Psychopharmacologia (Berl.) 43, 63–68 (1975)

Neuroleptic-Induced Deficits in Food and Water Regulation: Similarities to the Lateral Hypothalamic Syndrome

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Received November 11, 1974

Abstract. The role of central dopaminergic mechanisms in the regulation of food and water intake was assessed by examining the effects of haloperidol and pimozide on various measures of feeding and drinking in rats. Haloperidol (0.20 mg/kg) or pimozide (0.45 mg/kg) did not significantly affect 1-hr water intake in response to 24 hrs of water deprivation, nor did they influence 2-hr food intake after 24 hrs of food deprivation. However both pimozide and haloperidol significantly reduced drinking in response to injections of hypertonic saline. In addition, animals pretreated with these drugs drank less than controls in the absence of food (a measure of "non-prandial" drinking), and drank less than controls when the water was adulterated with quinine (a measure of "finickiness"). These drugs also significantly reduced food intake in response to injections of insulin and attenuated amphetamine anorexia. These deficits are similar to those observed after electrolytic lesions of the lateral hypothalamus or after 6-hydroxydopamine lesions of the substantia nigra. Because haloperidol and pimozide block central dopaminergic receptor sites, the present findings are consistent with the hypothesis that part of the lateral hypothalamic syndrome is the result of damage to the dopaminergic nigro-neostriatal projection. Finally, the data suggest that the changes in feeding and drinking induced by haloperidol and pimozide reflect genuine homeostatic deficits rather than being due to a neuroleptic-induced motor dysfunction.

Key words: Pimozide – Haloperidol – Dopamine – Lateral Hypothalamic Syndrome – Amphetamine Anorexia.

Introduction

Lateral hypothalamic (LH) lesions disrupt eating and drinking in rats (Anand and Brobeck, 1951; Teitelbaum and Stellar, 1954). Although animals with LH lesions ultimately resume eating and drinking behaviours, close observation of these animals has revealed residual and apparently permanent homeostatic deficits such as less drinking in the absence of food, increased finickiness to quinine adulteration of drinking water, reduced drinking in response to hypertonic saline injections, attenuation of amphetamine-induced anorexia, and reduced eating in response to administration of insulin (Teitelbaum and Epstein, 1972; Epstein and Teitelbaum, 1964; Epstein and Teitelbaum, 1967; Carlisle, 1964). Several laboratories employing different techniques have suggested that the lateral hypothalamic syndrome may in part be due to interruption of the dopaminergic nigroneostriatal bundle (NSB). Iversen (1971) showed that bilateral electrolytic lesions of the substantia nigra produced transient aphagia and adipsia in rats. Oltmans and Harvey (1972) found that electrolytic lesions of the LH which encroached upon the dopaminergic NSB produced more severe aphagia and adipsia than did hypothalamic lesions which did not disrupt this projection. Moreover the severity and duration of the effects of the LH lesions on water intake appeared to correlate with the depletion of striatal dopamine. In addition, Grossman and Grossman (1973) found that parasagittal knife cuts along the lateral border of the hypothalamus which transected most of the fibers that enter or leave the hypothalamus laterally reproduced the full spectrum of effects on food intake seen after lateral hypothalamic lesions. They suggested that these effects were due to interruption of fibers of passage rather than direct cellular damage to the LH itself.

Recently several laboratories have further studied this problem by taking advantage of the fact that 6-hydroxydopamine (6-OHDA) can, when injected intraventricularly or intracerebrally, induce rather

specific and extensive destruction of central catecholaminergic neurons. Ungerstedt (1971) originally observed that 6-OHDA lesions of the nigro-neostriatal dopaminergic pathway produced a condition similar to the aphagia and adipsia found in the lateral hypothalamic syndrome. Subsequently we examined in some detail the effects of destruction of central catecholaminergic pathways by 6-OHDA on food and water intake and regulation (Fibiger *et al.*, 1973). Extensive depletion of neostriatal dopamine by stereotaxic injections of 6-OHDA into the substantia nigra or by intraventricular injections of 6-OHDA in tranylcypromine-pretreated rats produced a syndrome similar to that seen in LH lesioned animals. These animals were initially aphagic and adipsic. After recovery of food and water intake they showed the same homeostatic deficits (although of a smaller magnitude) as were seen in LH lesioned rats. Since then several other laboratories have demonstrated similar alterations in consummatory behaviour after damage to central dopaminergic neurons induced by 6-OHDA (Breese *et al.*, 1973; Marshall and Teitelbaum, 1973; Myers and Martin, 1973; Stricker and Zigmond, 1974).

