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Neuroleptic-Induced Deficits in Operant Responding for Temperature Reinforcement

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ETTENBERG, A. AND H. J. CARLISLE. *Neuroleptic-induced deficits in operant responding for temperature reinforcement.* PHARMACOL BIOCHEM BEHAV 22(5) 761–767, 1985.—The hypothesis that neuroleptic drugs interfere with operant behaviors by attenuating the rewarding properties of positive reinforcers, was examined in rats trained to lever-press for external heat in a cold environment. Unlike traditional reinforcers, such as food and water, reducing the reward magnitude of heat (by reducing the intensity or duration of the stimulus) results in compensatory increases in operant responding. Neuroleptic pretreatment (0.1, 0.2, 0,4 mg/kg of alpha-flupenthixol) produced only dose-dependent decreases in responding thereby interfering with the animals' ability to behaviorally maintain their internal core temperature. In a temperature-gradient test paradigm (requiring less physical effort on the part of the subjects) alpha-flupenthixol did not alter the animals' preferred environmental temperature, nor did it disrupt behavioral thermoregulatory ability. These data suggest that at least part of the behavioral deficit observed during neuroleptic treatment is due to a disruption in the performance capabilities of the subjects.

Neuroleptics Reinforcement α-Flupenthixol Motor deficits Operant behavior

IT is well established that neuroleptic drugs interfere with positively reinforced operant behaviors in laboratory animals. However, a great deal of interest and controversy presently exists concerning the precise mechanism by which the neuroleptics produce these behavioral deficits. Essentially two differing explanations have been proposed. The first is that the effects of neuroleptic drugs on operant responding result from some form of motoric or performance incapacity. This view is supported by the fact that neuroleptics are known to have parkinsonian-like side-effects in a large proportion of psychotic patients treated with these drugs [3, 25, 33]. Parkinson's disease is, of course, an extrapyramidal motor system disorder characterized by an impairment in the patient's ability to initiate and maintain normal voluntary movements [5,19]. Neuroleptics have also been shown to produce dose-dependent reductions in non-reinforced behaviors [11, 20, 22] and at high doses have strong sedative and cataleptic actions [4, 14, 22]. Finally, it has been demonstrated that neuroleptics have their most pronounced behavioral effects when tested in operant paradigms in which the kinetic requirements of the response are relatively high [11,30]. Reducing the kinetic characteristics of the operant (i.e., making the response easier to perform) greatly reduces the magnitude of the behavioral deficit observed during neuroleptic treatment [12,17].

A second, and perhaps more interesting possibility, is that neuroleptics disrupt the behavior of animals responding for positive reinforcers by attenuating the rewarding impact of those reinforcers [23,37]. This view is supported by the observation that the response patterns generated by animals under the influence of neuroleptics are in many instances comparable to the patterns of responding observed during actual reward attenuation [15,16]. At relatively high doses of drugs such as pimozide, haloperidol and butaclamol, animals commence the test session at response rates very near those of undrugged animals. Only after sampling the reinforcer do the animals demonstrate a reduction in responding. Consequently, the resultant behavioral deficit emerges only after the session has begun and somewhat resembles the pattern of responding that is observed during no-drug extinction trials when the reinforcer is removed. This neuroleptic-induced extinction pattern of behavior has been observed in animals responding for food, water and brain-stimulation rewards [37]. Although neuroleptic-induced "extinction curves" are not, in fact, equivalent to the response patterns observed during "real" extinction [11, 27, 34], proponents of the reward hypothesis have argued that the animals demonstrate that they are capable of responding by doing so during the initial portion of the test sessions. Consequently, the behavioral disruption is not likely to be the result of a simple sedative or incapacitating deficit, since one would expect such deficits to produce a general and constant suppression of responding throughout the test session [15,37].

Of course, one cannot overlook the very real possibility that both types of deficits are present in drugged animals. This provides us with a particularly relevant interpretative problem, since both reward and performance explanations of neuroleptic action predict a similar behavioral deficit, i.e., a reduction in operant reinforced behavior. One means of dissociating these two putative actions of neuroleptic drugs would be to employ a test paradigm in which a reduction in the rewarding properties of the reinforcer would result in an increased rate of operant behavior. This type of test would be particularly useful since one would predict reward deficits to increase responding, and motor or performance deficits to reduce operant responding.

