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Feeding and Drinking Interactions After Acute Butyrophenone Administration[1,2]

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ROWLAND, N. AND D. J. ENGLE. *Feeding and drinking interactions after acute butyrophenone administration.* PHARMAC. BIOCHEM. BEHAV. 7(4) 295–301, 1977. — The effects on feeding and drinking of various doses of droperidol, haloperidol and spiroperidol were studied in a number of paradigms. All three butyrophenones produced generally similar effects. After food deprivation, feeding was slightly increased at low doses but was decreased at the higher doses; the concomitant postprandial drinking was attenuated at all doses. Desalivate rats showed a marked attenuation of feeding (and prandial drinking) at low doses, but when wet mash was given instead of pellets and water a normal dose-response relationship was obtained. After water deprivation drinking was attenuated at all doses, and when food was also available during the drinking test the food intake was decreased in proportion to the drinking. Drinking was blocked more when food was present than in its absence. Insulin and 2-deoxyglucose induced feeding in sated rats was attenuated but not abolished by haloperidol. The findings are discussed relative to the role of activation and brain catecholamines in feeding and drinking.

Butyrophenones Feeding Drinking Deprivation Insulin 2-Deoxyglucose
Brain catecholamines Salivarectomy

BUTYROPHENONES with neuroleptic activity are thought to exert their behavioral effects through their action in the central nervous system and in particular by their ability to selectively block dopamine receptors [1, 6, 23]. As such they are potent tools for the study of the roles of brain dopamine in a variety of behaviors.

Contemporary interest was focussed upon the motivational and sensorimotor roles of the nigroneostriatal dopamine pathway. Chemical lesions of this pathway (using 6-hydroxydopamine to obtain at least 95% depletions of brain dopamine levels) produce a syndrome of sensorimotor dysfunction and aphagia from which there is partial recovery [12,24] bearing some parallels and some differences to the classical lateral hypothalamic syndrome [7, 15, 16, 24]. Because the results of such lesion studies are always subject to difficulties of interpretation (e.g., [16,20]) it is important to consider complementary approaches to the general problem area. Dopamine receptor blockade is one such approach yet the number of reports is disproportionately small – at least for ingestive behavior.

Moreover the existing neuropharmacological studies are incomplete and there is no absence of inconsistencies. Rolls and colleagues [19] found that dopamine receptor blockade with spiroperidol caused dose-related decreases of drinking in water deprived rats and of feeding in food deprived rats, with the former being less affected by this neuroleptic. In contrast, papers by Block and Fisher [5] and Zis and Fibiger [25] using haloperidol and pimozide as blocking agents report greater decreases in drinking than feeding after the respective deprivations. (As an extension, it seems that behaviors produced by electrical intervention in the brain are more easily disrupted by neuroleptics than any ingestive behavior [16,19]). Is this apparent difference in the susceptibilities to disruption of feeding and drinking a function of the particular neuroleptic, or some other factor? The comparison of neuroleptics in the present work is, in part, to resolve this problem.

In a study in which only a single dose of neuroleptic was used, Zis and Fibiger [25] found no decrease in drinking by thirsty rats when food was available during the one hour drinking test, but there was a significant 30% decrease of drinking when food was not available (compare their Tables 1 and 5). The interpretation of this finding is not clear, and does point to an interaction between feeding and drinking, yet no neuroleptic study has simultaneously measured food and water intake (but see [22] for effects of norepinephrine manipulations). In the present study we have measured both food and water intakes in a number of paradigms to resolve if one of these behaviors is indeed more susceptible to blockade and on the nature of any interaction of feeding and drinking. We have, in addition to normal rats, used a preparation in which feeding and drinking responses alternate rapidly in time, namely the surgically salivaless rat [7].

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METHOD

General

Mature male Sprague Dawley rats (Zivic Miller Pgh; 6–12 months old, 400–800 g) were used throughout. They were individually housed in hanging wire cages with ad lib access (except as noted) to Wayne rat pellets on the floor and water from a metal spout. A natural lighting cycle was used, with overhead fluorescent lights additionally on between about 0800 and 1900 hr. All testing was performed in the home cage in the middle of the day (1300–1600 hr) when the animals were invariably resting.

