Revista Mexicana de Análisis de la Conducta,
1983, Vol. 9, Núm. 1, págs. 39-53

Mechanisms of neuroleptic-induced performance deficit. A critical review

Mecanismos involucrados en las deficiencias de ejecución inducidas por neurolépticos. Una revisión crítica.

Roberto A. Prado-Alcalá

Departamento de Fisiología, Facultad de Medicina,
Universidad Nacional Autónoma de México
y
Escuela de Psicología, Universidad Anáhuac, México

ABSTRACT

Wise (1978) has advanced the hypothesis that the performance decrets seen in instrumentally-trained animals after neuroleptic treatment are due to blockade of the rewarding properties of reinforcers, rather than to motor debilitation. In this paper a review is made of relevant experiments that support or contradict Wise's hypothesis and a re-interpretation of some results is offered. Taken Together, these results indicate that such neuroleptic-induced performance decrets are, indeed, due to a reduction in the rewarding impact of reinforcers.

DESCRIPTORS: neuroleptics, dopamine, intracranial self-stimulation, food reward, performance deficits.

RESUMEN

Wise (1978) ha propuesto la hipótesis de que los decrementos en la ejecución de tareas instrumentales inducidos por la aplicación de neurolépticos, son debidos al bloqueo de las propiedades gratificantes de los reforzadores, y no a un efecto de debilitación motora. En esta comunicación se presenta una revisión de experimentos relevantes que apoyan o refutan la hipótesis de Wise, así como una reinterpretación de algunos de estos experimentos. En conjunto, estos resultados indican que dichos decrementos en la ejecución producidos por los neurolépticos se deben, ciertamente, a una reducción en los efectos gratificantes de los reforzadores.

DESCRIPTORES: neurolépticos, dopamina, autoestimulación intracraneal, reforzamiento alimenticio, deficiencias de ejecución.

This paper is dedicated to Dr. Alberto Guevara Rojas on his 50 th anniversary as Professor at the National University of Mexico. The author gratefully acknowledges a Fellowship granted by Consejo Nacional de Ciencia y Tecnología de México. Author's address: Department of Physiology, Faculty of Medicine, National University of Mexico, P.O. Box 70250, México, D. F., Mexico 04510.

It was not until 10 years after the publication by Olds and Milner (1954) describing the rewarding effects of intracranial stimulation (ICS), that a major hypothesis about its neurochemical basis was proposed. The catecholamine (CA) hypothesis of brain stimulation reward was first proposed by Stein (1964), and in its simplest terms it states that central catecholamine-containing neurons mediate the reinforcing properties of ICS.

During the decade which followed, evidence accumulated which suggested that "The CA hypothesis is capable of integrating a large body of data, all of which converge on the conclusion that both dopamine (DA) and norepinephrine (NE) systems can serve as substrates for ICS" (German and Bowden, 1974; p. 381). These data have been derived from mapping, lesion, and pharmacological studies. It had been found that the best ICS sites are near or within the major CA systems (Crow, 1972; German and Bowden, 1974; Prado-Alcala, *et al.*, 1975; Routtenberg, 1971, etc.), and that drugs that interfere with CA synthesis, storage, turnover rate or synaptic efficacy produce a decrement in ICS while drugs that improve CA efficacy produce a facilitation of ICS (Fibiger, 1978; Wise, 1978a, b).

It soon became evident that the involvement of NE systems in ICS was not critical for this phenomenon to occur. Lesions of the NE pathways or of their nuclei of origin produce no effect, or only a transient disruption of ICS, and drugs that interfere with NE metabolism seem to exert their influence through non-specific motor debilitation or sedation (Fibiger, 1978; Wise, 1978a, b).

At present, the available evidence indicates that DA is essential for the rewarding properties of ICS (Wise, 1978a). Furthermore, it has been suggested that DA is critically involved in the rewarding functions of naturally occuring primary reinforcers (Wise *et al.*, 1978a) and of some drugs of abuse (de Wit and Wise, 1978; Yokel and Wise, 1975, 1976).

However, despite some clear-cut evidence supporting the view that DA is intimately associated with the rewarding properties of reinforcing stimuli, there is still controversy about the way in which this amine is involved in reinforcement. It is still argued that DA may be involved in the motor aspects of rewarded behaviors and not necessarily (or to a lesser extent) in the basic mechanisms of reward.

In this paper I will review the relevant literature (up to 1980) on this controversy, and re-evaluate the DA hypothesis of reinforcement, which has been stated by Wise: "The evidence suggests that there is a dopamine system in the brain that plays a critical role in the rewarding quality of brain stimulation and at least some other rewards. In this sense it can be concluded that dopamine plays a specialized role in reward processes" (Wise, 1978a, p. 238).

THE EVIDENCE

The original evidence that gave directs support to the DA hypothesis of

reward was derived from experiments in which the effects of neuroleptics were assessed in rats trained to lever press for a reward. In these studies the reinforcers were made available every time the animals produced a particular response (CRF schedule).