It has long been known that rats placed into a cold environment will learn to make operant responses that result in the delivery of external heat (i.e., momentarily turn on a heat lamp) [6, 8, 36]. As in the drug self-administration paradigm, animals will respond for heat at a rate that enables them to maintain a preferred stable amount of reinforcer over time [7,35]. Consequently, changing the parameters of the reinforcer (by altering the intensity or duration of the heat stimulus) results in compensatory changes in operant behavior. For example, in animals trained to lever press for heat, reducing the reward strength of the reinforcer produces a reliable increase in lever-press rates [6,7]. Consequently, treatments that attenuate the reinforcing properties of heat should be distinguishable from treatments that alter performance factors, since reward deficits might be expected to produce a compensatory increase in responding while performance deficits should produce a dose-dependent decrease in operant behavior.

In addition to the lever-press task, we have examined the effects of neuroleptic treatment on the performance of animals in a temperature-gradient consisting of a long cylinder in which the temperature at one end is extremely cold and the temperature at the other end, extremely hot. In this apparatus the animal demonstrates a preference for an environmental temperature by choosing a location to sleep inside the cylinder. Note that one of these two tasks (lever-press) requires a relatively large amount of effort for the rat to maintain its core body temperature while the other (gradient) merely requires that the animal locomote to a comfortable location and then remain there. Comparisons of the results from these two temperature reinforcement paradigms provides information on both neuroleptic-induced reward deficits (do the rats increase responding in the lever-press task—if so, is the increase greater than that which would be expected by any drug-induced drop in body temperature?) and performance deficits (do the animals show a reduction in lever-pressing without a change in the preferred gradient temperature?). The present study was devised to examine the effects of the neuroleptic drug, alpha-flupenthixol, in these two temperature reinforcement paradigms.

METHOD

Lever-Press Test

Apparatus. Male albino rats (300–350 g) were individually housed and provided with ad lib access to food and water. The test apparatus consisted of a circular 24 cm diameter wiremesh chamber with Plexiglas rod flooring. A Plexiglas lever protruded 5 cm into the cage, 2 cm above the floor. Depression of the lever activated two 250 W red-bulb infrared heat lamps mounted at opposite sides of the chamber. The total power dissipated by the lamps was set for 300 W, which produced a radiant flux density (measured with an Eppley Thermopile) of 180 mW/square cm in the center of the cage. Pressing the lever once, activated the lamps for 3 sec; responses made while the lamps were on neither prolonged the ongoing reinforcement nor provided for a subsequent reinforcement. Dim illumination was provided by a 7 W red-bulb incandescent lamp mounted outside the test cage. The cage and heat lamps were placed inside a 17 cubic foot freezer, maintained at $-7°\pm2°$C. Programming and recording equipment were located in a room adjacent to the test room. Responses and reinforcements were recorded on electromechanical counters, a cumulative recorder and a print-out counter which provided cumulative totals at 5 min intervals. Unless stated otherwise, all test sessions were 120 min in duration.

Procedure. The rats were shaved the day prior to each test day so as to reduce their natural insulation against cold. During the first training day, the heat lamps remained on as long as the lever was depressed. When stable performance was observed, usually within a couple of hours, the rat was switched to a continuous reinforcement schedule in which a lever-press was reinforced by 3-sec of radiant heat. Typically, 2 or 3 sessions of 4-hour duration were sufficient to produce stable responding for 3-sec radiant heat rewards.

Six animals were tested three times a week (with a minimum of 48 hours between tests) throughout the course of the experiment. At one week intervals the subjects were administered an intraperitoneal injection of either 0.1, 0.2 or 0.4 mg/kg of the dopamine antagonist neuroleptic drug, alpha-flupenthixol, four hours prior to testing. The drug was prepared in a vehicle solution of 0.9% physiological saline and injected in a volume of 1.0 ml/kg body weight. Forty-eight hours prior to each drug trial, a baseline was computed in which animals were pretreated with the saline-vehicle solution alone.

