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MEETING REPORT

Dissociating the Effects of Altered Dopaminergic Function on Performance and Learning

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BENINGER, R. J. *Dissociating the effects of altered dopaminergic function on performance and learning*. BRAIN RES BULL **23**(4/5) 365–371, 1989.—Since the early days of physiological psychology it has been recognized that the behavioral effects of many manipulations often could not easily be attributed to impairments in learning because of possible changes in performance. Current psychopharmacological research concerned with evaluating the possible role of dopamine in reward-related learning is faced with the same problem. It is well known that manipulations that increase dopaminergic neurotransmission increase locomotor activity and manipulations that decrease dopaminergic neurotransmission decrease locomotor activity. These performance effects potentially influence any possible effects of manipulations of dopaminergic function on learning. To untangle these possible effects researchers have developed a number of approaches. These include observing patterns of responding on operant schedules within and across sessions, comparing avoidance responding in trained and untrained animals, conditioned reward and place conditioning procedures that separate drug and test sessions, stimulant self-administration procedures and the use of more than one conditioned stimulus to control responding. In each case data continue to support the conclusion that dopamine is involved in reward-related learning.

Dopamine Operant responding Avoidance learning Conditioned reward Place conditioning

ONE of the best known results in psychopharmacology is the locomotor activity enhancing effects of dopamine (DA) agonists and the locomotor activity reducing effects of DA antagonists (1) (see Figs. 1 and 2). In hundreds of experiments every year these effects are used as control conditions against which the effects of other pharmacological or neurophysiological manipulations are evaluated. There can be little doubt that manipulations that alter dopaminergic neurotransmission have an unconditioned effect on the level of locomotor activity of animals. Any experiment that involves the assessment of dopaminergic manipulations on behavioral dependent variables will be faced with these locomotor effects. The unconfounded conclusion that a manipulation of DA resulted in some other effect, for example an effect on learning, is only possible if it can be shown that the effect is not the result of these unconditioned changes in locomotor activity.

This problem of dissociating the well-established locomotor effects of manipulations of dopaminergic neurotransmission from possible effects on learning is an example of one of the oldest problems in physiological psychology, i.e., are the effects on performance or learning. Many textbooks of physiological psychology contain some reference to this problem. For example, Milner (20) pointed out that "Claims of improved learning should never be made on the basis of improved performance of a single type of response in a single species" (p. 457). Grossman (15) stated that ". . . if we find that an animal with a particular brain lesion no longer performs a preoperatively learned response, we have no reason to assume that memory itself is afflicted" (p. 378) and Thompson (26) remarked that:

> ". . . the student must remember the importance of the distinction between learning and performance. Learning is assumed or inferred to occur in the brain as a person or animal learns something. However, many other processes may be occurring, such as fear, arousal, habituation, or fatigue, that are different from learning but very strongly affect the performance of the subject at any particular time in the experiment." (pp. 504–505).

Although the methods of physiological psychology have changed to include many new techniques, including the use of pharmacological compounds relatively specific for various neurotransmitter systems, the old problem persists and challenges behavioral researchers to find procedures that unconfound interpretations of results based on performance versus learning.

Many data now suggest that DA may be involved in reward-related learning (1,28). However, the unequivocal demonstration of a role for DA in this type of learning has been dogged by the problem of performance effects of manipulations of DA systems. Perhaps in no other area of psychopharmacology has the debate been keener than that between those claiming a role for DA in reward-related learning and those who attributed the changes in responding for reward following manipulations of DA to perfor-