Injections

Neuroleptics were administered intraperitoneally 30 min before testing, in a volume of 1 ml/kg. The butyrophenones used were Droperidol (Inapsin, McNeill), Haloperidol (Haldol, McNeill) and Spiroperidol (Spiperone, ZR 5147), Janssen) all appropriately diluted with a vehicle (VEH) of 0.2 mg/ml tartaric acid in water.

EXPERIMENT 1: NATURAL HUNGER AND THIRST

Food Deprivation

Food was removed 24 hr before the test but water remained available until the time of neuroleptic injection. During the feeding test either three pellets of food alone or both food and water were available. Intakes of food (allowing for collected spillage) and water (graduated burette) were recorded to the nearest 0.1 g and ml over a one hr test period which started 30 min after the injection. Twenty-four rats were used in this experiment, divided into subgroups of six.

Water Deprivation

Water was removed 24 hr before the test but food remained available until the time of neuroleptic injection. During the one hr drinking test (again starting 30 min after injection) either water alone or water and food were available with intakes recorded to the nearest 0.1 ml, g. Additionally in the latter condition the water which had been ingested at the onset of feeding was also recorded. Twenty-four rats were used in this experiment, divided in two equal subgroups.

Baseline Intakes

Before the experiment proper began the animals were adapted to their respective deprivation conditions at least twice (without injection) before starting to collect baseline data with VEH injection. These baseline values were checked periodically throughout the experiment and were not found to change significantly. This finding also precludes the possible effects of drug build up in these multiply injected animals: test days were separated by 3–5 days of no injection, and all rats maintained or gained weight throughout.

Salivarectomy

Twelve of the rats which had served in the food deprivation experiments (hence were experienced) were surgically totally desalivated. Under Equithesin anesthesia (2.5 ml/kg) the sublingual and submaxilliary glands were removed through a midline neck incision and the parotid ducts of Stenson were litigated and cut as they cross the masseter muscle of the cheek. All were offered wet mash for a few days to facilitate postoperative recovery, were weaned onto dry food and within two weeks all were showing typical prandial drinking [7] as evidenced by daily water intakes of 100–250 ml and food particles in the water bottles. These symptoms persisted for the duration of testing (i.e., no regeneration occurred). Food deprivation testing was then resumed using food and water access as above; in addition, tests were run in which they were given wet mash (1 part w/w powdered chow to 2 parts water) after food deprivation.

Data Analysis

Groups of six or more animals were run under a variety of injection conditions; any given neuroleptic dose was repeated in at least two different groups and a dose response curve for each drug was completed within one group. Because the results across groups were generally consistent the data are averaged. Each animal is compared with its own VEH intakes, and a $p<0.05$ from a paired 2-tailed t-test was considered statistically significant (in graphs).

RESULTS AND DISCUSSION

Food Deprivation: Normal Rats

Food deprived rats immediately initiate a large meal. When feeding is completed a draft of water is consumed, generally commensurate with the meal size and a little less than 1 ml per g food. No further intake occurs within one hr. Representative data are shown in Table 1. When the test was conducted in the absence of water there was no alteration in the food intake (which is to be expected because the feeding is over before drinking begins). A moderate dose of droperidol did not antagonize this feeding either in the presence or absence of water (Table 1). We may conclude that any block of drinking observed in the following experiments will not compromise the feeding response in any causal way.

TABLE 1

ONE HR TEST INTAKES OF 24 HR FOOD DEPRIVED RATS TESTED WITH WATER PRESENT AND ABSENT

	Vehicle injected	Droperidol 0.1 mg/kg
Water Present		
Food (g)	9.9 (1.0)*	10.0 (0.6)
Water (ml)	5.8 (0.7)	1.7 (0.7)†
Water Absent		
Food (g)	9.3 (1.1)	9.1 (1.3)

*Mean (SEM) for N = 6, within subjects design; values rounded to nearest 0.1.

†Different ($p<0.01$) from vehicle injection condition.