A. *Intracranial Self-Stimulation.* When rats are tested under the influence of the synaptic dopaminergic blocker pimozide (PIMO), overall rates of ICS are reduced in a dose-dependent fashion. Close inspection of lever pressing behavior reveals, however, that early in the sessions response rates are near or above normal, and then progressively decline as a function of time. This response pattern resembles that which is seen when animals are no longer rewarded for their instrumental performance. These data indicate that PIMO did not induce a decreased level of performance by producing a motor debilitation, but rather by blocking the rewarding quality of ICS (Fouriezos and Wise, 1976).

These results were confirmed and extended in subsequent experiments. PIMO produced extinction-like decrements in ICS that were dose-dependent, very similar to those observed when ICS current was reduced in non-treated animals. To control for the possibility that the decrements in ICS seen in the later portions of the test sessions were due to fatige, or other potentially interfering effects of PIMO, rats were tested for 10 min after pre-treatment with this drug, were then given a 10 min rest period which was followed by another 10 min of testing. A typical extinction curve was observed during initial testing and "spontaneous recovery" on the second test period, i.e., the animals initiated lever pressing after the rest period (Fouriezos *et al.*, 1978).

It is of interest to note that similar extinction-like effects of neuroleptics were observed a few years before the publication of the two studies that had been just described. In one study it was found that "Animals treated with pimozide tended to self-stimualte vigorously at the beginning of the sessions but tappered off after several min. . . Sedation or obvious motor disabilities were not present" (Liebman and Butcher, 1973, p. 311). In another study it was stated that ". . .after treatment with intraperitoneal spiroperidol rats often self-stimulated for 1-2 min when first tested for self-stimualtion before a total abolition of self-stimulation became evident" (Rolls *et al.*, 1974, p. 228). Unfortunately, the authors of these experiments did not seem to realize the theoretical significance of their finding, as they did not elaborate beyond the behavioral descriptions quoted above.

When more discriminative of performance were used, it was found that PIMO did not interfere with latency to initiate running, running speed, nor with ICS rates during the first trials given in a runway. Again, it was only after substantial feedback of the consequences of responding was obtained that the animals showed a drop in performance (Fouriezos *et al.*, 1978).

Franklin (1978) also found that PIMO proced a dose-dependent reduction of the rewarding effecst of ICS, without depressing running speed in a runway; the larger dose of the drug produced extinction of the runway performance.

B. *Drug self-administration.* If DA systems are significantly involved in reinforcement, it would be expected that blockade of DA receptors would produce a reduction of the rewarding impact not only of ICS but also of ther rewarding stimuli.

Both PIMO and butaclamol increased rates of lever pressing for intravenous amphetamine reward. At low doses (which supposedly produce only partial blockade of DA receptors), these agents induced response rates that were indicative of partial reduction of reinforcement, *i.e.*, animals increased amphetamine intake as if they were compensating for reduced reinforcement. With higher doses, the high response rates were followed by extinction. These response patterns resemble reward reduction and reward termination, respectively (Yokel and Wise, 1975, 1976). Essentially the suma reward-reducing effects of PIMO have been observed in the case of cocaine self-administration in rats (de Wit and Wise, 1978).

C. *Food Reward.* As in the case of ICS and drug self-administration, blockade of DA receptors produces marked reductions in conditioned responses that are maintained by food reward.

Food-rewarded lever-pressing behavior was studied in rats. When they were tested after injections of PIMO, response patterns that are equivalent to those seen in the ICS studies discussed above were seen. Both non-rewarded animals and animals that received food contingent upon lever-pressing, but that had been treated with PIMO (before each of four test sessions), showed normal response rates during the first test session, but progressively decreasing rates in subsequent sessions. Another group of rats that received as many injections of the neuroleptic as the letter group was tested for lever-pressing only after the last injection. This group displayed normal performance, thus showing that reduced response rates were not due to any cumulative effects of the drug (Wise *et al.*, 1978a). In this study it was also shown that latencies to initiative running and running speed increased as the number of trials was increased in both PIMO-treated and non-rewarded animals. The two measures of performance (latency and speed) were normal at the beginning of the test session.

The finding that PIMO produces extinction-like patterns of response, in rats that have been trained to lever press for food under a CRF schedule, has been confirmed in subsequent experiments (Gray and Wise, 1980; Mason *et al.*, 1980; Wise *et al.*, 1978b).

Taken together, these studies show that, at the doses that were used, the neuroleptics do not interfere with the motor functions that are required for instrumnetal perfomance. Normal or near-normal response levels were seen at the beginning of the test sessions in which food or ICS had been used as reinforcers, and supranormal rates when the animals were working for amphetamine or cocaine. The response patterns that were observed in these neuroleptic-treated animals closely resemble those that are seen in conditions of extinction, and can be interpreted in terms of a reward deficit mediated by DA-receptor blockade.