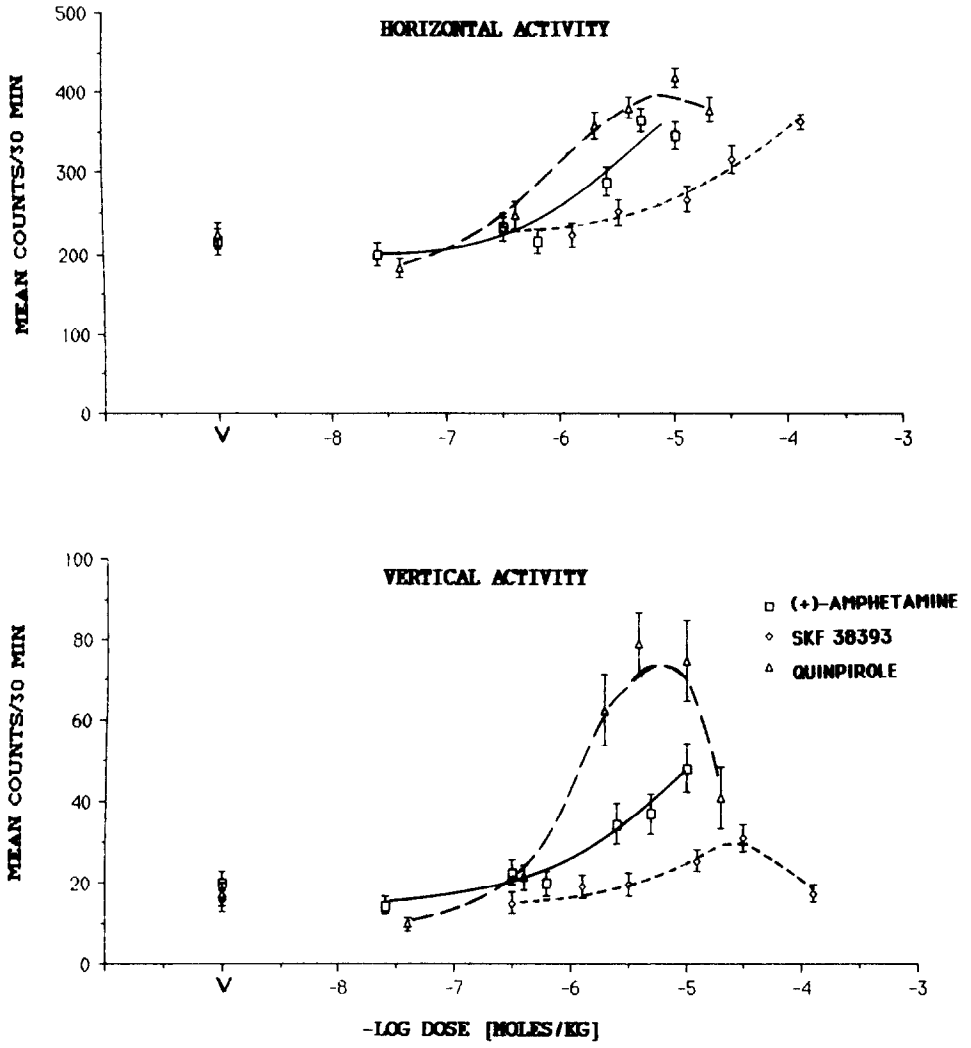

FIG. 1. Dose-response curves illustrating mean (±SEM) horizontal and vertical activity following administration of the indirect-acting dopamine agonist, (+)-amphetamine, the D1 agonist, SKF 38393 or the D2 agonist, quinpirole. For each drug, 12 rats that had previously been habituated to the testing environment were treated (IP) with all doses in a random order. Sessions in automated chambers [see (3)] assessing horizontal and vertical activity were 4 hr in duration and occurred 48 hr apart. (+)-Amphetamine [vehicle, (V), 0.01, 0.1, 0.25, 1.0, 2.0 and 4.0 mg/kg], quinpirole (V, 0.01, 0.1, 0.5, 1.0, 2.5 and 5.0 mg/kg) and SKF 38393 (V, 0.1, 0.4, 1.0, 4.0, 10.0 and 40.0 mg/kg) doses have been transformed (log of moles/kg) to facilitate comparisons among drugs. (From Mazurski, E. J., unpublished Ph.D. thesis, Queen's University, Kingston, 1988.)

mance effects. This debate has generated a number of modifications of old techniques and new techniques for evaluating the behavioral effects of manipulations of DA systems. The present paper will review some of the approaches that have been taken to identify the contribution of DA to reward-related learning. There is no wish to claim that DA is not involved in the control of locomotor activity. Clearly it is. Rather, the claim is that with appropriate techniques sensitive to the problem of identifying effects on performance versus learning, it can be demonstrated convincingly that DA is also involved in reward-related learning.