In addition to response and reinforcement data, internal body temperatures were also recorded for each animal, (a) prior to injections (on drug and saline trials), (b) immediately prior to behavioral testing, and (c) immediately after testing. Core temperatures were determined by rectally inserting a 6 cm thermister probe connected to a Tele-thermometer (Yellow Springs Instrument Co. Model 46 TUC) from which the readings were taken.

Upon completion of the drug trials, the lever-press rates produced by altering the duration of the heat reinforcement were determined for each animal. During a single test session, animals were provided with 1-sec, 3-sec, and 5-sec radiant heat reinforcement. The order of presentation was random and testing consisted of 30 min at each reinforcer duration with 5 min timeouts between differing conditions. Two baseline sessions (3-sec, 300 W radiant heat reinforcement) were subsequently conducted followed by an additional single test during which reinforcer duration was held constant and the intensity of the heat stimulus was varied. The effects on lever-press rates of 200 W, 300 W, and 400 W reinforcer intensities were assessed using the same test procedures as those just described for varying reinforcer duration. Two more baselines were followed by a final 75 min test session during which no heat reinforcement was delivered (i.e., an extinction procedure).

Temperature Gradient Test

Apparatus. Another group of six animals was tested in a simple temperature-gradient paradigm. The apparatus (see Fig. 1) consisted of a long hollow Plexiglas cylinder (180 cm in length; 7 cm in diameter), the entire length of which was tightly wrapped with copper tubing. Hot water (50°C) was pumped into one end of the upper tubing by means of a small Lauda B-1 pump. The entire apparatus was contained within a large cold-room maintained at 5°C. This resulted in a temperature gradient within the cylinder that ranged from 45°C at the "hot" end of the apparatus (where the water was pumped in) to 7°C at the far "cold" end of the cylinder. Three times a week (with a minimum inter-trial interval of 48 hours) each animal was placed for 2 consecutive hours into the cold end of the cylinder. A temperature preference was determined from the temperature corresponding to the loca-

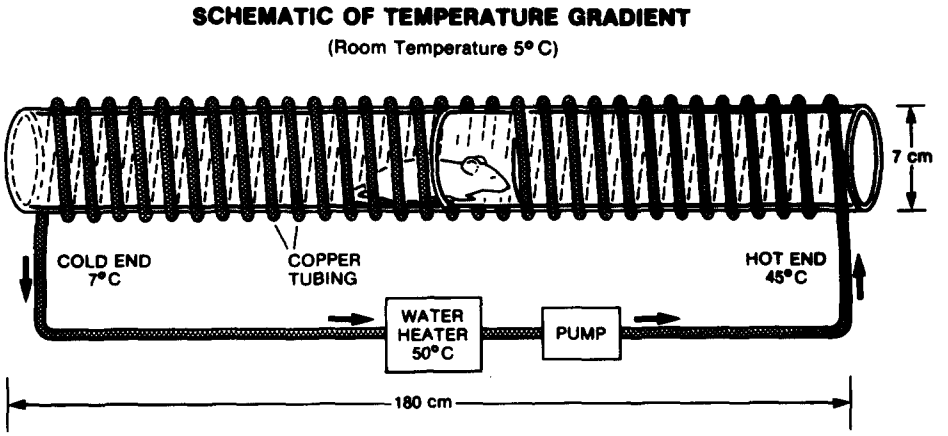

FIG. 1. Schematic representation of the Temperature Gradient Apparatus. Animals placed into the cold end of the chamber move towards more "preferred" ambient temperatures before falling asleep. This provides a simple and reliable "low effort" index of thermoregulatory behavior.

