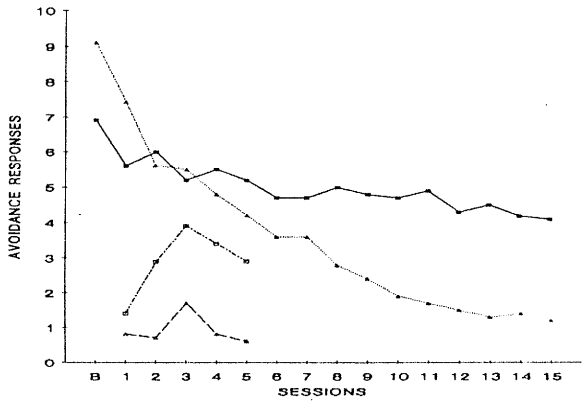

FIG. 10.1. Mean number of avoidance responses per session (10 trials) for groups of rats receiving pretraining or no pretraining prior to testing with pimozide. For the pretrained groups (n=48) the last training session is shown (B) and 15 sessions where they were treated with doses of 0.5 (■) or 1.0 (▲) mg/kg. The nonpretrained groups (n=16) received 5 sessions following injections of 0.5 (□) or 1.0 (△) mg/kg. (Adapted from Beninger et al., 1983.)

2-10 days on a one-way avoidance task with 10 trials per day. One group then received 0.5 mg/kg and the other 1.0 mg/kg pimozide prior to each of the next 15 sessions. Two additional nonpretrained groups (n=16) received the same doses of pimozide for 5 sessions. The results showed that the high dose of pimozide blocked the acquisition of avoidance responding in the nonpretrained groups. Pimozide also impaired the avoidance responding of the pretrained animals, gradually reducing performance over 15 sessions to a level near that seen in the nonpretrained group (Beninger et al. 1983). What is particularly noteworthy, however, is the initial large difference in the level of performance of the pretrained and nonpretrained animals when given pimozide. Clearly it is inadequate to argue that the disruptive effects of dopamine receptor blockade on the acquisition of avoidance responding in nonpretrained animals was due to an effect of the drug on the animals' ability to initiate avoidance responses. The initial high level of performance observed in pretrained animals given pimozide argues against this position. These results suggest that intact dopaminergic neurotransmission is required for the acquisition of avoidance responding. Once animals have been trained, they can for some trials perform the avoidance response when dopamine receptors are blocked but with

continued testing in the presence of the drug, the ability to avoid gradually is lost.

If the deficits in avoidance responding following treatments that disrupt dopaminergic neurotransmission cannot be attributed to impairments in the animals' ability to initiate responses, to what can they be attributed? One possibility is that the learning of an association between preshock stimuli and shock itself or between safety related stimuli and safety itself requires dopamine for its initial establishment and for its maintenance once that learning is established. However, research has shown this hypothesis to be incorrect. The results of a number of studies showed that animals with impaired dopaminergic neurotransmission were unimpaired in their ability to form associations between stimuli.

Some of the earliest reports were anecdotal. For example, Fibiger et al. (1975) observed that haloperidol disrupted the acquisition of avoidance responding but noted that when in the presence of stimuli that regularly preceded shock (conditioned stimuli; CSs), the drugged animals "...urinated, defecated and showed other signs typically associated with fear in this species, suggesting that these animals were aware of the significance of the CS" (p. 313). In a subsequent study Beninger et al. (1980b) took advantage of the conditioned suppression paradigm to systematically test the hypothesis that animals treated with dopamine receptor blockers, although failing to avoid, learn the association between preshock stimuli and shock. Conditioned suppression was first reported by Estes and Skinner (1941). They trained rats to lever press for food and then presented them with a CS followed by footshock. During subsequent presentation of the CS, responding was observed to be suppressed indicating that the rats had learned the association between the CS and shock. Beninger et al. (1980b) similarly trained rats to lever press for food. They then subjected them to five sessions of one-way avoidance training in which a 10-sec tone was used to signal shock in the shock side of the test chamber. Prior to each of these sessions groups received saline, 0.5 or 1.0 mg/kg pimozide. As already discussed (see figure 10.1), the pimozide-treated animals failed to acquire the avoidance response. All groups were then replaced into the lever press apparatus when drug-free and tested for their response to the tone. Conditioned suppression was observed in the saline and pimozide groups but not in rats never receiving tone-shock pairings. Thus, the animals had learned the association between the preshock stimuli and shock while under the influence of pimozide even though avoidance responding was not observed.