DA AND REWARDED OPERANT RESPONDING

When untrained rats were injected with the DA receptor blocker, pimozide, prior to undergoing lever-press response training for food reward, they were significantly impaired in acquisition (27,30). Although this effect is consistent with the conclusion that intact dopaminergic neurotransmission may be necessary for reward-related learning, the effect also might be expected if the drug produced a decrease in locomotor activity, a performance effect. On the basis of acquisition data alone it is not possible to decide between these two alternatives. Another possibility that will not be discussed here is that pimozide may affect the primary motivation to eat. However, the results of previous studies do not support this hypothesis (18).

The performance versus learning interpretations of the effects of DA receptor blockers on lever pressing for food reward can be assessed when observing the effects of pimozide on the responding of trained rats. However, here too, care must be taken to avoid confusing the two effects. When rats well-trained to lever-press for food are injected with pimozide, their response rates are seen to show an overall dose-dependent decline. This observation alone

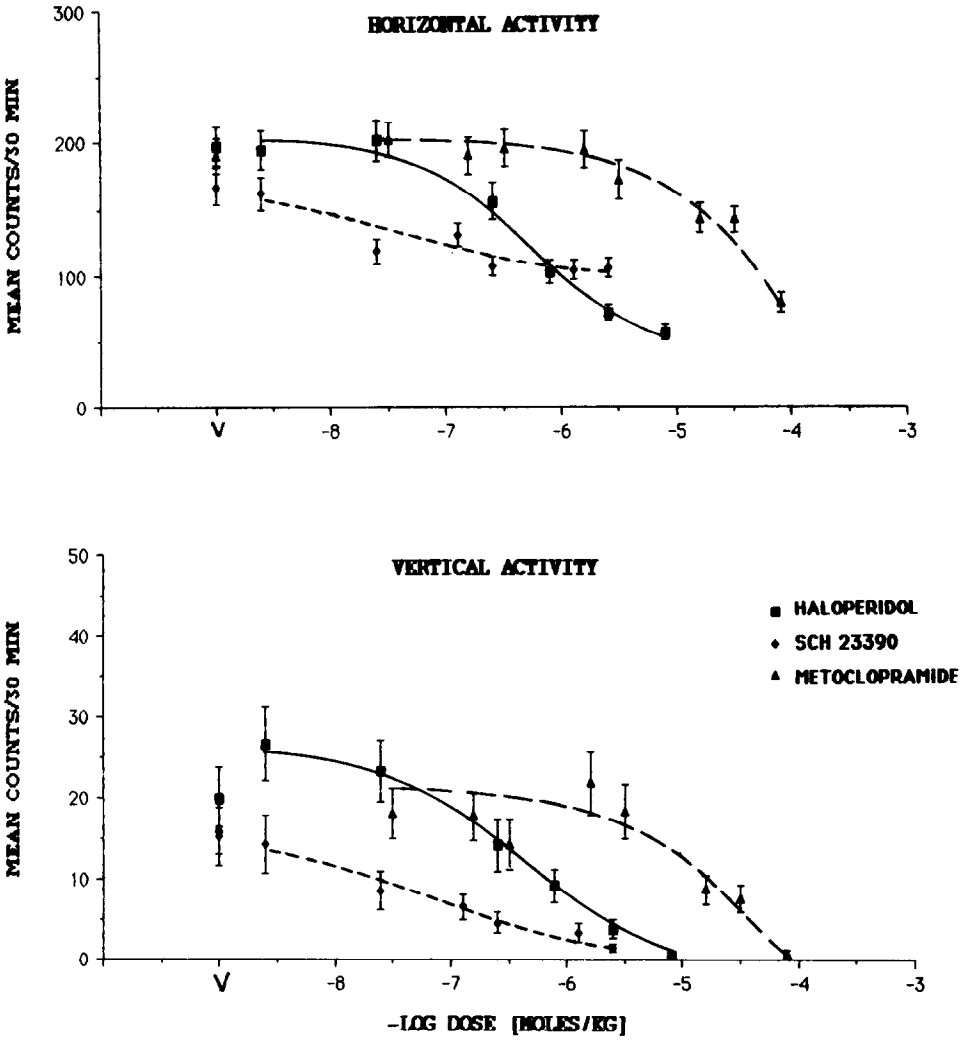

FIG. 2. Dose-response curves illustrating mean (±SEM) horizontal and vertical activity following administration of the dopamine antagonist, haloperidol, the D1 antagonist, SCH 23390 or the D2 antagonist, metoclopramide. Twelve rats were treated with each drug (see Fig. 1 caption for procedure). Haloperidol [vehicle (V), 0.001, 0.01, 0.1, 0.3, 1.0 and 3.0 mg/kg, IP], SCH 23390 (0, 0.001, 0.01, 0.05, 0.1, 0.5 and 1.0 mg/kg, SC) and metoclopramide (0, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, 10.0 and 25.0 mg/kg IP) doses have been transformed to facilitate comparisons among drugs. (From Mazurski, E. J., unpublished Ph.D. thesis, Queen's University, Kingston, 1988.)

could reflect either an effect on performance or reward-related learning. To decide between the two, Wise *et al.