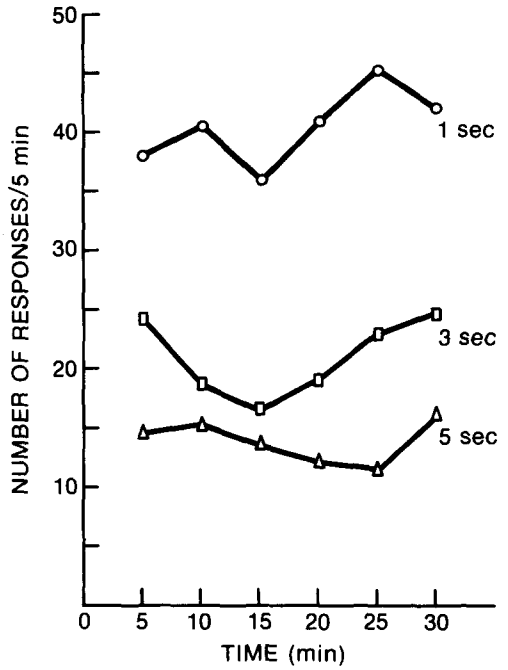

FIG. 2. Effects of changing the duration of heat reinforcement on the lever-press rates of animals working for 300-W bursts of radiant heat.

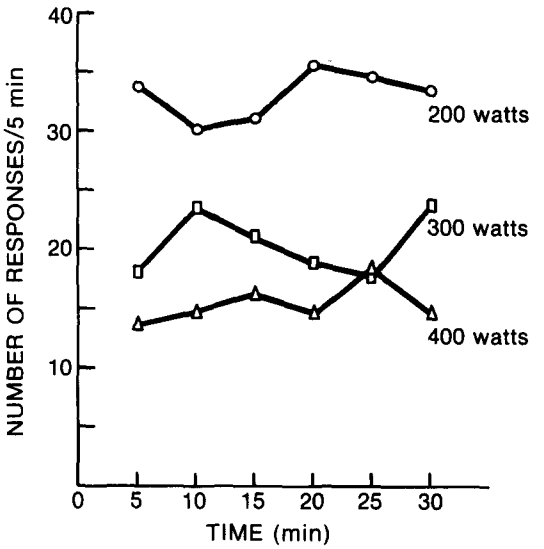

FIG. 3. Effects of changing the intensity of heat reinforcement on the lever-press rates of animals working for 3-sec bursts of radiant heat.

tion in the cylinder where the animal fell asleep. Once place/temperature preferences had stabilized (after 2–3 sessions), baseline and drug trials were initiated according to the same test procedures as those described for the operant lever-press task. This procedure included shaving prior to each test, and the determination of body core temperature as already described.

RESULTS

Lever-Press Test

The data confirmed that an inverse relationship exists between the reinforcing properties of heat and operant response rates. Figures 2 and 3 illustrate the effects of altering either the duration of the heat (keeping the heat intensity at 300 W) or the intensity of the heat (while keeping the duration constant at 3 sec) on lever-pressing in a single group of six rats. As in drug self-administration studies [29,39] increasing the reward administered per response produced a drop in operant behavior while decreasing the reward resulted in a compensatory increase in responding. Internal core temperatures recorded immediately before and after testing confirmed behavioral results. On control days, the animals' mean (±S.E.M.) core temperature, upon removal from the freezer, was 38.4°C (±0.1°), a value which was, in fact, slightly higher than pre-test levels (37.2°C (±0.2°)).

