Pharmacology Biochemistry & Behavior, Vol. 30, pp. 917–923. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Sulpiride Injections in the Lateral Hypothalamus Induce Feeding and Drinking in Rats

MARCO A. PARADA,[1] L. HERNANDEZ AND B. G. HOEBEL

Laboratorio de Fisiologia de la Conducta, Universidad de los Andes, Merida, Venezuela and Department of Psychology, Princeton University, Princeton, NJ 08544

Received 25 August 1987

PARADA, M. A., L. HERNANDEZ AND B. G. HOEBEL. *Sulpiride injections in the lateral hypothalamus induce feeding and drinking in rats.* PHARMACOL BIOCHEM BEHAV 30(4) 917–923, 1988.—Amphetamine injections into the lateral hypothalamus inhibit feeding. This effect is blocked by local administration of neuroleptics, suggesting a role for dopamine in feeding inhibition. However, the type of dopamine receptor involved in satiety is not known. Therefore, we tested the effect of intrahypothalamic injections of sulpiride, a specific D_2 receptor blocker, on amphetamine anorexia in food-deprived rats, and on spontaneous feeding and drinking in satiated rats. Sulpiride attenuated by 36% the anorexia produced by intrahypothalamic injections of amphetamine. In satiated rats, sulpiride (8 μg/0.5 μl) elicited feeding (mean food intake after sulpiride: 5.4 g, and after vehicle 1.6 g, $p<0.001$), and drinking (mean water intake after sulpiride: 12.3 ml, and after vehicle: 0.9 ml, $p<0.001$). A dose response relationship was found between sulpiride dose and feeding or drinking. Sulpiride-induced drinking was observed in the absence of food, showing that it is not a postprandial phenomenon. These results suggest that hypothalamic D_2 receptors might be involved in feeding and drinking regulation.

Hypothalamus Sulpiride Amphetamine Dopamine Drinking Feeding D_2 receptors

THE perifornical region of the lateral hypothalamus (along the lateral edge of the fornix) contains a fairly dense catecholaminergic innervation which includes dopamine (DA), norepinephrine (NE), and epinephrine (E), as shown by fluorescence microscopy [13, 15, 22, 29, 41]. DA in this region has also been detected biochemically [35,42], and it is suspected that this catecholamine is contained in some of the varicosities present in the area [25]. The anatomical source of dopaminergic projections to the perifornical hypothalamus has not yet been clearly established; however, some evidence suggests that DA cell bodies in the mesencephalic ventral tegmental area (VTA) are the most probable origin [6, 19, 24, 25]. The incerto-hypothalamic dopamine system [4] has also been suggested as a less probable source for the DA innervation of the perifornical region [24,25].

Dopamine receptors in the lateral hypothalamus may be involved in the inhibition of feeding and, to a lesser extent, of drinking. Amphetamine, a drug which is knwon to release endogenous DA [10, 11, 30], suppresses feeding [21,22] and drinking [20] after injections into the perifornical hypothalamus of food-deprived rats. The attenuation of the amphetamine feeding suppression by dopaminergic receptor blockers such as haloperidol and pimozide [22,23] clearly shows the involvement of DA in the anorectic effect of amphetamine. However, the reduction in water intake is attributed to the activation of alpha-adrenergic receptors [20]. In a more direct approach to the anorectic role played by the perifornical dopaminergic receptors, it has been shown that direct administration of DA caused a strong suppression of feeding in hungry pargyline-pretreated rats [23, 24, 27]. This decrease in food intake is antagonized by locally applied neuroleptics. Haloperidol and chlorpromazine at doses higher than those required to inhibit the action of exogenous DA facilitate feeding in hungry rats [24]. Perifornical DA administration also reduces water intake, and this effect is inhibited by alpha-adrenergic blockers but not by DA antagonists. For this reason DA drinking suppression is believed to be a phenomemon mediated by an alpha-adrenergic receptor activation [24].