In one of the studies by Archer (1982) discussed in the serotonin section, one of his control groups received the high dose of 2.2 mg/kg of pimozide prior to pairings of environmental stimuli with footshock. When tested for immobility in the presence of the shock-associated stimuli while undrugged on the following day, this group evidenced a level of conditioning comparable to saline-treated controls. This result is in good agreement with the findings of Beninger et al. (1980b). Anisman et al. (1982b) injected animals with vehicle or pimozide and then presented zero or ten pairings of light plus tone with shock. Several days later when tested undrugged for avoidance acquisition with the light plus tone

stimulus signalling shock, animals previously receiving vehicle injections and ten pairings acquired the avoidance response significantly faster than those receiving zero pairings. The same effect was observed in animals receiving pairings while under the influence of pimozide. This result, along with those of Beninger et al. (1980b) and Archer (1982) provides strong support for the conclusion that blockade of dopaminergic neurotransmission does not impair an animal's ability to learn the association between environmental cues that signal shock and shock itself.

Data also suggest that animals undergoing avoidance training while under the influence of dopamine receptor blockers learn the association between environmental stimuli signalling safety and safety itself, i.e., they learn the location of safety. This was shown in the study of Beninger et al. (1980b) when mean escape or avoidance latencies of pimozide-treated rats were examined from trial to trial in the first test session. As shown in figure 10.2, mean escape latencies were seen to decline across trials for

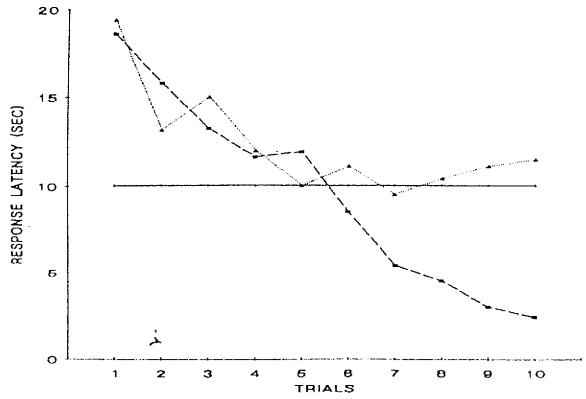

FIG. 10.2. Mean latency (sec) to escape (>10 sec) or avoid (< 10 sec) for groups of 8 rats receiving 10 trials of one-way avoidance training. Groups were pretreated with vehicle (■) or 1.0 mg/kg (▲) pimozide. (Adapted from Beninger et al., 1980a.)

both the saline-treated group and the drug group. However, whereas the mean latencies of the control group continued to decrease to values of less than 10 sec, indicating avoidance responses, the pimozide group failed to acquire the avoidance response. The declining curve in the pimozide-treated group over the first five trials suggests that they were learning the location of safety from trial to trial in a manner similar to the control group. Anisman et al. (1982a) tested this possibility directly by requiring pimozide-treated mice to perform a discriminated avoidance response. In a Y-maze, shock escape or avoidance could only be made by entering the appropriate arm of the maze as indicated by visual or positional cues. They found that although pimozide impaired acquisition

of the avoidance response, it had no significant effect on the animals' ability to select the appropriate arm. Thus, the association of cues signalling safety and safety itself was learned in animals treated with a dopamine receptor blocker.

These results illustrate another interesting aspect of the effects of treatments that reduce dopaminergic neurotransmission on behaviour. Although pimozide-treated animals failed to acquire the avoidance response, they readily escaped when shock was presented. Apparently intense or nociceptive stimulation like that provided by unconditioned aversive stimuli such as electrical shock can induce running responses in pimozide-treated rats even though the presentation of conditioned aversive stimuli such as environmental cues signalling shock cannot. Some researchers have taken advantage of this fact in studying the possible role of dopamine in learning. Price and Fibiger (1975) found that bilateral 6-OHDA lesions of the substantia nigra failed to affect learning of a brightness discrimination in an electrified Y-maze. Corradini, Tombaugh and Anisman (1984) reported that pimozide, although slowing escape times, failed to affect the learning of a place or cue discrimination in a T-maze partially submerged in water requiring the mice to swim to safety. These findings are consistent with the view that disruption of dopaminergic function does not impair the ability of animals to learn associations between stimuli.