In the present series of experiments, the role of central dopaminergic neurons in the regulation of food and water intake was further investigated by examining the effects of two neuroleptic drugs on these behaviours. In small doses, haloperidol and pimozide have been reported to block selectively central dopamine receptors (Andén *et al.*, 1970). These drugs therefore can produce a selective but reversible functional blockade of central dopaminergic mechanisms. This being the case, it was hypothesized that these compounds might produce similar homeostatic deficits as those which have been observed after physical or chemical damage to the dopaminergic nigro-neostriatal projection.

Methods

Thirty male Wistar rats were used (Woodlyn Farms, Ontario, Canada, weighing 320–360 g at the start of the experiment). Animals were housed individually, food (Purina rat chow) and water were available *ad lib.* unless otherwise specified. The animals were randomly divided into 3 groups. The haloperidol group ($n = 10$) was injected intraperitoneally with 0.2 mg/kg of haloperidol (Haldol, McNeil Laboratories) 45 min prior to the beginning of each test. The pimozide group ($n = 10$) was injected with 0.45 mg/kg of pimozide, as a solution in hot tartaric acid, 90 min prior to each test. The remaining 10 animals served as controls and received saline (0.9%) injections (1 ml/kg) 45 min before each test. A 3-day drugfree period was interposed between the different tests. The tests were performed in the same sequence for the 3 groups. The results were evaluated statistically by analysis of variance and by Student's t test.

Homeostatic Tests

1. Deprivation-Induced Water Intake. Animals were deprived of water for 24 hrs during which food was available *ad lib.* Water intake was then measured for 1 hr following the deprivation period. Food continued to be available during the 1-hr drinking period. No drugs were administered to any of the groups during this test. Three days later, this procedure was repeated, preceded by drug administration to the haloperidol and pimozide groups.

2. Hypertonic Saline Test. The animals were injected intraperitoneally with a hypertonic (1 M) NaCl solution (20 ml/kg). The amount of water consumed during the subsequent 1 hr was measured.

3. Deprivation-Induced Food Intake. The animals were food deprived for 24 hrs during which water was available *ad lib.* Food intake was measured for 2 hrs following the deprivation period during which water continued to be available. No drugs were administered before this test. The same measurement was repeated 3 days later; preceded by drug administration to the haloperidol and pimozide groups.

4. Amphetamine Anorexia Test. The animals were food deprived for 24 hrs. They were then injected with *d*-amphetamine sulfate (1.5 mg/kg, expressed as the salt). Twenty minutes after the amphetamine injection, food was made available and the food intake over the subsequent 2 hrs was measured.

5. Non-Prandial Drinking. The animals were water deprived for 24 hrs during which food was present. Water was then made available but food was removed from the animals' cages and water intake under these conditions was measured for 1 hr.

6. Quinine Aversion Test. The animals were deprived of water for 24 hrs during which food was available. Following this deprivation period, water adulterated with quinine hydrochloride (0.01%) was made available and intake during 1 hr was recorded. Food was available during the 1 hr test.

7. Insulin-Induced Eating. The animals were injected subcutaneously with 80 U/kg of crystalline zinc insulin (Connaught Laboratories). Food consumption during the subsequent 2 hrs was measured.

Results

Deprivation-Induced Water Intake. The 1 hr pre-drug baseline water intake after 24 hrs of water deprivation did not differ significantly among the 3 groups ($F = 0.04$, df 2,29, n.s.). These results are seen in Table 1. In addition pimozide (0.45 mg/kg) and haloperidol (0.2 mg/kg) did not significantly affect water intake (1 hr) after 24 hrs of water deprivation ($F = 0.72$, df 2,29, n.s.).

Hypertonic Saline Test. The results of this experiment are given in Table 2. There was a significant difference among the groups in the amount of water consumed after the hypertonic saline injection ($F = 27.25$, df 2,29, $P < 0.01$). Further analysis revealed that both the haloperidol- and the pimozide-treated groups drank significantly less than controls in response to hypertonic saline ($P < 0.01$). The intake of the 2 drug treated groups did not differ significantly from each other.