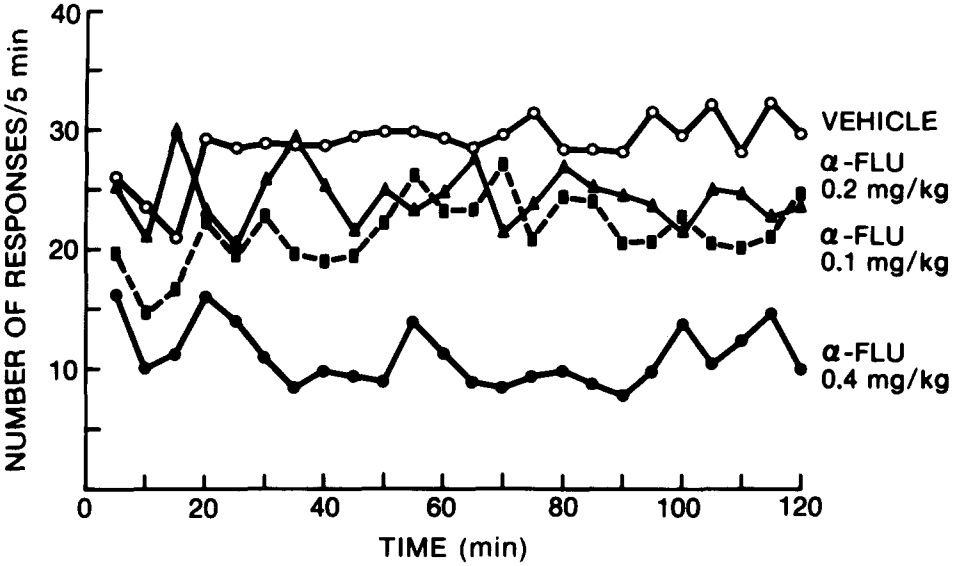

FIG. 4. Effects of the neuroleptic drug, α-flupenthixol, on lever-press rates of animals working for (300-W/3-sec) bursts of heat reinforcement.

Therefore, animals do respond in a manner which serves to maintain their body temperature. When heat duration was altered during the test session, the rats made compensatory changes in their lever-press rates and were thereby able to still maintain core temperature (post-test temp. = 38.4°C (±0.2°)). Animals similarly worked to compensate for changes in the intensity of the heat reinforcer (post-test temp. = 38.5°C (±0.3°)). There were, of course, no reliable differences in the post-test core temperatures across these three parametric conditions, $F(2,10)=0.65$, n.s., suggesting that animals adjust their thermoregulatory behavior in order to maintain homeostasis.

Neuroleptic effects on heat-reinforced behavior did not resemble the effects of reducing the reinforcing value of the heat. Figure 4 illustrates the effects of pretreating animals (the order of treatment was counterbalanced within the group) with varying doses of alpha-flupenthixol. There was a statistically reliable dose-dependent decrease in lever-pressing. A two-factor ANOVA (with repeated measures on both factors) computed on the data from Fig. 4 confirmed a main effect for Group, $F(3,15)=7.68$, $p<0.01$. There was no statistically significant effect of time nor a Group × Time interaction, suggesting that while animals responded at different levels during each drug dose, they maintained a relatively stable response output during the course of each test session.

These effects cannot be explained by a drug-induced alteration in core temperature. At peak drug effects (i.e., immediately prior to testing, 4 hours after injection) there was no change in temperature relative to pre-injection values. Mean core temperature prior to injection was 37.2°C (±0.2°), while pre-test body temperatures were 37.1°C (±0.1°), 37.2°C (±0.1°) and 37.3°C (±0.1°) for the low to high drug dose, respectively. Upon removal from the cold, drugged animals showed reliable dose-dependent reductions in body temperature that paralleled the reductions observed in operant response rates (i.e., post-test temperatures: 38.4°C (±0.2), 38.5°C (±0.2); 37.5°C (±0.2) and 36.0°C (±0.2) for the 0.0, 0.1, 0.2 and 0.4 mg/kg doses, respectively). These