Following is a list of points that summarizes the results of studies of the effects of disrupting dopaminergic neurotransmission on avoidance learning:

1) Unconditioned aversive stimuli (e.g., electrical footshock) retain their ability to elicit escape behaviour.
2) The learning of associations between environmental stimuli signalling unconditioned aversive stimuli and those unconditioned aversive stimuli themselves is intact.
3) The learning of associations between environmental stimuli signalling safety and safety itself (i.e., the location of safety) is intact.
4) The ability of pretrained animals to perform the avoidance response is initially intact but becomes lost with repeated testing.
5) The nonpretrained animal has an impaired ability to learn the avoidance response.

The nonpretrained animal with dopaminergic function reduced can learn that shock is imminent and can learn the location of safety in an avoidance task but apparently cannot learn to move to safety prior to shock onset. The use of the term "learn" with respect to the avoidance response is important. It is not simply the case that disrupted dopaminergic function leads to an inability to perform the avoidance response because pretrained animals given dopamine receptor blockers are observed to perform the avoidance response. This learned response is lost, however,

with repeated testing while under the influence of dopamine receptor blockade. It can be concluded that dopamine is involved in learning and maintaining the ability to avoid unconditioned aversive stimuli.

DOPAMINE AND INCENTIVE MOTIVATIONAL LEARNING

The type of learning that dopamine appears to mediate in one-way avoidance tasks can be understood in the context of incentive motivational learning theory (Beninger, 1983, 1987; Bindra, 1974). This type of learning is said to take place when reward is presented. In avoidance tasks reward occurs at the time of shock offset. According to incentive motivational learning theory, environmental stimuli that are presented in close temporal contiguity with reward become associated with reward and through this association those stimuli acquire the motivational properties of the reward itself; reward has the unconditioned ability to attract the animal. As a consequence, environmental stimuli associated with reward become conditioned incentive motivational stimuli, having acquired an enhanced ability to attract the animal. In one-way avoidance tasks, the stimuli that are most closely associated with reward (shock offset) are the safety related stimuli, i.e., the side of the chamber where shock never occurs. Thus, the safety related stimuli would be the ones that become conditioned incentive motivational stimuli.

Studies of the effects of disrupted dopaminergic neurotransmission on avoidance learning have revealed important details concerning the components of incentive learning in which dopamine may be involved (figure 10.3). Thus, in the absence of intact dopaminergic function, animals apparently can learn the association between reward (shock offset) and safety related stimuli. However, without intact dopaminergic neurotransmission, the incentive motivational properties of the reward may not be transferred to the safety related stimuli. Ironically, therefore, animals can learn where safety is but cannot learn to go there when dopaminergic neurotransmission is blocked. The studies of the effects of dopamine receptor blockers on avoidance learning further reveal that if animals are pretrained before drug testing, their ability to perform the avoidance response initially is intact and is only seen to diminish with repeated testing. This would suggest that the incentive motivational learning that may be mediated by dopamine involves a change in a nondopaminergic system in the brain. This putative dopamine-mediated change apparently can influence avoidance responding at least transiently even when dopaminergic neurotransmission is blocked. Again it seems ironic that a pretrained animal, when given dopamine receptor blockers initially can avoid but then loses this ability gradually even though the animal retains previous learning concerning the imminence of shock in the shock side of the chamber and the location of safety.

The profile of effects of disrupted dopaminergic neurotransmission on incentive motivational learning in avoidance tasks is in excellent agreement

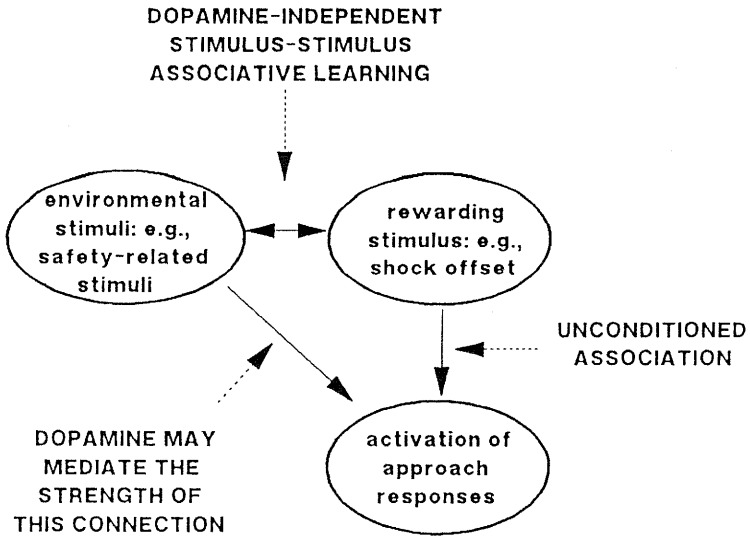

FIG. 10.3. Summary of some of the elements of learning an avoidance response and the possible role of dopamine in each.