D. *Transfer Effects.* If DA-receptor blockade produces a reduction in lever-pressing by a mechanism that is equivalent to extinction, then animals that have significantly extinguished learned performance should maintain the same, or lower, response rates when they are transferred to a condition in which they earn reinforcers for performing the task, but are also pre-treated with PIMO or other neuroleptics. This was found to be the case in two independent studies: response rates were very similar during the third (Wise *et al.*, 1978a) or fourth (Wise *et al.*, 1978b) extinction session to response rates in the next session, during which the animals were under the influence of PIMO and had been rewarded with food for lever-pressing.

E. *Conditioned Reinforcement.* The hypothesis that DA-receptor blockade produces a decrement in the rewarding value of primary reinforcers leads to the predicition that DA-receptor blockade will also attenuate the reinforcing properties of secondary (conditioned) reinforcers.

When rats are presented with tone-food associations, they later show increased lever-pressing rates for the tone, relative to their pressing rates prior to the tone-food pairings. When treated with PIMO before such associations, the rats no longer show increased lever-pressing (Beninger and Phillips, 1980). It thus seems that DA is intimately involved in the processes that underlie the establishment of conditioned reinforcement.

Consistent with this idea is the finding that psychomotor stimulant drugs that are known to increase the synaptic efficacy of catecholamines (*e.g.*, amphetamine, methamphetamine, methylphenidate), markedly facilitate conditioned reinforcement (Hill, 1970; Robbins, 1975, 1976).

THE CONTROVERSY

As stated above, the original studies that indicated that the neuroleptics produced decrements in instrumental behavior by blocking the reinforcing properties of normally rewarding stimuli involved the use of continuous reinforcement.

At one time it was proposed, on the basis of available data, that in order for extinction to ocurr in neuroleptic-treated animals, animals should have had some experience with the "new" quality of the reward, i.e., "responding under neuroleptic treatments slows or drops out only after the animal is given exposure to the normal rewarding event; thus, it is the failure of the rewarding event to maintain its characteristic positive feedback effect that is most critical for the performance patterns of the neuroleptic-treated rat" (Wise *et al.*, 1978b, p. 83). From this proposition it would be predicted that initial normal rates of responding should be observed in neuroleptic-treated animals that are subjected to extinction, or to intermittent schedules of reinforcement in which the first reward is delayed for a relatively long period of time.

A. *Intracranial Self-Stimulation.* Ettenberg *et al.*, (1979) tested the effects of PIMO on response rates under conditions of extinction, in rats that had

been trained for ICS on a CRF schedule. As was seen in the CRF experiments reported above, there were normal response rates at the beginning of the extinction sessions and a dose-related reduction in pressing rate as the sessions progressed. When compared with a placebo-treated group, however, the PIMO animals extinguished responding significantly faster. This finding was interpreted by the authors as a drug-induced motor deficit.

The neuroleptic haloperidol has also been studied in relation to the DA hypothesis of reward. Rats were trained to obtain ICS on a variable-interval (VI) 60 sec schedule and then tested under conditions of haloperidol pretreatment, extinction, or haloperidol plus extinction (Phillips and Fibiger, 1979). Congruent with the earlier CRF studies, pressing rates in the extinction and in the haloperidol conditions were very similar (these was an initial period of responding followed by reduced responding), although close inspection of the cumulative records that were shown by the authors reveals that the haloperidol condition induced a "smoother" extinction curve, *i.e.*, the animals pressed at a low but steady rate. This response pattern differed from that of the extinction condition (without drug) in that, durign extinction, the animals ceased to respond for variable periods (ranging from 2 to 10 min). From this comparison the authors draw the obvious conclusion that the drug effects are not identical to the effect of non-reinforcement.

When submitted to the haloperidol plus extinction condition, response rates suffered a drastic reduction, suggesting the existence of independent but additive effects of extinction and haloperidol. This finding seems to be inconsistent with the prediction that extinction and neuroleptic treatments should be equivalent. In other words, animals under either, or both, conditions should be incapable of "feeling good" since, on the one hand, during extinction the reinforcers are no longer available and, on the other, the neuroleptics should block the "pleasure" derived from ICS. Hence, if there were such an equivalence, no additive effects should have been observed.

It is not difficult, however, to look at the same data from a broader perspective. First, the low but regularity spaced response rate that was seen when the rats had been pre-treated with haloperidol and tested on the VI schedule can be explained by an incomplete blockade of the reinforcing properties of ICS (this effect will be referred to as "fractional reinforcement"). In this way, we can think of the neuroleptics as having a qualitative similarity to extinction; by increasing the dose of these drugs, a state could be reached where total blockade of the rewarding value of the reinforcers is produced. At this stage, the neuroleptics could also have an effect that is quantitatively similar to extinction. Second, the neuroleptics could also block, completely or partially, the rewarding properties of secondary reinforcers.