There are at least two types of dopaminergic receptors, D_1 and D_2, according to the classification of Kebabian and Calne [18]. It has not been established which type is responsible for dopamine-mediated satiety in the lateral hypothalamus. One suggestion came with the observation that long-term daily intraperitoneal sulpiride injections resulted in moderate hyperphagia and body weight increase [1]. As sulpiride is considered a selective D_2 receptor blocker [16, 18, 40], its effect was taken as evidence suggesting the D_2 nature

[1]Request for reprints should be addressed to Dr. Marco A. Parada, Apartado de correos 109, Merida, Venezuela, 5101-A.

of the dopaminergic receptors involved in satiety. However, subsequent experiments showed that intraperitoneal sulpiride might not only be acting through a direct blockade of dopaminergic satiety receptors, but also through an increase in pituitary prolactin secretion and impairment of ovarian steroidogenesis as well (manuscript submitted); therefore the question of the nature of the hypothalamic dopamine receptors involved in satiety remains open.

This paper reports the results obtained in two different kinds of experiments. In one of them sulpiride blocked amphetamine anorexia when both drugs were directly administered in the lateral hypothalamus of hungry rats. In the remaining experiments intrahypothalamically applied sulpiride induced feeding and drinking in satiated rats. The results suggest that hypothalamic dopaminergic receptors of the D2 subtype appear to be involved in satiety, and provide strong evidence in favor of D_2 receptors involved in drinking suppression as well.

METHOD

Animals

Forty adult male Sprague-Dawley rats, weighing between 330 and 380 g at the time of the surgery, were individually housed on a 15-hr light, 9-hr dark cycle (lights on at 7.00 a.m.). Standard chow pellets and tap water were continuously available in the home cages. Room temperature was mantained between 21 and 23°C.

Surgery

Under ketamine anesthesia (20 mg/100 g) each rat was implated with chronic bilateral, 26 gauge stainless steel guide cannulas aimed 2 mm above the perifornical region. The corrdinates for each cannula, with the incisor bar placed 3.5 mm below the interaural line, were: 6.5 mm anterior to the interaural line, 1.6 mm lateral to the midsagittal sinus, and 5.7 mm perpendicularly below the surface of the cortex; injectors protruded 2 mm further (A: 6.5, L: 1.6, V: 7.7). All the experiments were carried out after at least one week of postsurgical recovery.

The injector cannulas were 33 gauge stainless-steel tubes attached by PE 20 tubing to two 10 μl syringe mounted on a syringe pump. The injection rate was 0.5 μl in 40 sec. d-Amphetamine sulphate (Sigma) was dissolved in physiological saline. l-Sulpiride (Ravizza) was dissolved in 3 parts of physiological saline and one part 0.1 N HCl. This vehicle was used as a sulpiride injection control. All injections were 0.5 μl volume delivered while the rats were hand-held. Food spillage was collected and taken into account for the food intake measurements. Water was available in 100 ml graduated cylinders. All the injections were made in counterbalanced order.

Testing Procedures

Experiment 1—Sulpiride attenuation of amphetamine anorexia. Eighteen rats were food-deprived for 24 hr every four days. Twenty days were allowed for adaptation to this deprivation schedule; then each rat was tested in four experimental sessions which started after the 24 hours of food deprivation. At the beginning of each experimental session each rat received a sequence of two bilateral intrahypothalamic injections 5 minutes apart. After the second injection the animals were placed in their cages with a measured amount of food, and total intake was measured 30 minutes later. Injection sequences were vehicle and saline, sulpiride (2.5 μg/0.5 μl) and saline, vehicle and amphetamine (20 μg/0.5 μl) or sulpiride and amphetamine. At the end of the experiment each rat had been tested with all the pairs of injections.

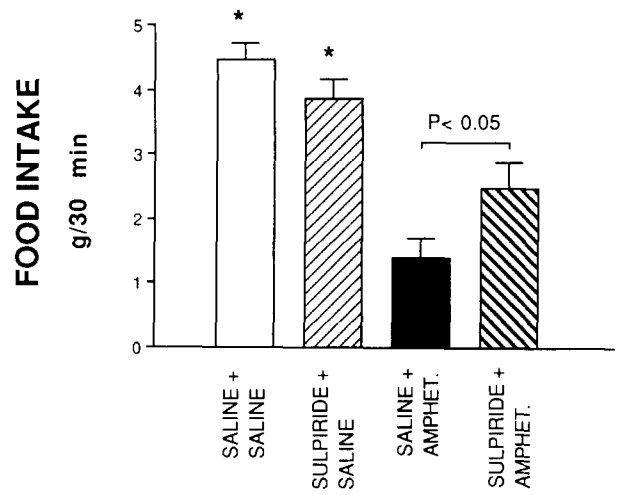

FIG. 1. Food intake (means±S.E.) in hungry rats (n=18) after bilateral intraperifornical administration of sulpiride (2.5 μg/0.5 μl), amphetamine (20 μg/0.5 μl) or a combination of both drugs (*$p<0.01$ relative to the last 2 columns.)