The complete dose-response curves for the effects of neuroleptics on postdeprivation feeding and the associated postprandial drinking are shown in Fig. 1. The data are presented as per cent of vehicle injected intakes. For the

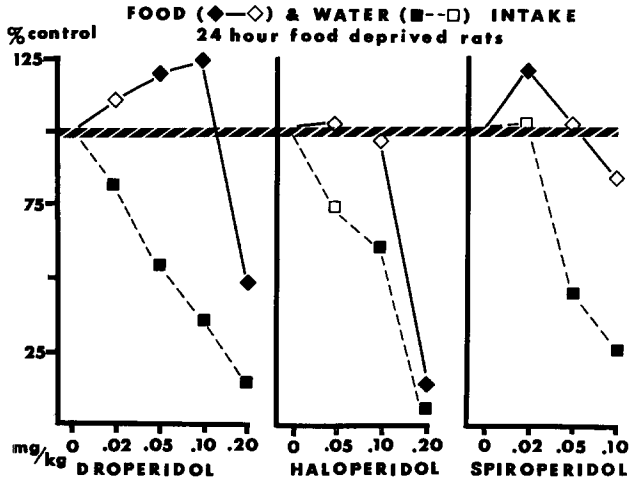

FIG. 1. Dose-response curves of three butrophenones on feeding after food deprivation, and concomitant drinking. The filled symbols indicate statistically reliable difference ($p<0.05$) from the 100% (vehicle injected) control values.

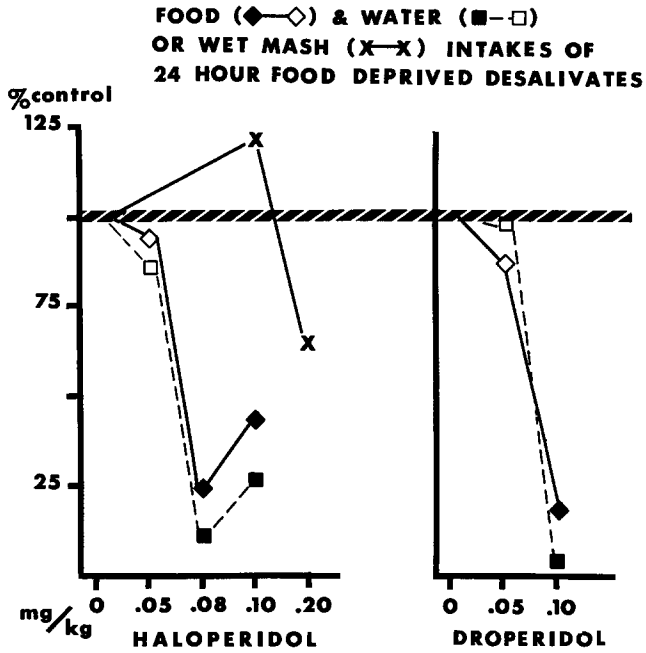

FIG. 2. As Fig. 1, in surgically desalivate rats. Water was available but not ingested during the wet mash tests (x) both of which differed $p<0.05$) from control.

four groups of six rats used in this experiment these vehicle (control) means ranged from 8.3 to 8.6 g and 5.8 to 7.8 ml. Feeding was often significantly elevated at the lower doses of spiroperidol and droperidol, and was sharply attenuated at the highest doses. In contrast to the feeding, the postprandial drinking was more severely attenuated and at even the lowest doses. There were no major differences between the three neuroleptics.

These results are consistent with two hypotheses: (a) feeding is less susceptible to blockade than drinking (irrespective of the particular mechanism or level of that action), (b) the primary drive of hunger is far more intense than minor postprandial thirst, and as such the neuroleptics are acting according to level of motivation.

Food Deprivation: Desalivate Rats

Desalivate rats cannot eat if they do not drink; accordingly, both drinking and feeding are equivalently affected by neuroleptics (Fig. 2). However, feeding was severely attenuated by less than half the dose which had been effective before salivarectomy (and also, because they lost 10–20% body weight after salivarectomy the absolute amount of drug given per rat was less) – compare with Fig. 1. When wet mash was the offered food, and eating proceeded without prandial drinking, the haloperidol dose response curve was now similar to that of intact rats, with facilitated feeding at 0.1 mg/kg and attenuation at 0.2 mg/kg (Fig. 2).