Thus, in the condition of extinction, responding is maintained primarily by the rewarding value of conditioned reinforcers. If we combine this condition with neuroleptic treatment, additive effects should be observed (no food+ total or partial blockade of secondary reinforcement), that would lead to reduced responding.

B. *Food Reward. a*). Instrumental conditioning. Results obtained in experiments dealing with the effects of neuroleptics on food-rewarded behaviors maintained by schedules of reinforcement other than CRF, or on response output during extinction, have led some investigators to challenge the proposition that neuroleptics attenuate or block the rewarding properties of reinforcers.

In one experiment, independent groups of rats were trained, on a CRF schedule, to press a lever to obtain food; they were later tested, under the effects of one of two doses of PIMO or of a placebo, for extinction of this learned behavior (Ettenberg, *et al.*, 1979). All groups responded with normal rates at the beginning of testing, and a dose-dependent reduction in lever-pressing was observed in the drugged animals as the session progressed. In contrast, while also showing a decrement, the placebo-treated animals displayed a significantly higher level of performance. Essentially the same results were obtained by Mason *et al.* (1980).

The additive effect (neuroleptic + extinction) that led to a marked decrement in lever-pressing was also seen in a study in which rats were trained to obtain food, on VI 60 sec or VI 4 min schedules of reinforcement (Phillips and Fibiger, 1979). In this case haloperidol was employed and each rat was tested in conditions of reinforcement, extinction, reinforcement plus haloperidol, and extinction plus haloperidol.

Again, the extinction condition produced response patterns that were very similar to those seen in the reinforcement plus haloperidol condition, while greatly reduced response rates were observed when testing was done under extinction plus haloperidol. Very similar results were obtained in a later study (Tombaugh *et al.*, 1980), in which the effects of PIMO on response rates during extinction of other intermittent schedules of reinforcemntn (FR, FI, and VI) were assessed.

In summary, DA-receptor blockade induced by neuroleptics produces consistent response patterns in behavior that are established through different schedules of reinforcement. When tested under conditions of reinforced responding, neuroleptic-treated rats behave as non-treated rats that are submitted to extinction.

A controversial issue stems from the fact that when animals are pre-treated with a neuroleptic and tested for extinction, their response rates are lower, by far, than response rates of non-treated animals that are similarly tested for extinction. In other words, there is an additive effect. Because of this phenomenon it has been argud that there is not a functional equivalence between neuroleptic treatment and extinction. It is argued that if neuroleptics blook the reinforcing properties of food, then animals treated with these compounds should behave as animals under extinction. This is a reasonable argument. Nevertheless, in this argument only primary reinforcers are taken into account, and the assumption is also made that neuroleptics (at the dose levels that have been used) should completely block the reinforcing quality of food. By making different, logical assumptions one can readily re-interpret

the additive effect, and explain the similarity of performance between neuroleptic-treated rats that are working for rewards and non-treated animals working in conditions of non-reward.

First, the neuroleptics may not only interfere with the hedonic quality of primary reinforcers but, as shown by Beninger and Phillips (1980), they also interfere with the acquisition of secondary (conditioned) reinforcers. This finding leads to the proposition that DA-receptor blockade can also reduce the rewarding effects of these conditioned reinforcers. Second, as shown by Gray and Wise (1980), doses of PIMO that fall within the range of doses that are commonly used in this type of studies produce fractional reinforcement (partial blockade of food reinforcement).

Thus, the low and stable level of performance observed in animals tha are treated with neuroleptics and tested on different schedules of reinforcement can be explained by an additive (algebraic) effect: the reduced rewarding value of secondary reinforcers is counterbalanced by fractional reinforcement provided by food. In the case of the neuroleptic plus extinction condition, there is a reduction in the potency of conditioned reinforcers and also a lack of primary reinforcement (absence of food). The sum of these factors yields a further decrement in response rate.

In the study by Gray and Wise (1980) the effects of neuroleptics on instrumental performance maintained on an intermittent schedule of food reinforcement were also studied. They used a VI 2.5 min schedule, and compared pressing rates between PIMO- and vehicle-treated rats that were tested when the VI schedule was in effect and when the reinforcers were withheld. In order to assess the effects of the neuroleptic on the instrumental response before food was made available, no primary reinforcers were given to any of the groups during the first 20 min of the 120 min test session. This experimental manipulation produced a marked difference with respect to prevous similar experimental in which a long delay in the delivery of the first reinforcer was not imposed.

It was found that overall pressing rates of the two PIMO groups were significantly reduced, as compared with each of the vehicle groups. A major difference was that, unlike previous experiments and in contrast with response rates of the vehicle-treated rats, response rates of the two PIMO groups were significantly reduced during the early postions of the sessions. Even though at first glance there did not seem to be differences in responding between the VI-PIMO and the extinction-PIMO groups (Gray and Wise, 1980, Fig. 2), a detailed analysis of pressing rates revealed that the VI-PIMO animals responded at a very low, but stable rate, whereas the extinction-PIMO animals showed virtually no responding.