Experiment 2—Food and water intake induced by sulpiride in satiated rats. Six rats housed with food and water ad lib were divided in two groups of three rats each. Animals of the first group received a bilateral intrahypothalamic injection of vehicle, and four days later a bilateral hypothalamic injection of sulpiride (8 μg/0.5 μl). The second group received sulpiride injections first, and four days later vehicle. Food and water intake were measured 30, 60 and 90 minutes postinjection.

Experiment 3—Food intake: Dose-response relationship. In eleven nondeprived rats, four different doses of sulpiride (1, 2, 4, and 8 μg/0.5 μl) and a vehicle control injection were bilaterally applied into the hypothalamus in counterbalanced order two to four days apart. Each rat was tested with all the doses. Food and water were given ad lib. Food intake was measured 90 minutes after the injections.

Experiment 4—Water intake: Dose-response relationship. The aim of this experiment was to look for a relationship between the dose and the magnitude of the drinking response, and to determine whether the drinking behavior induced by sulpiride would occur without food available. The effects of 3 doses of sulpiride (2, 4 and 8 μl) and vehicle were tested on separate days 2–4 days apart in a group of five nondeprived rats. Again, bilateral intrahypothalamic injections were administered in counterbalanced order to all the rats. Immediately after the injections they had free access to water but not to food. Water intake was measured 30 min after injections.

Statistical Analysis

The data on the amphetamine-sulpiride interaction were analyzed with a one-way ANOVA followed by the

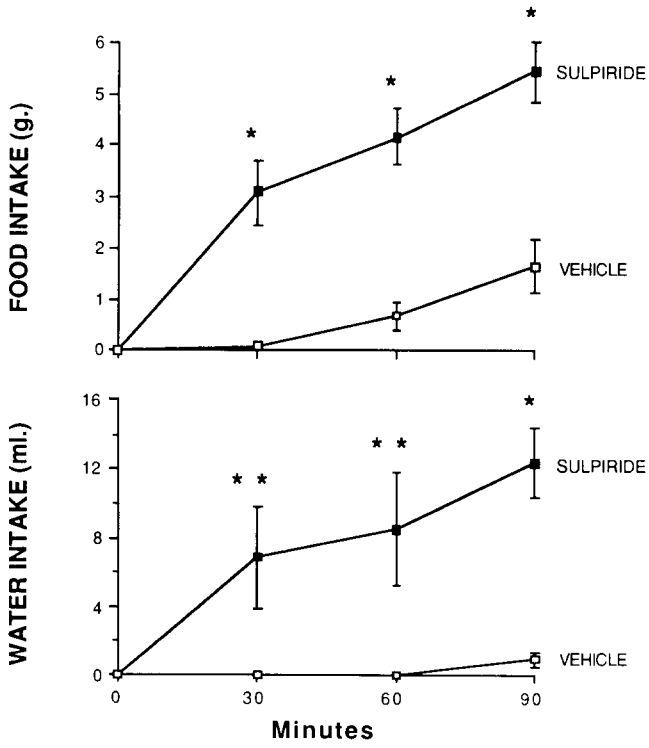

FIG. 2. Accumulated food (top) and water intake (bottom) induced by sulpiride (8 μg/0.5 μl) when administered in the lateral hypothalamus of satiated rats (n=6). Each point represents the mean±S.E. (*$p<0.001$; **$p<0.05$, relative to the corresponding control.)

Newman-Keuls test for multiple comparisons. Measurements of food and water intake after sulpiride injections were compared with vehicle controls by means of a two-tailed, unpaired t-test. Linear regression analysis was carried out on the dose-response data.