These data suggest it is the additional effort of swallowing dry food (by drinking) in the desalivate rat which produces a greater sensitivity to the blocking actions of neuroleptics. The animals did not appear any more sedated than controls. We cannot rule out a palatability argument to explain the wet mash result. However, we also note that the block of ingestion is similar to the block of drinking observed in the hungry intact rats (Fig. 1), and it is plausible that the anorexia on dry food is secondary to a drug-induced hypodipsia.

Water Deprivation

Water deprived rats show short latency drinking which consists of a single long draft lasting some 10 min, and then a series of smaller drafts interspersed with grooming before satiation [9]. The neuroleptics caused a dose-related reduction of water intake with food absent (Table 2). The inconsistent results between the two groups for droperidol 0.1 mg/kg are included as by far the greatest failure to replicate a result in the present series: it is to be noted that when Groups A and B are combined, the difference is significant ($t(20) = 3.42$, $p<0.01$).

When food is also present, thirsty rats drink for about 10 min, groom, eat a normal sized meal, and drink postprandially (Table 2). The neuroleptics again caused a dose-related decrease in drinking, a decrease which was equally distributed between the pre- and post-prandial components (Table 2, Fig. 3). Feeding was attenuated to about the same extent as drinking.

It is of interest that at the highest doses the drinking response was more severely attenuated in the presence of food than in its absence, even in those animals which ate negligible amounts. Thirteen rats which ate 0.3 g or less after droperidol 0.1 mg/kg drank 5.3 ml when food was available and 12.1 ml when not available; with spiroperidol 0.1 mg/kg, eleven rats drink a mean of 6.9 ml without eating the available food, yet drink 10.9 in its absence (both p's<0.01). Such a difference was not noted with haloperidol 0.2 mg/kg.

These data are not consistent with the notion that drinking is more severely attenuated than feeding, and do not support the findings of Zis and Fibiger ([25], Table 1) who found no block of drinking. It is well known that a water deprived animal is anorexic, and so when water is again presented the motivational state is complex. We should expect the hunger to be much less than when the

TABLE 2

ONE HR TEST INTAKES OF 24 HR WATER DEPRIVED RATS TESTED WITH FOOD PRESENT AND ABSENT

		No Food	Food Present		
		Water (ml)	Premeal water (ml)	Total water (ml)	Food (g)
Group A (N = 10)					
Vehicle		20.4 (1.3)	14.5 (0.8)	24.3 (1.0)	4.9 (0.3)
Droperidol	0.05‡	16.6 (1.0)†	10.2 (0.8)†	18.9 (1.5)†	5.2 (0.6)
Droperidol	0.10	11.4 (1.8)*	5.5 (1.7)*	8.4 (2.1)*	1.0 (0.4)*
Haloperidol	0.10	12.5 (1.1)*	10.1 (0.9)*	15.9 (1.9)*	4.3 (0.7)*
Haloperidol	0.20	5.2 (1.4)*	—	9.1 (2.0)*	1.1 (0.4)*
Spiroperidol	0.05	—	12.1 (1.1)*	17.0 (1.5)*	3.1 (0.4)*
Group B (N = 11)					
Vehicle		18.5 (1.7)	17.1 (1.2)	25.6 (1.5)	4.0 (0.4)
Droperidol	0.10	16.8 (2.3)	6.0 (1.4)*	8.2 (1.9)*	1.1 (0.6)*
Spiroperidol	0.05	18.1 (2.2)	12.0 (2.1)*	15.7 (2.4)*	3.3 (0.6)
Spiroperidol	0.10	10.9 (1.0)*	—	7.8 (1.6)*	0.3 (0.1)*

Values are means (SEM); † $p<0.05$. *$p<0.01$, compared with appropriate vehicle.
‡Drug dose (mg/kg) injected IP 30 min before start to test.

animal is totally food deprived and have shown that the feeding in thirsty rats is blocked by neuroleptic doses which are ineffective in the hungry animal (e.g., compare Figs. 1 and 3 for droperidol 0.1 mg/kg and spiroperidol 0.05 mg/kg).