Since all the gropus were tested under conditions of extinction during the first 20 min of the test session, it can be stated, again, that the high rates of responding seen in the non-drugged groups were maintained by the presence of secondary reinforcers, and that the contrasting low response rates of the PIMO groups were due to the blockade of the reinforcing

properties of conditioned reinforcers. The further decrement in lever-pressing shown by the PIMO group that was kept in extinction throughout the test session was produced by the lack of primary reinforcement.

The results of another study apparently fail to support the proposition that DA-receptor blockade reduces the rewarding impact of food. In one of the experiments of this study rats were trained to obtain food under a schedule of differential reinforcement of low rates of responding (DRL) (Mason *et al.*, 1980). When tested under the effects of PIMO the animals continued to respond with pressing rates that were equivalent to those seen in baseline (no drug) conditions. Two additional groups of rats were tested in three sessions of extinction; one of the groups was treated with the neuroleptic and the other with a placebo. The two groups displayed a gradual decrement in response rates, both within and across sessions. In concordance with the studies discussed above, the performance of the PIMO group was significantly inferior to that of the placebo group.

The controversial aspect of this study is that the neuroleptic failed to produce a reduction in DRL responding. It thus would seem that in this particular case PIMO did not interfere with the rewarding quality of food. However, data from an experiment that was conducted by the same authors, in which rats had been pre-treated with PIMO and then tested in a CRF schedule, show that extinction-like patterns appeared only after the animals had consumed more than twenty 45 mg food pellets (Mason *et al.*, 1980, Fig. 1). In an earlier study, decrements in response rates also became evident after the first five min of CRF testing, when PIMO-treated rats had earned more than 30 pellets (Wise *et al.*, 1978b, Fig. 1).

It thus seems that, as proposed by Wise *et al.* (1978b), animals must have a minimal amount of experience with the new "blunted" quality of food before decrease lever-pressing performance ensues. In the case of the DRL experiment, the authors did not specify the actual number of reinforcers (also 45 mg food pellets) that each group of animals had consumed. If an estimate of these quantities is made from the inter-response interval graphs of their article (Mason *et al.*, 1980, Fig. 14), it turns out that the PIMO group that was tested for DRL performance always received, on average, less than 30 pellets in any of the test sessions. Failure to observe a decrement in performance of this group may only indicate that these animals did not have sufficient experience with the reinforcer, which may be needed to establish a new association (lever-pressing under PIMO = low reward), which in turn would eventually lead to low responding (extinction).

The effects of PIMO were also assessed in the acquisition and extinction of an alley-running response (Mason *et al.*, 1980). Rats were rewarded with five pellets of food for running an L-shaped alleyway, and were given one trial per day. Some rats were rewarded after each run (CRF schedule), one group was rewarded on only one half of the trials (partial reinforcement, PR), and a third group was maintained on the CRF schedule but was pre-treated with the DA-receptor blocker on one half of the trials. After train-

ing, all groups were given five extinction trials in each of three sessions, and were tested in a drug-free condition.

It was predicted that the PIMO group would show a performance that would be similar to that of the PR group. There were no significant differences among the groups during the acquisition trials. During extinction the CRF and the PIMO groups showed increasing latencies to run the alleyway, both across trials and across sessions, while the PR group displayed low latencies in the five trials of the first two sessions, and a tendency to slow down in the third sesions.

It is clear from the results of this experiment that PIMO did not produce the same effects as omission of food, as would be expected. However, this expectation is only valid if at least two assumptions are correct: 1) that the 1.0 mg/kg dose of PIMO that was administered completely blocked the rewarding properties of food, and 2) that there is an immediate effect of PIMO on the rewarding value of food. Neither of these assumptions is tenable. As stated before, it has been shown that: 1) the dose of the neuroleptic that was used does not completely block the rewarding impact of food (Gray and Wise, 1980), and 2) in order for PIMO to produce extinction- like behaviors a minimum of experience with the reinforcer has to occur (Mason *et al.*, 1980; Wise *et al.*, 1978b). It should be remembered that in the alleyway experiment the PIMO animals received only five food pellets on each acquisition session.

Although not discussed by the authors of the experiment under analysis, it is interesting to note that this experiment provides a good control for potential motor debilitation that might have been produced by the neuroleptic. The neuroleptic-treated animals acquired the conditioned response at the same rate as non-treated animals. This fact can be used as supportive evidence against the interpretation that reduced responding, produced by neuroleptics in other paradigms, is due to interference with motor capacity.

b) Free feeding. The most direct and critical test for the DA theory of reward that is now available is represented by tests of the effects of neuroleptics on water and food consumption in *ad libitum* conditions, or in conditions in which the experimental subjects are not required to perform complex instrumental behaviors. These tests have, unfortunatelly, yielded contradictory results; these results can, nevertheless, be accounted for by the different procedures that have been followed in different laboratories.