Table 1
Water intake (1 hr) following 24 hrs of water deprivation

Group	A Baseline (no drug)	B Neuroleptic drug pretreatment	Difference (A−B)
	water intake (ml)		
Control	16.0 ± 2.9	16.3 ± 2.1[a]	− 0.3 ± 1.6
Haloperidol	15.9 ± 2.2	15.1 ± 1.7	+ 0.8 ± 1.1
Pimozide	15.7 ± 1.2	14.8 ± 2.4	+ 0.9 ± 2.5

Data represent means (± S.D.) of 10 animals in each group. For procedural details see Methods.
[a] Received injections of 0.9% NaCl (1 ml/kg).

Table 2. Effects of hypertonic (1.0 M) saline load on water intake (1 hr)

Group	Water intake (ml)	% Control
Control	13.3 ± 2.7	100
Haloperidol	4.4 ± 2.8*	35
Pimozide	6.6 ± 2.6*	43

Data represent means (± S.D.) of 10 animals in each group. For procedural details see Methods.
* Significantly different from controls $P < 0.01$.

Deprivation-Induced Food Intake. Food intake over 2 hrs after 24 hrs of food deprivation did not differ significantly among the 3 groups in the undrugged state ($F = 0.07$, df 2,29, n.s.). These results are seen in Table 3. In addition neither pimozide (0.45 mg/kg) nor haloperidol (0.2 mg/kg) significantly affected food intake (2 hrs) after 24 hrs of food deprivation ($F = 2.54$, df 2,29, n.s.).

Amphetamine Anorexia. The results of this experiment are given in Table 4. *d*-Amphetamine (1.5 mg/kg) significantly decreased food intake in the control animals ($P < 0.01$). After haloperidol or pimozide pretreatment however, amphetamine no longer significantly decreased food intake. These conclusions are also supported by the fact that there was a significant difference among the groups when the decrease from baseline (neuroleptic alone) produced by amphetamine was calculated for each animal ($F = 5.63$, df 2,29, $P < 0.01$). Thus relative to baseline intake, amphetamine decreased food intake significantly less in the haloperidol ($P < 0.02$) and in the pimozide ($P < 0.05$) pretreated animals than it did in controls.

Non-Prandial Drinking. The groups differed significantly on the amount of water consumed during 1 hr in the absence of food after 24 hrs of water deprivation ($F = 6.23$, df 2,29, $P < 0.01$). Both the haloperidol treated animals and the pimozide group drank significantly less than controls ($P < 0.01$ and $P < 0.05$, respectively). These data are seen in Table 5.

Quinine Aversion Test. There was a significant difference among the groups on intake (1 hr) of quinine-adulterated water after 24 hrs of water deprivation ($F = 19.67$, df 2,29, $P < 0.01$). These results are given in Table 6. Both haloperidol and pimozide pretreated groups drank significantly less than controls (both $P < 0.01$).

Insulin-Induced Eating. There was a significant difference among the groups in the amount of food consumed during 2 hrs after insulin ($F = 11.98$, df 2,29, $P < 0.01$). Both the haloperidol and the pimozide

Table 3
Food intake (2 hrs) following 24 hrs of food deprivation

Group	A Baseline (no drug)	B Neuroleptic drug pretreatment	Difference (A−B)
	food intake (g)		
Control	8.5 ± 2.0	9.0 ± 1.4[a]	− 0.5 ± 1.1
Haloperidol	8.3 ± 2.3	7.6 ± 2.0	+ 0.7 ± 3.6
Pimozide	8.5 ± 2.2	9.3 ± 1.5	− 0.8 ± 1.4

Data represent means (± S.E.) of 10 animals in each group. For procedural details see Methods.
[a] Received injections of 0.9% NaCl (1 ml/kg).

Table 4. Effect of neuroleptics on amphetamine anorexia

Group	A Intake (2 hrs) after neuroleptic drugs	B Intake (2 hrs) after neuroleptic drugs + *d*-amphetamine (1.5 mg/kg)	Difference (A−B)
Control	9.0 ± 1.4[a]	5.2 ± 0.8[b] *	3.8 ± 1.6
Haloperidol	7.6 ± 2.0	6.8 ± 1.1	0.8 ± 2.6**
Pimozide	9.3 ± 1.5	7.9 ± 1.2	1.4 ± 1.9**

Animals were food deprived for 24 hrs and then given access to food for 2 hrs. Data represent means (± S.D.) of 10 animals in each group. For further procedural details see Methods.
[a] Injected with 0.9% NaCl (1 ml/kg).
[b] Injected with 0.9% NaCl (1 ml/kg) followed by *d*-amphetamine sulphate.
* Significantly different from intake under condition A, $P < 0.01$.
** Significantly different from controls, $P < 0.05$.