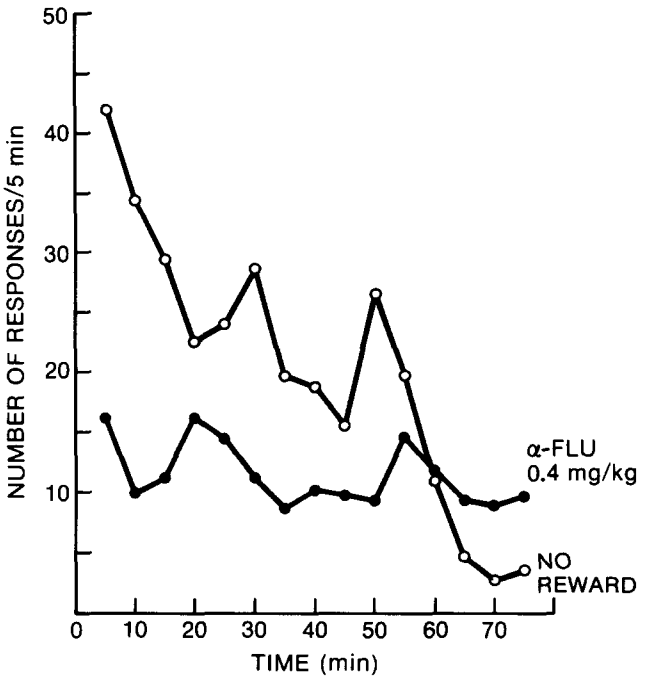

FIG. 5. A comparison of the response patterns generated during "real" extinction (i.e., no reward conditions) and during challenge with a high (0.4 mg/kg) dose of α-flupenthixol.

data further substantiate the conclusion that the animals were unable to behaviorally maintain normal core temperatures.

It has been suggested that high doses of neuroleptic drugs produce a behavioral disruption in operant responding that closely resembles the effects of eliminating the reinforcer—i.e., produces an extinction-like response curve (e.g., [37]).

TABLE 1

EFFECTS OF ALPHA-FLUPENTHIXOL ON MEAN (±S.E.M.) BODY TEMPERATURES (C°) IN A COLD ENVIRONMENT

Group	Pre-injection	Pre-test	Time in Cold (min) 40	80	120
Drug (0.4 mg/kg)	37.6 (±0.2)	37.2 (±0.1)	36.6 (±0.3)	34.2 (±0.4)	32.9 (±0.6)
Vehicle	37.8 (±0.3)	37.1 (±0.1)	36.0 (±0.3)	33.7 (±0.6)	31.4 (±1.0)

TABLE 2

MEAN (±SEM) PREFERRED ENVIRONMENTAL TEMPERATURE: ALPHA-FLUPENTHIXOL VS. SALINE BASELINE

Test Condition	Saline	Drug
Low dose	31.2°(±3.3)	29.2°(±5.7)
Medium dose	30.3°(±2.7)	28.5°(±4.1)
High dose	30.0°(±4.8)	29.7°(±7.1)

In the present study, "real" extinction conditions resulted in a substantial increase in responding during the initial portion of the trial, followed by a gradual reduction in emitted operant behavior as the session progressed (see Fig. 5). The resulting extinction-curve closely resembles extinction patterns observed in drug self-administration studies when the reinforcing drug is replaced with saline [13,41]. No dose of alpha-flupenthixol produced a behavioral effect in any way comparable to "real" extinction. At the high (0.4 mg/kg) dose, alpha-flupenthixol produced a flattened response curve in which the disruption in responding was constant throughout the entire session (Fig. 5).

It should be noted that the disruptive effects of alpha-flupenthixol on operant behavior cannot be accounted for by some unique action of the drug on body temperatures observable only under conditions of cold stress. To assess this possibility, body temperatures were compared in two new groups of rats (n=6/group) immediately before, at several times during, and immediately after being placed into the same freezer environment for 120 min without any heat sources. One group of rats was pretreated with 0.4 mg/kg of alpha-flupenthixol and the other group with the saline-vehicle solution. There were no reliable differences in body temperatures of the two groups at any time during the test (see Table 1).

Temperature Gradient Test

Pretreatment with α-flupenthixol had no effects on temperature preference in the gradient test. The animals preferred the same location within the cylinder regardless of whether or not they were administered saline or drug. Table 2 provides the mean (±SEM) preferred environmental temperatures (inside the gradient) for each drug trial and its preceding saline baseline. Although placed into the cold end of the cylinder, all animals were able to ambulate towards the middle of the gradient and choose essentially the same environment to sleep in as they did on non-drug trials. Unlike the lever-press test, this gradient test requires relatively little effort on the part of the subjects and indeed drugged animals were able to maintain their core temperature in this paradigm. Mean post-test body temperatures were constant across all saline and drug conditions (mean core temperature after saline trials was 37.1° (±0.1); mean core temperature after drug trials=36.9° (±0.2), 37.0° (±0.1) and 37.0° (±0.3) for low, medium and high doses of α-flupenthixol, respectively). These values were essentially identical to preinjection and pretrial temperatures.