* (31), in one of the now-classic papers in this field, observed the *pattern* of responding in animals given pimozide. What they saw was that the drugged rats showed a gradual, extinction-like day-to-day decline in responding for food. Others have replicated this effect (19) and also reported intrasession extinction-like declines in responding following injection with DA receptor blockers (19). Control studies ruled out some possible interpretations of these results including: 1) an accumulation of drug with repeated dosing or 2) a gradual onset of drug action as the drug slowly reached the brain. If the effects of the drug were on performance it might be expected that response rates would not change over time as they did. Results seemed to support the hypothesis that DA neurons participated in the learning underlying the effects of reward on behavior.

From the point of view of the performance hypothesis, it might still be possible to account for the apparent extinction-like declines seen in trained animals treated with DA receptor blockers. Thus, Mason *et al.* (19) have suggested that perhaps animals injected with pimozide gradually learn that it is aversive to perform responses while under the influence of the drug. From this point of view the gradual decline in operant responding in animals treated with pimozide may actually be a curve reflecting learning of these putative aversive effects. If this hypothesis is correct, it might be expected that animals having extensive experience with the drug in their home cage prior to the first administration in the context of the operant task would learn about these putative aversive effects. As a result they might show less responding than animals without similar experience. However, results have shown that prior experience with home cage injections does not influence the extinction-like pattern produced by administration of the drug in the operant test situation (19,31). Again, from the point of view of the performance hypothesis it could be argued that learning about the putative aversive effects of the drug on operant responding is response-specific. This learning, therefore, does not transfer from the home cage to the test situation. This would account for the

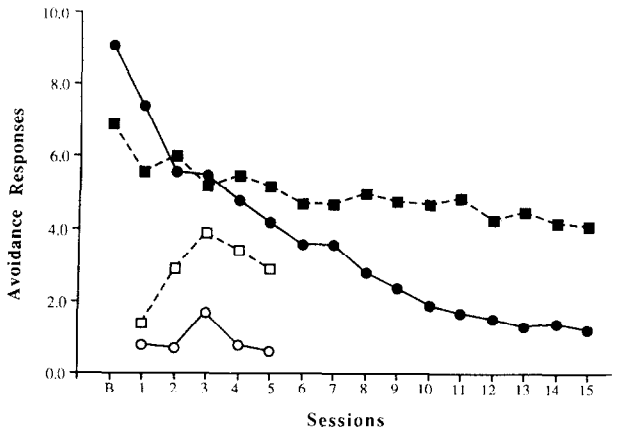

FIG. 3. Mean number of avoidance responses per session (10 trials) for groups of rats receiving pretraining or no pretraining prior to testing with pimozide. For the pretrained groups (n = 48) the last training session is shown (B) and 15 sessions where they were treated with doses of 0.5 (■) or 1.0 (●) mg/kg. The nonpretrained groups (n = 16) received 5 sessions following injections of 0.5 (□) or 1.0 (○) mg/kg. [Adapted from (7).]