Histology

After the experiments the rats were anesthetized with pentobarbital and the brains perfused with formalin. After at least 5 days of fixation the brains were sliced and the tracks of the injector cannulas were localized histologically.

RESULTS

Experiment 1—Sulpiride Attenuation of Amphetamine Anorexia

The overall difference between the four groups was statistically significant, $F(3,16)=6.23$, $p<0.01$, Fig. 1 shows that after hypothalamic amphetamine the rats ate 1.4 g in 30 minutes compared to 4.5 g for controls. The difference (3.1 g) represented a 70% reduction in food intake due to the amphetamine injection and was statistically significant ($p<0.01$). When sulpiride was administered locally before amphetamine, food intake was 2.5 g. Thus the anorectic effect of amphetamine was reduced by 36%. The animals ate more after sulpiride and amphetamine than after amphetamine alone ($p<0.05$). Sulpiride in the lateral hypothalamus did not have any effect on its own (3.9 g) when compared with the control injections in these food deprived animals.

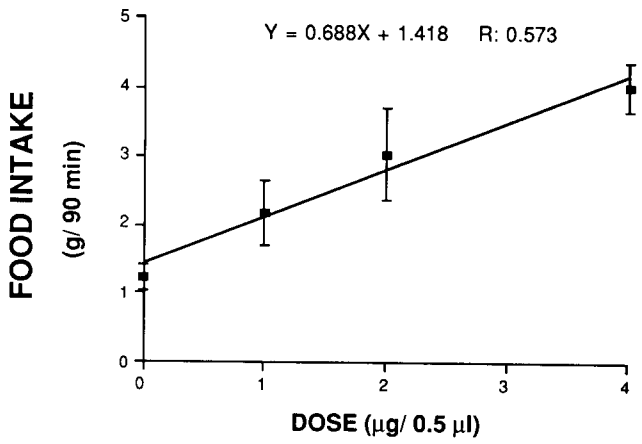

FIG. 3. Relationship between different doses of bilateral intrahypothalamic injections of sulpiride and food intake during 90 minutes after the injections in satiated rats (n=11).

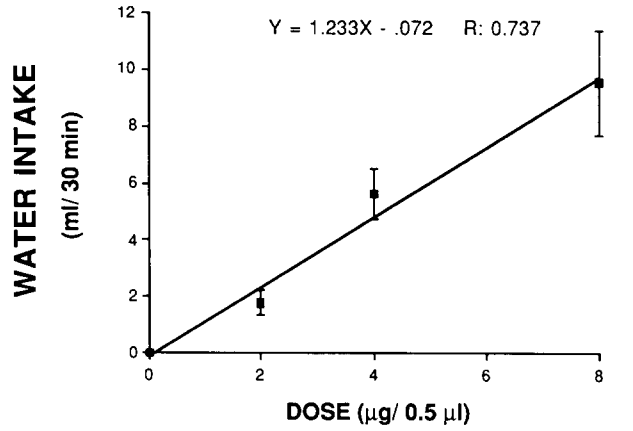

FIG. 4. Water intake in the 30-minute interval after 3 doses of intrahypothalamic sulpiride tested in satiated rats (n=5). Only water was available after the injections.

Experiment 2—Food and Water Intake Induced by Sulpiride

Hypothalamic administration of sulpiride in satiated rats induced a complex repertoire of responses reminiscent of those seen with electrical stimulation of the lateral hypothalamus. The animals showed, in different degrees, an increase in locomotion, exploratory behavior and rearing activity (manuscript in preparation), as well as gnawing, licking, food and water consumption, and stereotypic behaviors such as sniffing and repetitive movements of the head and forepaws. The behavioral effects of sulpiride were evident immediately after the injection of the drug. The rat engaged in all these behaviors in alternate bouts of variable duration. A careful analysis of the relative proportion of these behaviors has not been done yet. The latency for the display of feeding and drinking varied between 1 second and 35 minutes. The cumulative food and water intake after 8 μg of sulpiride is shown in Fig. 2. Both food and water intake were significantly higher 30, 60 and 90 minutes after the sulpiride injec-