One experiment that was specifically designed to determine the effects of DA-receptor blockade on food and water consumption was carried out by Rolls *et al.* (1974). These authors pre-treated rats with one of several doses of spiroperidol, or with a placebo, and measured the amounts of solid food and water that had been ingested during four-hour long sessions. The neuroleptic produced a dose-dependent reduction in both feeding and drinking. In contrast with the placebo treatment, it was seen that in the spiroperidol was very low for the next three h. Since the authors only gave overall data

for the full four-hour sessions, it is not possible to exactly determine the latency of the onset of decline of the consumatory behaviors. What is clear, nevertheless, is that spiroperidol induced the animals to stop eating and drinking.

Since no specific tests for potential motor debilitation were provided in this experiment, interpretation of the results is difficult. It could be argued that the animals stopped eating and drinking because, as the sessions progressed, some kind of motor impairment emerged. On the other hand, the case can be made that under these experimental conditions, it took at least 45 min to learn the new association between the physical characteristics of the primary reinforcers and their "new", blunted rewarding quality.

A chain of events must be taken into account when dealing with instrumentally-procured food or water. In the lever-pressing situation food is earned after the animals produce a sequence of behaviors, most of which are thought to be under the control of secondary reinforcers, which are, in turn, established through their temporal and spatial contiguity with primary reinforcers. In contrast, in the free-feeding situation the role of conditioned reinforcers is rether limited. The unconditioned consummatory response, which by definition is pre-programmed in the innate behavioral repertoire of the animals, depends mainly on the presence and availability of the primary reinforcers.

The case was made, in the preceding sections, that neuroleptics are capable of reducing the reinforcing actions of both primary and secondary reinforcers. Hence, it was not surprising to see that DA-receptor blockade had differential temporal effects on free-feeding (slow onset of the effect) and on instrumentally-mediated food consumption (fast onset of the effect).

Two additional studies dealing with the effects of neuroleptics on ingestive behaviors were subsequently published. In their 1975 paper, Zis and Fibiger reported that haloperidol and PIMO did not significantly affect water and food comsumption. Likewise, Tombaugh *et al.* (1979) showed that home cage food intake of rats that had been pre-treated with PIMO was not impaired (except for the latency to initiate the consumatory response).

In the first of these two studies (Zis and Fibiger, 1975), water intake was measured for only one h, and food intake for two h; furthermore, the dose of one of the neuroleptics that was administered (0.45 mg/kg of PIMO) falls below the effective dose that has been used in studies on instrumental learning (1.0 mg/kg), in which reduced consumption of food was produced. Failure to observe deficits in drinking and eating can thus be explained by the relatively reduced time of testing and, in part, by the low dose of PIMO, which may have not been sufficient to block the rewarding impact of food and water.

In the second study (Tombaugh *et al.*, 1979), rats were pre-treated with PIMO (1.0 mg/kg) and then tested four times. In each test a food cup containing five 45 mg food pellets was offered to the animals, and there was an interval of one h between each test. No significant differences were

evident, between the PIMO– and the placebo-treated animals, regarding the time needed to consume the pellets. As discussed above, it seems that animals that are under the effects of neuroleptics need to taste the food for a minimal number of trials (20-30 pellets in the CRF situation), or for a minimum lenght of time (about 45 min in the free-feeding situation) in order to show a significant reduction in food consumption. The animals in this experiment had the opportunity to ingest only five pellets in each of the test sessions.

In this second study under consideration, rats that were pre-treated with PIMO were also submitted to magazine training. There were three sessions of 30 trials each, and the rats received PIMO before each of the first two sessions. When compared with a placebo group, it was found that on the first session the PIMO animals consumed less pellets; at the second session there were no significant differences between the groups, and in the third session, in which no drugs had been administered, food consumption was virtually identical in both groups. In their discussion of the results the authors state that ". . .it is clear that although performance was impaired, some degree of learning did take place as revealed by the day 2 enhancement of response rates". They go on to say: "the very fact that such learning occurred indicates that reinforcement was not totally eliminated by the drug treatment" (p. 224). One could not agree more with these statements. Experimental support for the second statement has been provided by Gray and Wise (1980).

C. *Transfer Effects.* In one of the earlier studies on the effects of neuroleptics on instrumental performance it was shown that a shift from extinction to PIMO treatment, where lever-pressing produced food, did not alter the decline in response rate (Wise *et al.*, 1978a). While this finding indicated that there is a functional equivalence between non-reward and DA-receptor blockade, other studies have shown that by doing the opposite test (transfer from PIMO to extinction) a substantial increase in response rate is produced. Thus, the idea of a functional equivalence of the two conditions has been questioned, and still remains a controversial issue.

Tombaugh *et al.* (1979) trained rats to lever press for solid food on a CRF schedule. After training, response contingent reward were made available to PIMO-treated animals, while food was not made available to a placebo-treated group. The groups showed the expected decline in performance over the three first test sessions. In a fourth session half the group in the PIMO condition was treated with the placebo and tested in extinction, whereas the rest of the rats continued to receive their original treatment. The animals that were not shifted from their drug and reinforcement condition showed very similar rates to those of their previous (third) session. In contrast, the group that was shifted from PIMO to placebo showed a high response output, which was more than twice that of its previous session.