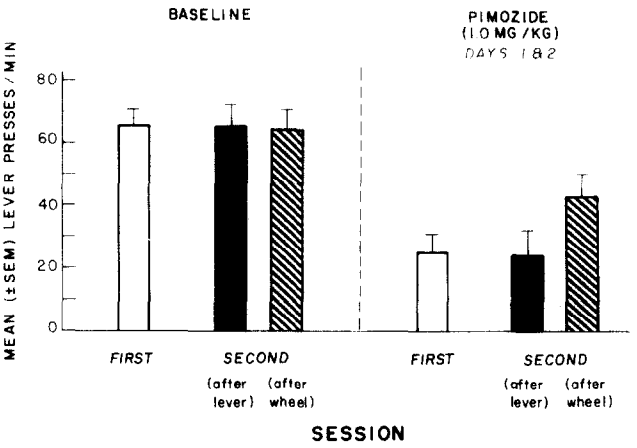

FIG. 4. Mean (±SEM) lever-press rate (responses/min) during the first 8 training days (baseline) and the 2 pimozide test days. The open bar represents the first 15-min session of lever-pressing. The solid bar represents lever-pressing in the second 15-min session when it followed a lever-pressing session; the cross-hatched bar represents lever-pressing in the second session when it followed wheel running N = 12. [From (4).]

failure to see transfer.

The above discussion points out the extreme difficulty in unequivocally ruling out a performance effect in the experiments evaluating the effects of pimozide on operant responding for reward. If data from only these studies were available, the issue would remain unresolved. However, data from many additional approaches, as discussed below, support the hypothesis that DA is involved in reward-related learning.

DA AND AVOIDANCE LEARNING

One task that consistently has been shown to be impaired by treatment with DA receptor blockers is learning to avoid an aversive stimulus by running to the safe side of a shuttle box (2). In fact, so reliable is this effect that it is used by the pharmaceutical industry to screen new compounds for possible DA receptor blocking activity. Although animals treated with DA receptor blockers fail to learn to avoid an aversive stimulus (usually mild electric footshock), they readily escape when shock is presented. Therefore, it is difficult to argue that the drug has blocked the ability of the rat to perform the response. However, a somewhat more specific performance interpretation has continued to dominate the explanation of the observed deficits in this task. It is frequently suggested in the literature that animals treated with DA receptor blockers are impaired in their ability to *initiate* the avoidance response. According to this argument, the onset of footshock provides additional sensory input that allows the animal to overcome the initiation deficit and escape responding is seen.

It is possible, however, to show that a deficit in the ability to initiate responses cannot explain the effects of DA receptor blockers in the avoidance paradigm. Thus, if rats are pretrained in the avoidance task before receiving testing with DA receptor blockers, the drugs fail to eliminate avoidance responding on first administration (7) (Fig. 3). With repeated drug testing, the avoidance response gradually is lost but *the initial resistance of the avoidance response to the effects of the DA receptor blocker clearly shows that the drug does not simply block the ability of rats to initiate the response.*

Avoidance responding can be understood to involve the learning of stimulus-stimulus associations and reward-related learning. Previous studies have shown that DA is not involved in the learning of stimulus-stimulus associations; for example, animals receiving pairings of a tone with shock while under the influence of pimozide learn the association between the two stimuli (5). In avoidance learning, the reward is the offset of the aversive stimulus. It has been argued that the effects of reward are to increase the incentive value of environmental stimuli that signal reward (1,2). In the case of avoidance, the incentive learning effects of rewarding shock offset might be to increase the subsequent ability of safety-related stimuli to elicit approach responses; an approach to these stimuli would be an escape or avoidance response. The acquisition of this type of learning is impaired in animals treated with DA receptor blockers (5,7). Thus, DA may play a role in reward-related learning in avoidance tasks [for further discussion see Beninger (2)].