Table 5
Prandial drinking: Effect of food deprivation on water intake

Group	Water intake (ml)	% Control
Control	12.4 ± 2.9	100
Haloperidol	8.5 ± 1.6*	67
Pimozide	9.7 ± 2.5**	78

Data represent means (± S.D.) of 10 animals in each group. For procedural details see Methods.
* Significantly different from controls, $P < 0.01$.
** $P < 0.05$.

Table 6. Effect of quinine (0.01%) on 1 hr water intake following 24 hrs water deprivation

Group	Water intake (ml)	% Control
Control	7.8 ± 1.9	100
Haloperidol	4.0 ± 1.9*	51
Pimozide	3.7 ± 1.3*	47

Data represent means (± S.D.) of 10 animals in each group.
* Significantly different from controls, $P < 0.01$.

Table 7. Effect of neuroleptic drugs on insulin (80 U/kg) induced eating

Group	Food intake (g)	% Control
Control	5.1 ± 1.6	100
Haloperidol	1.6 ± 1.4*	31
Pimozide	2.5 ± 1.6*	49

Data represent means (± S.D.) of 10 animals in each group.
* Significantly different from controls, $P < 0.01$.

treated animals ate significantly less than controls ($P < 0.01$). These results are given in Table 7. However, there was not a significant difference between the 2 drug-treated groups.

Discussion

The effects of pimozide and haloperidol on the homeostatic tests were qualitatively similar to those observed after recovery from aphagia and adipsia in rats with lateral hypothalamic or dopaminergic nigro-neostriatal bundle lesions. With regard to water intake, these changes after drug treatment included drinking less than controls (1) in the absence of food (a test for "prandial" drinking), (2) when water had been adulterated with quinine hydrochloride, and (3) after intraperitoneal injections of hypertonic saline. With regard to food intake, the drug effects included diminution of the anorectic action of amphetamine and less eating in response to subcutaneous insulin injections. The observed reduction in the anorectic action of *d*-amphetamine after haloperidol is consistent with a recent report by Frey and Schulz (1973).

At the doses used in these experiments pimozide and haloperidol had no significant influence on 2 hrs food consumption after 24 hrs food deprivation or on 1 hr water intake after 24 hrs of water deprivation. The lack of effect on water intake agrees with a report by Nielsen and Lyon (1973) that pimozide (0.4 mg/kg) does not disrupt water intake (15 min) after 24 hrs of water deprivation. However, our results are not consistent with a report by Fisher (1973) who found that haloperidol (0.17 mg/kg) substantially reduced deprivation-induced drinking. The reasons for this discrepancy are not presently clear but may be due to procedural differences. For example, the animals in the present experiments had been given prior experience on the deprivation-induced (baseline) water intake measure before the effects of haloperidol and pimozide were determined. Insofar as we have recently demonstrated that the disruptive effects of haloperidol on a behavioral task are very substantially reduced if the animals have had previous experience on that task (Fibiger *et al.*, 1975), it would be interesting to know if Fisher's (1973) rats were naive or experienced on the drinking task when the effect of haloperidol was assessed.

On the basis of a series of experiments designed to determine the role of dopaminergic mechanisms in conditioned avoidance responding, we have proposed that surgical or pharmacological disruption of the nigro-neostriatal projection impairs the ability of rats to initiate voluntary motor responses (Fibiger *et al.*, 1975; Price and Fibiger, 1975; Zis *et al.*, 1974). With regard to food and water intake, Baillie and Morrison (1963) and Morrison (1968) have proposed that the LH syndrome reflects a lesion-induced apraxia of feeding. However in the present experiments, the fact that pimozide and haloperidol did not affect deprivation-induced food and water intake but did have significant effects on all of the other feeding and drinking tests, suggests that the observed deficits resulted from drug-induced interference with regulatory homeostatic mechanisms rather than from specific motor deficits. It could be argued that the motivation to eat and drink was not as great in the other test situations as it was in the baseline conditions and consequently in the baseline measurements the effect of a subtle motor deficit was nullified by the greater motivational state. This explanation appears unlikely however, in view of the fact that the amount of water consumed by the control animals after 24 hrs of water

deprivation (16.0 ± 2.9 ml) did not differ significantly from the amount consumed after hypertonic saline injections (13.3 ± 2.7 ml). This would suggest that the motivation to drink was similar in the 2 different experimental situations. Only after hypertonic saline injections however did the intake of the controls differ from the haloperidol and pimozide groups.