Essentially the same results were obtained from rats that had been trained to lever press for food under VI or FR schedules (Tombaugh *et al.*, 1980).

In addition, it was seen that rats that had been shifted from extinction to VI or FR under PIMO showed lower pressing rates than animals kept on extinction throughout. The authors failed to discuss the significance of this finding, which may help to clarify the apparent lack of equivalence between extinction and DA-receptor blockade seen in transfer experiments.

It has already been discussed that during extinction the relatively high levels of performance of animals that were trained on intermittent schedules are maintained by the reinforcing quality of secondary reinforcers. When animals are shifted from extinction to a condition in which they are tested on the intermittent schedules under the influence of a neuroleptic, the rewarding impact of food will be greatly reduced, as well as the reinforcing properties of conditioned reinforcers. Thus, an additive effect will be manifested by reduced response rates in this condition. In contrast, when animals are tested on these schedules under the effects of a neuroleptic and are then shifted to extinction (with no drugs) an increase in responding could be expected to occur, because now the behavior is under the control of the secondary reinforcers that were established during original learning. In other words, the animals would be in a situation that resembles that of the first extinction test.

By the same token, animals that are tested in extinction while under the influence of a neuroleptic and then shifted to a drug-free extinction test should also show an increased responde rate. Indeed this is the case (Tombaugh *et al.*, 1980).

D. *"Non-Rewarded" Behavior.* Some investigators have reasoned that if the neuroleptics primarily block reward, then DA-receptor blockade should not interfere with a behavior that is not maintained by reinforcement. If a decrement in such behavior occurs it could then be concluded that the treatment produced a debilitation in response mechanisms. To experimentally test this possibility, rats were put inside a box which had a hole in one of its walls, and the latency for the first nosepoke and the number of nosepokes in a test session were recorded. The session was terminated when a rat did not respond during any five min period.

No significant differences in latency were found between the groups that had been pre-treated with one of two doses of PIMO or with a placebo. On the other hand, a dose-dependent reduction in the number of responses was seen. According to the authors, ". . .as no reward was present in this experimental test situation, nor had the rats ever been rewarded in this (or any other) experimental situation, it is not possible to atribute the observed effect of pimozide to a blockade of reward" (Ettenberg *et al.*, 1979, p. 560). Consequently, they interpreted these results as being due to a response deficit.

If this were indeed a true reward-free test situation, one is then faced with an instance where low doses of the neuroleptic PIMO (0.25 and 0.5 mg/kg) seem to produce a motor impairment. As described in preceding sections, it had been shown in other experiments that a dose of 1.0 mg/kg

of this drug did not interfere with the execution of more complex behaviors at the beginning of the test sessions, during the extent of relatively long sessions, or during each of several alleyway running trials. Furthermore, increased response rates are seen when neuroleptics are given to animals reinforced with amphetamine. At present, it is difficult to understand why in the nosepoke situation PIMO would produce a motor impairment, and only tentative explanations could be advanced; for example, in this particular task, which is a typical habituation task, PIMO might have induced faster learning than the placebo treatment.

CONCLUSIONS

The review of the literature germane to the effects of the neuroleptics on positively reinforced behaviors leads to the following conclusions:

1. The neuroleptics exert their influence on intracranial self-stimulation, drug self-administration, and on feeding behaviors through a reduction in the rewarding properties of both primary and secondary reinforcers.
2. At the doses that have been used in the studies reviewed here, the neuroleptics do not completely block the rewarding properties of primary reinforcers.
3. The available evidence suggest that the neuroleptics may produce a greater interference with the processes that underlie secondary reinforcement, than in those that mediate primary reinforcement.
4. In none of the studies that were reviewed, in which the neuroleptics produced decrements in response rates, was there unequivocal evidente to show that the effects on learned behaviors had been due to interference with motor functions.
5. The results of the studies that were reviewed lend strong support to the hypothesis that dopaminergic systems play a critical role in the rewarding effects of primary and secondary reinforcers.

REFERENCES

Beninger, R.J. & Phillips, A.G. The effect of pimozide in the establishment of conditioned reinforcement. *Psychopharmacology*, 1980, *68*, 147-153.

Crow, T.J. A map of the rat mesencephalon for electrical self-stimulation. *Brain Research*, 1972, *36*, 265-273.

de Wit, H. & Wise, R.A. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide but not with the noradrenergic blockers phentolamine or phenoxybenzamine. *Canadian Journal of Psychology*, 1978, *31*, 195-203.

Ettenberg, A., Cinsavich, S.A. & White, N. Performance effects with repeated response measures during pimozide-produced dopamine receptor blockade. *Pharmacology, Biochemistry and Behavior*, 1979, *11*, 557-561.