DA AND CONDITIONED REWARD

As treatments that reduce dopaminergic neurotransmission clearly lead to a reduction in locomotor activity, some researchers have attempted to separate the time of drug administration from the evaluation of the effects of the drug. Procedures of some conditioned reward paradigms provide a useful tool for this purpose. In one example, rats receive pairings of a conditioned stimulus (CS) with an unconditioned stimulus (UCS) during several sessions. They are then tested in later sessions to evaluate the ability of the CS to act as a reward in its own right. For example, the ability of the CS to control lever-press responding might be evaluated. With this procedure, animals can be treated with a DA receptor blocker during the pairing sessions when response demands are low (the only requirement being that the rat consume the UCS, for example, food) and can subsequently be tested for learning later when in a drug-free state. This may permit an evaluation of the effects of DA receptor blockade on learning that is unconfounded by possible effects on performance.

In two studies the effects of pimozide on the establishment of conditioned reward have been evaluated. In both, rats received several sessions of exposure to a chamber outfitted with two levers. Pressing one of the levers produced a brief stimulus (tone or light) but otherwise lever-presses had no programmed conse-

quences. The levers were then removed from the test chamber and the rats received several sessions of pairings of the tone or light CS with food. During this phase some groups were treated with pimozide or its vehicle. Rats were then retested in several sessions again with the two levers inserted into the chamber and again with presses on one of them producing the CS. Note that rats never received food for pressing the levers. Results revealed that vehicle-treated rats pressed the lever producing the CS significantly more than the other lever and more than they had pressed it during the initial preexposure sessions thereby showing that the CS had acquired the ability to act as a conditioned reward. Animals treated with pimozide during the pairing phase showed a dose-dependent decrease in the conditioned reward effect during the test. Pimozide did not reliably affect the latencies of rats to eat in the conditioning phase ruling out the possibility that performance effects in that phase resulted in the failure to observe conditioned reward. Apparently intact DA neurotransmission was required for reward-related learning to take place (6,17).

Procedures that separate the time of DA receptor blockade from the time of testing provide an excellent tool for evaluating the role of DA in learning while minimizing possible performance effects. The results of the studies discussed above are in agreement with those of studies of avoidance conditioning and rewarded operant responding in supporting the hypothesis that DA is not only involved in performance but also in learning.

DA AND PLACE CONDITIONING

Another paradigm that shares the advantages of the conditioned reward procedure is place conditioning. The design of place conditioning studies involves repeatedly pairing one side of a shuttle box with reward and the other side with no reward. Animals are subsequently tested in the box with access to both sides and show a place conditioning effect if they reliably spend more time on the side previously associated with reward. Many studies have shown that treatments with DA receptor blockers during the pairing phase (for example, the pairing of one side with food) eliminate conditioning effects in the test phase (24). Furthermore, DA agonists given during the pairing phase can lead to conditioning of preferences for that side during the test (21, 22, 25). For further discussion of this procedure in the context of performance versus learning effects see the paper by Hoffman (16) in the current proceedings.

As was the case for conditioned reward experiments, place conditioning experiments provide a tool for separating the effects of DA receptor blockade on performance from possible effects on learning. Results provide good support for the hypothesis that DA is involved in reward-related learning.

DA AND STIMULANT SELF-ADMINISTRATION

Animals can be trained to self-administer certain drugs via chronic indwelling cannulae when a lever is available providing the opportunity to do so. With this paradigm it has been found that rats and monkeys self-administer a number of compounds that act as DA agonists. Many of the relevant data have been reviewed by Wise (28,29). These results provide further support for the hypothesis that DA is involved in reward-related learning.

The maintenance rates at which an animal will self-administer a DA agonist have been shown to be exquisitely sensitive to the concentration of the injection fluid. Results have shown that the rate of self-administration increases as the concentration decreases down to some minimal level after which responding is seen to extinguish. This paradigm provides perhaps one of the best tests of the performance versus learning interpretation of the effects of DA receptor blockers. If it could be shown that low doses of DA antagonists given to animals self-administering DA agonists resulted in an *increase* in rate like that seen with a reduction of concentration, it would be very difficult to argue for a performance effect. Wise and his colleagues (8, 29, 32–34) have amply documented precisely this effect. The results provide an excellent test of performance versus learning effects and support the hypothesis that DA is involved in reward-related learning.