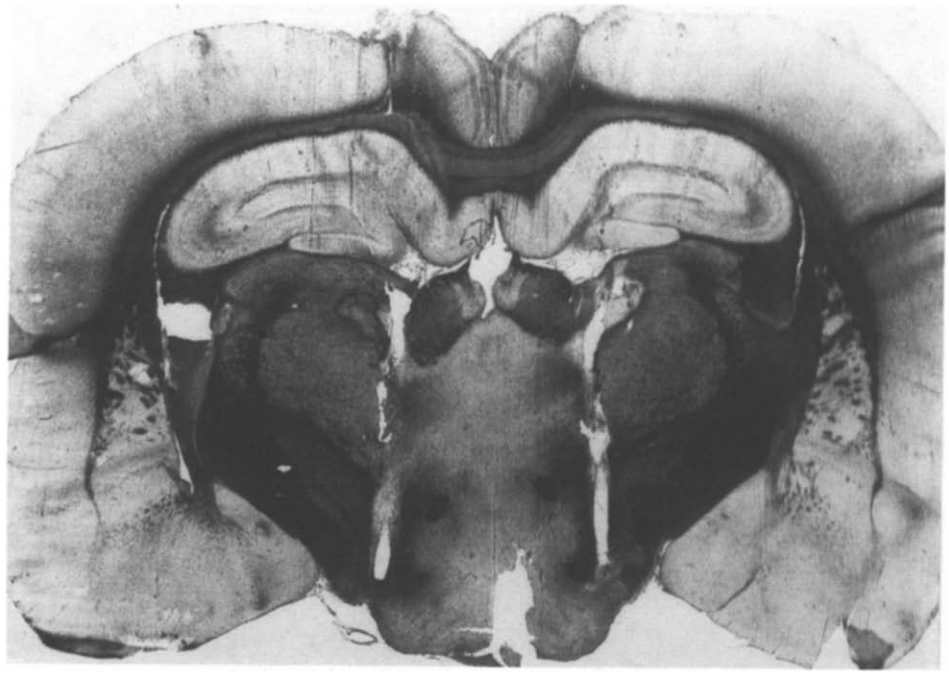

FIG. 5. Photography showing the tips of the two cannulas in the vicinity of the fornix in a typical rat.

tions than after the control injections ($p<0.001$). The total amount consumed 90 minutes after the drug was 5.4 g compared to 1.6 g after the vehicle injections, $t(10)=4.8$, $p<0.001$. Water intake 90 minutes after sulpiride was 12.3 ml, and after vehicle it was 0.9 ml, $t(10)=5.59$, $p<0.001$.

Experiment 3—Food Intake: Dose-Response Relationship

Figure 3 shows the dose-response relationship between the dose of sulpiride and food intake 90 minutes after the injections. The highest dose of sulpiride (8 μg) failed to induce some animals to eat, probably because of the high level of hyperactivity attained. At this dose the rats ate as an average the same amount of food as for the 4 μg dose. Therefore the three doses plotted were 1, 2, and 4 μg. The correlation coefficient in this experiment (R=.573) was highly significant ($t=4.53$; $p<0.001$).

Experiment 4—Water Intake: Dose-Response Relationship

The dose-response relationship between three doses of sulpiride (2, 4 and 8 μg) and water intake 30 minutes after the injections also showed a significant correlation (R=.73; $t=7.09$; $p<0.001$, Fig. 4).

The histological analysis showed the tips of injector cannulas in the vicinity of the perifornical area of the lateral hypothalamus (see Fig. 5).

DISCUSSION

Amphetamine is a potent anorectic drug believed to release and block the reuptake of catecholamines at nerve terminals for inhibition of feeding [10,21]. The reduction in food intake induced by peripherally administered amphetamine may also be partially due to a form of behavioral competition [17,31]. According to this view, the stereotypy and hyperactivity brought about by amphetamine-induced release of DA interferes with complex sequences of responses such as eating behavior. There seems to be, nevertheless, a true motivational component related to the feeding suppression induced by the drug because its administration in the perifornical region of the lateral hypothalamus decreases food intake without evident motor distrubances when low doses are used (manuscript in preparation). This anorectic effect has been shown to be mediated by potentiation of endogenous DA, epinephrine or norepinephrine [22,23] and probably serotonin ([36] and manuscript in preparation). Other experiments also suggest that endogenous dopamine in the lateral hypothalamus inhibits feeding. For example, 6OHdopamine lesions of the dopaminergic pathway cause aphagia and adipsia. But neuroleptic injections into the hypothalamus reverse the aphagia by blocking the anorectic action of the excess of dopamine released by the 6OHdopamine injection [43].