with the results of parallel studies of appetitive tasks (cf., Beninger, 1983, 1987). For example, the acquisition of lever pressing for food was impaired by dopamine receptor blockade (Tombaugh, Tombaugh and Anisman, 1979; Wise and Schwartz, 1981) but if animals were trained first and then tested while drugged, responding initially was little affected but was seen to decline gradually within or across sessions (e.g., Wise, Spindler, deWit and Gerber, 1978).

Another form of learning that can be understood within the context of incentive motivational learning theory is stimulant-produced environment-specific conditioned activity. In this paradigm, animals are repeatedly given injections of a drug that enhances dopaminergic neurotransmission in a specific environment and are then tested in the same environment following a vehicle injection. Results showed that the activity level of animals previously receiving the drug in the test environment was significantly higher than that of control animals having a similar drug history and similar number of exposures to the test environment but not having the two associated. As increased dopaminergic neurotransmission is thought to occur when reward is presented, leading to incentive motivational learning, this effect can be understood as an incentive conditioning phenomenon, the stimuli in the test environment acquiring enhanced ability to activate approach responses by association with drug-induced increased dopaminergic neurotransmission. In agreement with the avoidance experiments, studies have shown that pimozide blocked the acquisition of environment-specific

conditioned acitivity based on amphetamine or cocaine but once conditioning had occurred, pimozide failed to block the expression of conditioned activity (Beninger and Hahn, 1983; Beninger and Herz, 1986). The results of these and numerous related studies suggest that dopamine may be involved in incentive motivational learning occurring in a wide variety of tasks.

It remains the task of future research to identify the mechanism by which dopamine produces changes in the ability of environmental stimuli to elicit approach responses. The work of Koob et al. (1984) showed that the observation of impaired acquisition of avoidance learning required destruction of the dopaminergic innervation of the caudate nucleus and nucleus accumbens suggesting that dopamine in these regions may mediate incentive learning. These dorsal and ventral striatal regions receive extensive neocortical and allocortical projections and their outputs project to globus pallidus and zona reticulata of the substantia nigra (Nauta and Domesick, 1984), nuclei that project in turn to the mesencephalic locomotor region (Garcia-Rill, 1986). This anatomical organization places the striatal dopaminergic terminals in the right place to modulate the ability of environmental stimuli to influence approach responses via striatal efferents. Environmental stimuli would activate corticostriatal projections. Many authors have emphasized the apparent role of the striatum in gating the influence that sensory input may have on motor output. Evarts and Wise (1984), for example, suggested that the striatum may play a higher order role in motor control than simply controlling movements. They saw the striatum as an interface between motor areas and cortical areas involved in higher brain function. Similarly, Schneider and his colleagues saw the striatum as affecting motor behaviour by gating sensory input to systems controlling movement (Lidsky, Manetto and Schneider, 1985; Schneider, 1984).

Electrophysiological studies have shown that the responses of some cells in the striatum of monkeys were unrelated to movement alone. Instead, these cells were seen to be activated by an auditory stimulus when that stimulus was a cue for food delivery (a conditioned incentive motivational stimulus) but not when that stimulus failed to predict reward (see Evarts and Wise, 1984). Mogenson (1984) and his coworkers showed that the responses of output cells of the nucleus accumbens to stimulation of inputs were modulated by stimulation of dopaminergic afferents to the accumbens. These results provide further support for the suggestion that the striatum may be actively involved in controlling the influence that sensory stimuli have on response systems. The results of Mogenson (1984) further support the suggestion that dopamine in the striatum may subserve this control.

In summary, the effects of reward on behaviour are to mediate a change in environmental stimuli that predict reward leading to an enhanced ability of those stimuli to elicit approach responses, i.e., those stimuli become conditioned incentive motivational stimuli. When reward is removed, conditioned incentive stimuli retain their ability to elicit approach responses transiently but this ability is lost with repeated exposure to those stimuli in the absence of reward. Dopamine in the

dorsal and ventral striatum appears to mediate the effects of reward on behaviour. In light of the anatomical organization of the striatum and the apparent function of dopamine in gating the influence of sensory stimuli on motor systems, it might be the case that dopamine modulates the effectiveness of synapses in the striatum where the presynaptic terminals are activated as a result of sensory events and the postsynaptic cells influence response systems.