In earlier work, certain interpretative problems have been created by the fact that after electrolytic lesions of the LH or 6-OHDA lesions of dopaminergic neurons, different baseline scores in food and water intake are apparent even in "recovered" animals (Breese *et al.*, 1973; Fibiger *et al.*, 1973; Oltmans and Harvey, 1972; Smith *et al.*, 1973; Stricker and Zigmond, 1974; Zigmond and Stricker, 1972). With these different baseline intakes it is difficult and perhaps hazardous to attempt to evaluate the nature and the extent of other potential regulatory deficits. However, the presence of the homeostatic deficits produced by the neuroleptics in the present experiments, in the absence of significant effects on the deprivation-induced intakes, provides strong evidence for the role of dopaminergic mechanisms in the regulation of food and water intake and suggests that a generalized deficit in feeding and drinking efficiency cannot account for the observed effects. In this regard it should be pointed out that this conclusion applies only to the regimen utilized in the present experiments because we have observed that higher doses of pimozide and haloperidol produce substantial decreases in baseline food and water intakes (unpublished observations).

Breese *et al.* (1973) reported that preferential depletion of brain dopamine by 6-OHDA caused rats to drink less in response to hypertonic saline injections. However, when the significantly lower body weights of the 6-OHDA treated animals were taken into consideration, this difference was abolished. Similarly, with respect to drinking in the absence of food the absolute water intake of the 6-OHDA treated animals was significantly less than controls, but this difference was not apparent in the intake/100 g body weight measure. While the experimental procedures reported here differ substantially from those of Breese *et al.* (1973), the present results nevertheless have a bearing on the conclusions reached by Breese and co-workers. In the present experiments, the body weights of the 2 experimental groups and the control groups were identical. Despite this, the haloperidol and pimozide treated animals differed significantly from controls on both "prandial" drinking and on the drinking in response to hypertonic saline. This observation raises the possibility that measuring food or water intake in terms of g intake/100 g body weight may not be the relevant measure in the study of the role of dopaminergic mechanisms in homeostasis, and that the changes in absolute water intake after lesions of dopaminergic neurons reflect genuine regulatory deficits which are not simply due to changes in body weight. Indeed, in this regard there is abundant evidence from normal rats that the relationship between body weight and food and water intake is complex and not linear (*cf.* Parks, 1970).

In the past several years, considerable new evidence suggests that the lateral hypothalamic syndrome may to a certain extent be due to damage to the dopaminergic nigro-neostriatal projection (Breese *et al.*, 1973; Fibiger *et al.*, 1973; Marshall and Teitelbaum, 1973; Myers and Martin, 1973; Stricker and Zigmond, 1974; Ungerstedt, 1971; Oltmans and Harvey, 1972). The fact that injections of pimozide or haloperidol can reproduce the more permanent deficits in consummatory behaviour observed after lateral hypothalamic lesions is consistent with this hypothesis. However, certain questions still remain. For example, the extent to which dysfunction of the dopaminergic mesolimbic pathway contributes to the observed deficits has not yet been determined. In addition, while destruction of dopaminergic neurons by 6-OHDA and electrolytic lesions of the lateral hypothalamus appear to produce qualitatively similar syndromes, quantitatively, lateral hypothalamic lesions result in more severe deficits despite producing smaller losses in neostriatal dopamine (Fibiger *et al.*, 1973; Stricker and Zigmond, 1974). The extent, therefore, to which damage to other neuronal systems also contributes to this syndrome remains to be elucidated. Similarly, the neuroleptic drugs did not produce deficits of the same magnitude as are typically observed after lateral hypothalamic lesions. It is possible however that higher doses of these drugs may have produced more quantitatively similar results.

Finally, the present results must be interpreted with reference to the possibility that haloperidol and pimozide have other properties in addition to their ability to block dopamine receptors. There is evidence for example that haloperidol, at considerable higher doses than that employed in the present experiments, may also block noradrenergic receptor sites (Andén *et al.*, 1972; Keller *et al.*, 1973). However, the fact that pimozide does not appear to share this property with haloperidol (Andén *et al.*, 1970; Keller *et al.*, 1973) suggests that blockade of noradrenergic receptor sites does not contribute significantly to the homeostatic deficits produced by these compounds.

Acknowledgements. We thank Janssen Pharmaceutic for a generous supply of pimozide. Supported by the Medical Research Council. A.P.Z. is an MRC Fellow and H.C.F. is and MRC Scholar.

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