EXPERIMENT 2: ACUTE HUNGER INDUCED BY INSULIN AND 2-DEOXY-D-GLUCOSE

Animals with catecholamine depleting lesions typically show rather short lived abnormalities in their spontaneous ingestive behavior, yet show an inability to cope with acute metabolic emergencies by increased feeding (or other behaviors) [12, 15, 24]. Neuroleptic studies [25] have also noted a more severe attenuation of ingestion to acute stresses than to the naturally-occurring drive states (see Experiment 1). In particular, Zis and Fibiger [25] found a 70% attenuation of feeding (maybe 100% since they did not report no-insulin baseline data) to a massive dose of 80 U/kg insulin, while the same dose of neuroleptic was without effect upon feeding after 24 hr food deprivation. Block and Fisher [5] obtained no evidence for a greater attenuation of eating (wet mash) to 750 mg/kg 2-DG than after food deprivation, although the N's (3) are too small for solid conclusions.

In the present experiment feeding to more modest doses of insulin and 2-DG were assessed as a function of haloperidol dose.

Method

The animals were maintained as before. Food and water were removed at the time of insulin (Lilly, 20 or 80 Units/kg, subcutaneous) or 2-DG (Sigma, 350 mg/kg intraperitoneal) injection. Thirty minutes later the neuroleptic or VEH was injected, and food pellets and water were presented a further thirty minutes later. Intakes were then recorded after one and two hr.

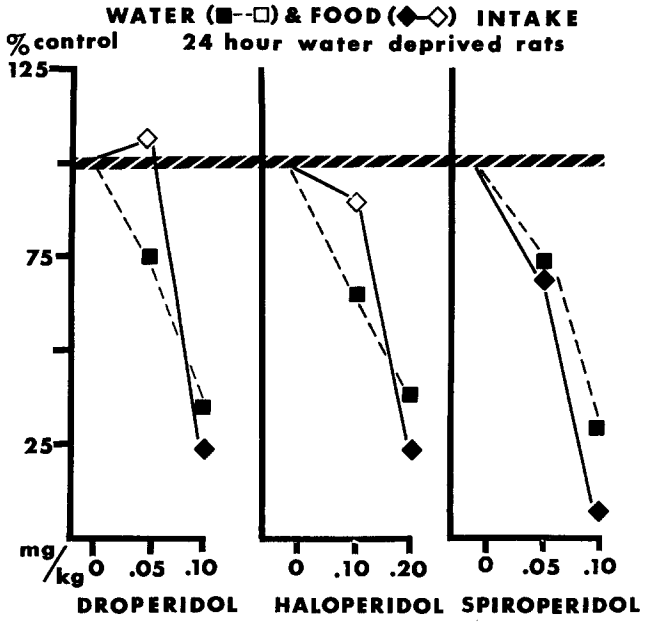

FIG. 3. Dose-response curves of three butyrophenones on drinking after water deprivation, and concomitant eating. Filled symbols indicate statistically reliable difference ($p<0.05$) from the 100% (vehicle injected) control values. The numerical data for many of these points are shown in Table 2.

RESULTS AND DISCUSSION

The baseline (VEH injected) food intakes were typically low at the time of testing and the water intakes (data not shown) were even lower. The results shown in Table 3 indicate, however, that the baseline feeding was actually enhanced by the lower dose of haloperidol.