There is evidence from electrophysiological studies of peripheral nervous system structures that dopamine can modulate synaptic effectiveness leading to an increased influence of presynaptic terminals on postsynaptic cells. The rabbit superior cervical ganglion, which contains cholinergic afferents and dopaminergic interneurons that synapse on the efferent cells, was employed in these studies. Using the sucrose gap method, it was shown that dopamine produced a long-term enhancement of the postsynaptic potential resulting from stimulation of muscarinic cholinergic receptors with exogenous muscarinic agonists (Libet, Kobayashi and Tanaka, 1975; Mochida, Kobayashi and Libet, 1987). It has also been shown that dopamine could similarly modify the response of the postsynaptic cells resulting from orthodromic stimulation of cholinergic afferents to the ganglion (Ashe and Libet, 1981). This modulatory action of dopamine has more recently been shown in the central nervous system. Recording from CA1 pyramidal hippocampal cells in vitro, Gribkoff and Ashe (1984) showed that dopamine produced a long lasting potentiation of the population response resulting from stimulation of the Schaffer-collateral pathway that is afferent to the pyramidal cells. These studies provide strong evidence that dopamine can modulate the effectiveness of nondopaminergic synapses leading to an increased influence of presynaptic terminals on postsynaptic cells.

Although this modulatory action of dopamine has not yet been demonstrated in the striatum, findings in the peripheral nervous system and the hippocampus provide clues to the possible mechanism by which dopamine may produce incentive motivational learning by altering the ability of reward-related stimuli to influence approach responses. It is noteworthy that there are cholinergic interneurons within the dorsal and ventral striatum that have been shown to be influenced by cortical afferents (Simon, 1982). The results of ultrastructural studies suggest that dopaminergic afferents and possibly cholinergic interneurons synapse on medium-size densely spiny neurons that are the major projection neurons of the striatum (Bolam, 1984). Thus, the major elements of the peripheral heterosynaptic mechanism demonstrating a role for dopamine in learning may be found in the central nervous system. These include cells receiving both dopaminergic and cholinergic afferents. Of course, it remains possible that dopamine may influence learning through a different mechanism, involving, for example, the modification of glutaminergic corticostriatal projections. The resolution of the mechanism awaits further study; however, work to date provides intriguing possibilities for the way in which dopamine may mediate the effects of reward on incentive motivational learning.

CONCLUSIONS

This chapter has focused on the possible role of the neurotransmitters serotonin and dopamine in one-way avoidance learning. Results revealed that animals with reduced serotonergic function showed enhanced rates of acquisition whereas animals with elevated levels of synaptic serotonin were impaired in their ability to learn and retain the one-way avoidance task. By integrating these results with others from studies employing various behavioural methodologies it was suggested that serotonin may be involved in tuning out or reducing responsiveness to nonrewarded or irrelevant stimuli. Although the mechanism by which serotonin produces these effects remains unknown, it was concluded that serotonin may be involved in the modulation of perceptual input and possibly in the modulation of the strength of synapses mediating the learning of associations between stimuli.

Research into the possible role of dopamine in avoidance learning has revealed a number of results that lead to a better understanding of the elements of learning in this task. Results showed that decreased dopaminergic function, unlike increased serotonergic function, apparently had little effect on the learning of associations between environmental stimuli signalling shock and shock itself or environmental stimuli signalling safety and safety itself. Instead, blockade of dopaminergic neurotransmission impaired animals' ability to learn to go to safety when presented with conditioned stimuli signalling imminent shock. If a pretrained animal received a dopamine receptor blocker prior to testing, the animal was found to transiently retain avoidance responding but with continued testing while drugged, it gradually lost the avoidance response. It was concluded that dopamine plays a role in reward-related incentive motivation learning, involving changes in the ability of reward-related stimuli to elicit approach responses. Possibly this involves a dopamine mediated modification of synapses in the dorsal and ventral striatum where environmental stimuli influence responses systems via corticostriatal projections.

It can be concluded that psychopharmacological studies of aversively motivated behavior have provided valuable insights into the role of the neurotransmitters serotonin and dopamine in learning. The continued integration of the results of these studies with anatomical, physiological and neurochemical results will eventually lead to a more complete knowledge of the mechanisms underlying the manner in which serotonin and dopamine influence learning.

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