DISCUSSION

Low doses of neuroleptic drug produced disruptions in operant responding for heat reinforcement that were directionally opposite to the effects predicted by a change in the rewarding properties of the heat stimulus. In addition, the high dose of alpha-flupenthixol produced a lever-press decrement that was qualitatively and quantitatively different from the behavioral effects of removing the reinforcer (i.e., extinction conditions). These data do not support the contention that neuroleptic treatments reduce the rewarding properties of all positive reinforcers. Instead, the results suggest that a significant portion of the behavioral disruption produced by these drugs, is a consequence of their performance-debilitating actions. When the response requirements of the behavioral test were minimal (the preference/place test), alpha-flupenthixol had no appreciable effects on either the reinforcing aspects of the temperature (i.e., no change in place/temperature preference within the cylinder), nor the animals' ability to maintain their internal core temperatures. In the more demanding operant lever-press task, neuroleptic challenge interfered with the animals' ability to behaviorally thermoregulate. Such results confirm previous findings that the degree of behavioral disruption produced by neuroleptic drugs is greatly influenced by the kinetic requirements of the response [12,17].

Taken together, the data from the present two test paradigms also suggest that the behavioral reductions observed in the lever-press task cannot easily be accounted for by some form of motivational deficit. Most traditional tests of motoric capability (e.g., treadmill, locomotor activity chambers, etc) do not differentiate between a reduced movement disability and a motivational disability where the animal may still be capable of movement, but in some way "unmotivated" to perform. In the present study, the demonstration that animals do thermoregulate in the simple gradient task (by ambulating towards a preferred temperature) clearly indicates the presence of a normal motivational component.

As indicated earlier, the present lever-press task is in many ways analogous to the drug self-administration paradigm—in both cases animals appear to respond in order to maintain a constant or homeostatic level of reinforcer during the test session. For example, animals trained to self-administer intravenous injections of psychomotor stimulants, work to keep a stable level of drug in their system over time [28,29]. Consequently, reducing the injection dose of the drug reinforcer, results in a compensatory increase in

operant self-administration responding. Conversely, increasing the amount of injection dose/response produces a compensatory reduction in operant behavior [29,38]. It would seem that unlike other positive reinforcers such as food, water, or rewarding brain stimulation, as one decreases the reward strength of the drug (by reducing the dose administered after each response) subjects increase their response rate, thereby returning net drug intake back to preferred equilibrium levels. Once again this is similar to what we have observed with heat reward (See Figs. 2 and 3).

In stimulant self-administration, pretreatment with neuroleptic drugs can produce behavioral results analogous to those observed with decreases in the injection dose of cocaine or amphetamine [10, 13, 40]. Such results are, of course, consistent with the notion that neuroleptics can attenuate reward. Since psychomotor stimulants such as cocaine and amphetamine are known to facilitate dopaminergic neurotransmission [2, 21, 32] and since the neuroleptics employed in these studies are believed to have dopamine antagonist properties [1,9], the self-administration data have been used to implicate dopamine mechanisms in the neural mediation of reinforcement ([31,37], see also [18]). Indeed, it seems reasonable to assume that if the exogenous activation of dopamine synapses is reinforcing, so must the normal endogenous activation of these same synapses also be reinforcing. However, it is undoubtedly premature to suggest from this that the same dopamine mechanisms subserve the rewarding properties of all other positive rewards. Intravenous self-administration of opiate agonists such as heroin, for example, is not altered by neuroleptic drugs nor by lesions of the dopamine terminals in the nucleus accumbens, a structure whose integrity is essential for cocaine and amphetamine reinforcement ([13,26], see also [24]). Neuroleptic drugs are also ineffective at attenuating the rewarding properties of sucrose solution [17], nor (in the present study) temperature reinforcement. Clearly a convincing case must be made independently for each reinforcer before we can presume dopamine substrates to be a crucial link in the brain's reward circuitry.

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