TABLE 3

EFFECTS OF HALOPERIDOL ON FEEDING ELICITED BY REGULAR INSULIN OR 2-DEOXY-D-GLUCOSE (2-DG) IN SATED RATS

First injection	Second injection	Food intake (g) 1 hr	2 hr	Statistical difference‡
Vehicle	Vehicle	0.6 (0.2)	1.3 (0.3)	
Vehicle	Haloperidol 0.1	1.8 (0.4)*	2.3 (0.5)	*<0.01 vs V-V
Vehicle	Haloperidol 0.2	0.4 (0.2)	0.7 (0.3)	
Insulin (20 U/kg)	Vehicle	2.8 (0.6)*	5.4 (0.8)*	*<0.01 vs V-V
Insulin (20 U/kg)	Haloperidol 0.1	3.5 (0.8)*	4.8 (1.0)*	*<0.05 vs V-H.1
Insulin (20 U/kg)	Haloperidol 0.2	1.8 (0.4)†	2.5 (0.5)*	†<0.06, *<.01 vs V-H.2
Insulin (80 U/kg)	Vehicle	3.5 (0.4)*	5.5 (0.7)*	*<0.01 vs V-V
Insulin (80 U/k)	Haloperidol 0.1	2.0 (0.5)*†	3.8 (0.7)	*<0.05 vs I80-V; † = .02 vs I20-H.1
Insulin (80 U/kg)	Haloperidol 0.2	2.5 (1.1)*	4.3 (0.5)*	*<0.01 vs V-H.2
2-DG (350 mg/kg)	Vehicle	3.5 (0.6)*	4.6 (0.7)*	*<0.01 vs V-V
2-DG (350 mg/kg)	Haloperidol 0.1	2.2 (0.5)	3.9 (0.7)*	*<0.05 vs V-H.1

‡Within or between animals *t*-tests. Abbreviations: V = vehicle, H.1,H.2 = haloperidol, 0.1, 0.2 mg/kg respectively.

2–DG reliably increased feeding above baselines at both 1 and 2 hr. The animals treated with 0.1 mg/kg still ate, but the amount ingested was not significantly above the (elevated) haloperidol baseline until the second hour. The intake was marginally less than the vehicle-2–DG condition ($t(12) = 1.78$, $p = 0.1$). Water intake was stimulated in the second hr in the vehicle-2–DG group, but not in the haloperidol animals.

80 units/kg insulin increased both feeding and drinking. As with 2–DG, the effect of haloperidol (0.1 mg/kg) was to delay the increase of feeding above baseline. However, neither dose of haloperidol completely abolished the feeding response which was adequate to allow 10 of 12 rats to survive the treatment.

20 units/kg insulin increased both feeding and drinking in the vehicle treated animals to the same extent as the higher insulin dose. The increase above baseline was again attenuated, but not totally abolished, by haloperidol. Eating after the 0.2 mg/kg dose of haloperidol was particularly low when compared to the effect of this dose on the eating elicited by 80 Units/kg insulin. This difference, which is merely suggestive, might indicate that the (presumably) greater metabolic stimulus provided by the larger dose was less readily overcome by the neuroleptic.

GENERAL DISCUSSION

The present experiments have repeated and considerably amplified previous work on neuroleptics and ingestive behavior [5, 19, 25]; it is apparent that there are both similarities and disagreements between these and the previous data.

Zis and Fibiger [25] reported that neither haloperidol (0.2 mg/kg) nor pimozide (0.45 mg/kg) attenuated post-deprivation feeding (but see [16]). Block and Fisher [5] reported a substantial blockade of feeding at 0.17 mg/kg haloperidol, but not at lower doses. Rolls *et al.* [19] found a dose related suppression of feeding using spiroperidol. We concur with these latter reports insofar as we find large doses of all three butyrophenones suppress feeding. It is of some interest that our Pittsburgh Sprague-Dawley rats show an attenuation of eating induced by electrical stimulation of the lateral hypothalamus (Antelman, Black and Fisher, unpublished results) at doses approximately half those found effective in the Vancouver Wistar rats [17]. It is quite possible that strain differences in catecholamine receptor sensitivity [21] could exist, and account for differential sensitivity to neuroleptics.

Insofar as drinking is concerned, Zis and Fibiger ([25], Table 5) again utilized approximately twice the dose of haloperidol to obtain a smaller blockade of deprivation drinking (in the absence of food) than did Block and Fisher [5]. Two other studies have found dose-related suppressions of postdeprivation drinking [14,19], much as in the present work. While Zis and Fibiger [25] surmised the differences between their data and those from Pittsburgh [5,8] might be due to pretraining differences, Fisher (personal communication) informs us that his rats received even more pretest experience with deprivation than did the Vancouver rats; in the absence of any other good explanation we reserve the possibility of a strain difference alluded to above.