It was suggested in an earlier study that the dopaminergic receptors involved in the amphetamine anorectic effect belong to the D_1 subtype [7]. In that report the D_2 antagonist, sulpiride, was not able to attenuate the suppressive effect of amphetamine when using a palatable food in nondeprived rats, but the D_1 antagonist SCH-23390 did so when tested against a small dose (0.3 mg/kg) of amphetamine. In addition, the D_1 agonist SKF-38393 had a suppressive effect on food intake. However, in this study all the drugs were systemically administered. Therefore, these results are not comparable to the ones reported here. First of all, the lack of effect of sulpiride on the anorectic effect of amphetamine might be explained by the fact that this drug only poorly penetrates the blood-brain barrier [2,3]. In fact an acute systemic injection of sulpiride does not cause hyperphagia. This effect is seen after two or three daily injections of sulpiride [1]. Second, we did not test a D_1 receptor blocker. Therefore, there still remains the possibility of two different dopaminergic receptors acting as substrates for amphetamine anorexia.

The results reported here show that sulpiride attenuated the anorectic effect of amphetamine when both drugs were directly applied in the lateral hypothalamus. Previous reports have shown an attenuation of the amphetamine anorexia by the dopaminergic blockers pimozide [22,24] and haloperidol as well [22, 24, 28]. An almost total blockade of amphetamine anorectic action was obtained when haloperidol (7 nmoles) and amphetamine (150 nmoles) were unilaterally injected into the perifornical area of hungry pargyline pretreated rats [28]. Our results confirm that dopamine blockers counteract amphetamine anorexia and suggest a possible involvement of D_2 receptors in this phenomenon. The observation that suppression of the amphetamine effect was only partial is in good agreement with the existence of other nondopaminergic receptor mechanisms in the lateral hypothalamus [22, 23, 36] involved in the inhibition of food intake by amphetamine. Thus, it may be argued that sulpiride is blocking only that part of amphetamine anorexia that is due to DA release. In view of the finding that sulpiride induces feeding behavior in nondeprived rats, it is worth noting that when administered alone in hungry animals it did not increase food intake. Of course the difference may have been in the ceiling effect, but it is also possible that some other behaviors like drinking, gnawing and the increase in locomotion and rearing triggered by sulpiride might have produced some kind of behavioral competition. A more trivial explanation is that food intake under the food-deprivation condition was measured only 30 minutes after the injections, and it is not known if some potentiation of eating could have been detected later.

Sulpiride induced food intake in satiated rats. This result confirms previous reports showing that intrahypothalamic injections of dopamine blockers induce feeding. Haloperidol and chlorpromazine have been shown to increase food intake in rats when administered into the perifornical area of the lateral hypothalamus [12, 23, 26, 28]. Both neuroleptics potentiate food intake in hungry animals [28]. In satiated rats chlorpromazine induces eating behavior [26] in amounts similar to those reported here, though the doses (between 300 and 1200 nmoles) unilaterally administered were much higher than the doses of sulpiride used in the present experiments (between 3 and 24 nmoles).

The food intake induced by sulpiride in nondeprived rats strongly supports the suggestion that postsynaptic D_2 dopamine receptors in the lateral hypothalamus are involved in the inhibitory regulation of feeding behavior. Receptor studies show that there are D_2 receptors in the lateral hypothalamus and that there are probably not D_1. This conclusion follows from the fact that dopamine and its agonist bromocriptine (D_2 agonist) inhibit adenilcyclase activity in the perifornical region of the lateral hypothalamus. This inhibition is blocked by sulpiride, and the specific D_1 agonist SKF 82526 does not increase adenilcyclase activity [37]. Nevertheless D_1 agonists and antagonists bind to receptors in the lateral hypothalamus (Leibowitz, personal communication). Therefore, a possible role of D_1 receptors in sulpiride hyperphagia cannot be discarded. Postsynaptic location of D_2 receptors may be inferred from the following argument. D_2 receptors may be pre- and postsynaptically located [32], and sulpiride is able to block pre- [32,38] and postsynaptic DA receptors [32,33], but the presynaptic DA autoreceptors appear to modulate impulse-induced release of DA by a local negative feedback mechanism [32,38]; therefore blockade of such receptors would yield an increase in DA release which in turn would decrease food intake [27,28], an effect that is the opposite of the one reported here.