THE USE OF TWO CSs

As noted earlier, a gradual decline in operant responding for food reward can not be taken as unequivocal evidence for a role for DA in reward-related learning. Interpretations based on learning that it was aversive to respond under the influence of the drug could not be ruled out. Some researchers have taken an approach that makes this interpretation of the results almost certainly wrong. The approach involves the use of two CSs for initiating operant responding.

Franklin and McCoy (14) trained rats to lever-press for electrical stimulation of the brain. The animals were trained according to a complex schedule that involved the use of two different CSs to signal periods during which the lever could be pressed for reward. After the animals were well-trained, they were tested with pimozide. As expected, responding in the presence of the first CS began at a high rate and showed the now familiar gradual decline. What is of particular interest here is the observation that when the second CS was then presented, responding on the same lever began anew and then underwent a similar extinction-like decline. This observation makes an interpretation based on learned aversive consequences of performing the operant under the influence of the drug seem very unlikely. If the initial decline in responding was a result of learned aversion of responding, why did responding resume when the second CS was presented? Control groups ruled out possible unconditioned activating effects of the CS. It appears that the acquired incentive properties of the second CS were sufficiently strong to reactivate responding in animals that had apparently extinguished responding. Just as avoidance responding was seen for a time in pretrained animals treated with pimozide, appetitive responding was seen in pretrained animals when the second CS was presented.

A similar approach was taken in a study by Beninger and Freedman (4). We trained animals daily in two 15-min sessions that followed one immediately after the other. In each session each day they either ran in a wheel for brain stimulation reward or they pressed a lever for reward. During baseline training they had equal exposure to each apparatus and they experienced every sequence, i.e., wheel-lever, wheel-wheel, lever-wheel and lever-lever, an equal number of times. On two test days animals were injected with pimozide and given the wheel-lever or the lever-lever sequence, half receiving the wheel-lever sequence on the first day and half receiving the lever-lever sequence on the first day, both groups receiving the other sequence on the second day. When the data for the two test days were combined, those receiving the wheel-lever sequence responded significantly more on the lever in the second session compared to those that received the lever-lever sequence (Fig. 4). These results support those of Franklin and McCoy (14). Thus, each manipulandum served as a CS for responding. Pimozide led to a decrease in the ability of the lever-related stimuli to control responding during the first session for the sequence, lever-lever and as a result responding was seen to be lower during the second lever session. For the sequence, wheel-lever the lever-related stimuli retained their ability to control responding and a higher rate of responding was seen on the lever in the second session.

The two experiments discussed in this section provide strong

support for the hypothesis that DA is involved in reward-related learning. Even complex performance hypotheses based on learning of aversive consequences of responding while drugged cannot account for the observed effects.

CONCLUSIONS

The problem of unequivocally attributing the effects of any physiological or pharmacological manipulation to changes in learning is compounded by the possible effects of these manipulations on performance. The potential for this confound has been recognized since the earliest days of physiological psychology and continues to demand the attention of researchers today. One area of inquiry has been particularly influenced by performance versus learning interpretations of results. That is the study of the effects of manipulations of dopaminergic neurotransmission on behavioral dependent measures. The performance versus learning problem has been so central in this research area as it is well-known that manipulations that increase dopaminergic neurotransmission increase locomotor activity whereas those that decrease dopaminergic neurotransmission decrease locomotor activity.

In taking up the challenge of evaluating the role of DA in reward-related learning in a manner that reduces the likelihood that results can be attributed to performance effects, researchers have devised a number of modifications of old techniques as well as new techniques. These include the observation of patterns of responding on schedules of operant behavior, comparisons of drug effects on acquisition versus maintenance of avoidance responding, conditioned reward and place conditioning procedures that separate drug and test sessions, stimulant self-administration procedures and the use of more than one CS to control responding. In each of these paradigms, as well as many others that cannot be covered here [e.g., (9–13, 23, 35)], data continued to support the conclusion that DA is involved in reward-related learning.

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