Fibiger, H.G. Drug and reinforcement mechanisms: a critical review of the catecholamine theory. *Anual Review of Pharmacology and Toxicology*, 1978, *18*, 37-56.

Fouriezos, G., Hansson, P. & Wise, R.A. Neuroleptic-induced attenuation of brain stimulation reward in rats. *Journal of Comparative and Physiological Psychology*, 1978, *92*, 661-667.

Fouriezos, G. & Wise, R.A. Pimozide-induced extinction of intracranial self-stimulation: responsse patterns rule out motor or performance deficits. *Brain Research*, 1976, *103*, 337-380.

Franklin, K.B.J. Catecholamines and self-stimulation: reward and performance effects dissociated. *Pharmacology Biochemistry and Behavior*, 1978, *9*, 813-820.

Franklin, K.B.J. & McCoy, S.M. Pimozide-induced extinction in rats: stimulus control of responding rules out motor deficit. *Pharmacology Biochemistry and Behavior*, 1979, *11*, 71-75.

German, D.C. & Bowden, D.M. Catecholamine systems as the neural substrate for intracranial self-stimulation: a hypothesis. *Brain Research*, 1974, *73*, 381-419.

Gray, T. & Wise, R.A. Effects of pimozide on lever pressing behavior maintained on an intermittent reinforcement schedule. *Pharmacology Biochemistry and Behavior*, 1980, *12*, 931-935.

Hill, R.T. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: E. Costa and S. Garattini (Eds.), *Amphetamine and related compounds*. New York: Raven Press, 1970, pp. 781-795.

Liebman, J.M. & Butcher, L.L. Effects on self-stimulation behavior of drugs influencing dopaminergic transmission mechanism. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 1973, *277*, 305-318.

Mason, T.S., Beninger, R.J., Fibiger, H.C. & Phillips, A.G. Pimozide-induced suppression of responding: evidence against block of food reward. *Pharmacology Biochemistry and Behavior*, 1980, *12*, 917-923.

Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of the rat brain. *Journal of Comparative and Physiological Psychology*, 1954, *47*, 419-427.

Phillips, A.G. & Fibiger, H.C. Decreased resistence to extintion after haloperidol: implications on the role of dopamine in reinforcement. *Pharmacology Biochemistry and Behavior*, 1979, *10*, 751-760.

Prado-Alcala, R.A., Kent, E.W. & Reid, L.D. Intracranial self-stimulation effects along the route of the nigro-striatal bundle. *Brain Research*, 1975, *84*, 531-540.

Robbins, T.W. The potentiation of conditioned reinforcement by psychomotor stimulant drugs. A test of Hill's hypothesis. *Psychopharmacologia (Berl.)*, 1975, *45*, 103-114.

Robbins, T.W. Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. *Nature*, 1976, *264*, 57-59.

Rolls, E.T., Rolls, B.J., Kelly, P.H., Shaw, S.G., Wood, R.J. & Dale, R. The relative attenuation of self-stimulation, eating and drinking produced by dopamine receptor blockade. *Psychopharmacologia* (Berl.), 1974, *38*, 219-230.

Routtenberg, A. Forebrain pathways of reward in Rattus norvegicus. *Journal of Comparative and Physiological Psychology*, 1971, *75*, 269-276.

Stein, L. Self-stimulation of the brain and the central stimulation action of amphetamine. *Federation Proceedings*, 1964, *23*, 836-850.

Tombaugh, T.N., Anisman, H. & Tombaugh, J. Extinction and dopamine blockade after intermittent reinforcement training: *Psychopharmacology*, 1980, *70*, 19-28.

Tombaugh, T.N., Tombaugh, J. & Anisman, H. Effects of dopamine receptor blockade on alimentary behaviors: home cage food consumption, magazine training, operant acquisition, and performance. *Psychopharmacology*, 1979, *66*, 219-225.

Wise, R.A. Catecholamine theories of reward: a critical review. *Brain Research*, 1978a, *152*, 215-247.

Wise, R.A. Neuroleptic attenuation of intracranial self-stimulation: reward or performance deficits? *Life Sciences*, 1978b, *22*, 535-542.

Wise, R.A., Spindler, J. de Wit, H. & Gerber, G.J. Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. *Science*, 1978a, *201*, 262-264.

Wise, R.A., Spindler, J. & Legault, L. Major attenuation of food reward with performance-sparing doses of pimozide in the rat. *Canadian Jorunal of Psychology*. 1978b, *32*, 77-85.

Yokel, R.A. & Wise, R.A. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. *Science*, 1975, *187*, 547-549.

Yokel, R.A. & Wise, R.A. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology*, 1976, *48*, 311-318.

Zis, A.P. & Fibiger, H.C. Neuroleptic-induced deficits in food and water regulation: similarities to the lateral hypothalamic syndrome. *Psychopharmacologia (Berl.)*, 1975, *43*, 63-68.