The induction of water intake in nondeprived rats was shown to be a robust effect. The drinking behavior may be considered as the expression of a specific motivational state directly induced by the drug, and not just postprandial drinking. This is supported by the observation that in several rats this behavior was the first displayed. The dose-response experiment carried out in rats with only water available showed that sulpiride induced reliable drinking even with the smallest dose tested and no food available. Interestingly the high dose of sulpiride (8 μg) interfered with feeding but not with drinking. Since this dose also increases locomotion (manuscript in preparation) it is possible that locomotor activity competes with feeding behavior better than with drinking. The reason for that is still a puzzle.

It was previously mentioned that injections of amphetamine [20] or DA [28] in the perifornical region of the lateral hypothalamus suppressed drinking in water-deprived animals. The role of dopaminergic receptors in such drinking suppression was questioned on the basis of the lack of an effective attenuation by neuroleptics, and the participation of alpha-adrenergic receptors was postulated instead [20,28], due to the fact that alpha-adrenergic blockers antagonized this drinking suppression. In view of the high selectivity of sulpiride in blocking D_2 receptors in central nervous system [16, 18, 34, 40], and because sulpiride has only a very weak alpha-adrenoreceptor blocking activity as compared with other neuroloeptics [34], it is highly probable that the effect of sulpiride is being mediated by D_2 receptors. Recently it has been reported that intrapertioneal sulpiride (30 mg/kg) increased consumption of water or 0.125% NaCl solution in water-deprived rats [8,9]. This effect was not mimicked by the D_1 receptor blocker SCH-23390 or other neuroleptics with miscellaneous DA-antagonist activity, which on the contrary reduced fluid intake. But again, since we did not inject D_1 receptor blockers in the hypothalamus, it is premature to conclude that sulpiride-induced drinking is a purely D_2 receptor blocking effect.

Other reports on the action of sulpiride on ingestive behavior appear to conflict somewhat with the present results. Systemic dopamine blockers have been shown to decrease sham drinking of sweet solutions [5,39]. However, systemic injections of sulpiride block D_2 receptors in many terminal dopamine fields while local injections act on a restricted hypothalamic area. This anatomical distinction creates different effects of the drug, depending on where it is working. Systemic sulpiride can block dopamine receptors in the striatum [14] and the nucleus accumbens to cause hypokinesia and anhedonia [44], while we have observed that intrahypothalamic sulpiride increases locomotor activity. In any case the effects of sulpiride reported here strongly suggest that DA in lateral hypothalamus plays an inhibitory role in feeding and drinking behavior, and that this might be accomplished through D_2 receptors.