However, putting aside the issue of absolute doses, we agree that post-deprivation feeding is less easily disrupted than post-deprivation drinking (compare the present Figs. 1 and 3 with Zis and Fibiger's [25] Tables 3 and 5; see also [5,8]). These findings disagree with the result of Rolls *et al.* [19] that drinking is less easily attenuated than feeding. In the present work we have shown that spiroperidol (used by Rolls) has no unusual properties compared with the other neuroleptics, and we are unable to account for the discrepancy. Rolls *et al.* [19] (see also [16]) found larger attenuations of feeding when a simple barpress operant was required compared with when the food was freely accessible. From the present work it is possible to suggest

the sensitivity of the desalivate rats may reflect the greater effort required (to eat and drink). It is also possible that the common feature of breaking off eating to do another task (drinking or a barpress) may be the reason for the apparently altered dose response curves. When the desalivate rat did not have to interrupt feeding, i.e., with the wet mash diet, normal responses to haloperidol and droperidol were obtained. The paradigm is also confounded by possible palatability factors. Either way, we are unable to say whether motor factors [19] or a combination of motivational and performance decrements [16] are indicated by these data.

The finding that feeding after water deprivation is attenuated at lower neuroleptic doses than after food deprivation (Table 2 and Figure 1) may reflect the secondary and primary (respectively) nature of the urge to feed in these two situations. This represents an attempt to integrate the psychological constructs into our analyses, as recently advocated by Mogenson and Phillips [12]. The greater sensitivity of some drinking performances to neuroleptic disruption (compared to feeding) might therefore mean that a 24 hr fasted rat is more hungry than a 24 hr water deprived rat is thirsty. This is, of course, pure conjecture but it is interesting to note that a rat deprived of both food and water will invariably feed first once food and water are restored [20]. Relevant to the issue of feeding and drinking interactions, the drinking which is elicited prior to feeding after intracranial norepinephrine [10] is completely blocked by doses of spiroperidol which leave the feeding unaffected (Eichler and Antelman, personal communication).

We consistently found facilitation of eating at the lower doses of neuroleptic; other classes of drug (not necessarily with dopamine blocking action) have also been reported to facilitate post-deprivation intake (e.g., [2, 3, 11]). It is not possible to point to common mechanisms at this time – undoubtedly the roles of any one neurotransmitter in a given behavior are complex (see [8]), but a recent model of norepinephrine-dopamine interactions [3] represents a move toward the recognition of interacting systems. In particular, moderate dopamine receptor blockade could modify norepinephrine activity which in turn might influence feeding behavior (e.g., [10,18]). Such a level of analysis may well be needed to explain why we found that thirsty rats tested with food present drank less than if tested with food absent (although feeding was completely attenuated at the dose of neuroleptic in question). It is possible that the absence of food frustrates the animal and the concomitant activation to some extent overcomes the effect of the neuroleptic (see [3] for a discussion of activated versus nonactivated situations). Neill and Grossman [13] were previously unable to account for a finding that amphetamine-induced hypodipsia (in thirsty rats) was aggravated by the presence of food, even though they did not eat; again we may speculate the presence of food has a calming or other arousal-related effect (although even if this view is accepted it is still not clear whether we should predict an increase or a decrease of drinking, which serves to highlight the problems surrounding hypothesis testing of any interactional model).

Zis and Fibiger [25] pointed to the greater effects of the neuroleptics upon acutely stimulated (NaCl and insulin) ingestion than that after natural deprivation. They suggest the acute regulatory mechanisms are more dependent upon brain dopamine, consistent with a large body of dopamine lesion data [24]. However, the role of these regulatory systems in normal behavior is unclear, and it is a truism that brain dopamine systems evolved long before acute homeostatic challenges, but did evolve during periods of natural deprivation. We must turn more attention to these considerations, such as in the work-for-food paradigms [19], or more global situations [12], if we are to understand the normal role of dopamine in behavior.

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