REFERENCES

1. Baptista, T.; Parada, M.; Hernández, L. Pharmacological evidence that dopaminergic satiety systems function with D2 type receptors. Pharmacol. Biochem. Behav. 27:399–405; 1987.
2. Benakis, A. Metabolism and pharmacokinetics of a substituted benzamide sulpiride in aniamals: specific localization and neuroendocrinological aspect. In: Deniker, P.; Radouco-Thomas, C.; Villeneuve, A., eds. Neuropsychopharmacology. Oxford: Pergamon Press; 1978:849–864.
3. Benakis, A.; Pongis, M. A.; Sugnaux, F.; Glasson, B. Localization, distribution, elimation and metabolism of ^{14}C-sulpiride in rats. Eur. J. Drug Metab. Pharmacokinet. 1:51–62; 1976.
4. Björklund, A.; Lindvall, O.; Nobin, A. Evidence of an incerto-hypothalamic dopamine neurone system in the rat. Brain Res. 89:29–42; 1975.
5. Davis, J. D.; Schneider, L. H.; Gibbs, J.; Smith, G. P. D1- and D_2-receptor antagonist reduce initial rate of intake in sham feeding rats. Soc. Neurosci. Abstr. 12:1557; 1986.
6. Fallon, J. H.; Moore, R. Y. Catecholaminergic innervation of the basal forebrain. IV: Topography of the dopamine projection to the basal forebrain and neostriatum. J. Comp. Neurol. 182:545–580; 1978.
7. Gilbert, D. B.; Cooper, S. J. Analysis of dopamine D1 and D2 receptor involvement in d- and l-amphetamine induced anorexia in rats. Brain Res. Bull. 15:385–389; 1985.
8. Gilbert, D. B.; Cooper, S. J. Salt acceptance and preference test distinguish between selective dopamine D-1 and D-2 receptor antagonists. Neuropharmacology 25:655–657; 1986.
9. Gilbert, D. B.; Cooper, S. J. Naloxone antagonizes the hyperdipsic effect of sulpiride in a salt-preference test in male and female rats. Neuropharmacology 25:743–747; 1986.
10. Glowinski, J. Effects of amphetamine on various aspects of catecholamine metabolism in the central nervous system of the rat. In: Costa, E.; Garattini, S., eds. Amphetamine and related compounds. New York: Raven; 1970:301–316.
11. Hernandez, L.; Lee, F.; Hoebel, B. G. Simultaneous microdialysis and amphetamine infusion in the nucleus accumbens and striatum of freely moving rats: Increase in extracellular dopamine and serotonin. Brain Res. Bull. 19:623–628; 1987.
12. Hoebel, B. G.; Leibowitz, S. F.; Brain monoamines in the modulation of self-stimulation, feeding and body weight. In: Weiner, H.; Hofer, M. A.; Stunkard, A. J., eds. Brain, behavior and bodily disease. New York: Raven Press; 1981:103–142.
13. Hökfelt, T.; Fuxe, K.; Goldstein, M.; Johansson, O. Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain. Brain Res. 66:235–351; 1974.
14. Imperato, A.; DiChiara, G. Dopamine release and metabolism in awake rats after systemic neuroleptics as studied by transtriatal dialysis. J. Neurosci. 5:297–306; 1985.
15. Jacobowitz, D. M.; Palkovits, M. Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. I. Forebrain (telencephalon, diencephalon). J. Comp. Neurol. 157:13–28; 1974.
16. Jenner, P.; Elliot, P. N. C.; Clow, A.; Reavill, C.; Marsden, C. D. A comparison of in vitro and in vivo dopamine receptors antagonism produced by substituted benzamide drugs. J. Pharm. Pharmacol. 30:46–48; 1978.
17. Joyce, E. M.; Iversen, S. D. Dissociable effects of 6-OHDA-induced lesions of neostriatum on anorexia, locomotor activity and stereotypy: The role of behavioral competition. Psychopharmacology (Berlin) 83:363–366; 1984.
18. Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. Nature 277:92–96; 1979.
19. Kizer, J. S.; Palkovits, M.; Brownstein, M. J. The projection of the A8, A9, and A10 dopaminergic cell bodies: evidence for a nigral-hypothalamic-median eminence dopaminergic pathway. Brain Res. 108:363–370; 1976.
20. Leibowitz, S. F. Alpha-adrenergic receptors mediate suppression of drinking induced by hypothalamic amphetamine injection. Fed. Proc. 32:754; 1973.
21. Leibowitz, S. F. Amphetamine: possible site and mode of action for producing anorexia in the rat. Brain Res. 84:160–167; 1975.
22. Leibowitz, S. F. Catecholaminergic mechanisms of the lateral hypothalamus: their role in the mediation of amphetamine anorexia. Brain Res. 98:529–545; 1975.
23. Leibowitz, S. F. Identification of catecholamine receptor mechanisms in the perifornical lateral hypothalamus and their role in mediating amphetamine and l-dopa anorexia. In: Garattini, S.; Samanin, R., eds. Central mechanisms of anorectic drugs. New York: Raven Press; 1978:39–82.
24. Leibowitz, S. F. Neurochemical systems of the hypothalamus. Control of feeding and drinking behavior and water electrolytic excretion. In: Morgane, P.; Panksepp, J., eds. Handbook of the hypothalamus. vol. 3A. New York: Marcel Dekker Inc.; 1980:299–438.
25. Leibowitz, S. F.; Brown, L. Histochemical and pharmacological analysis of catecholaminergic projections to the perifornical hypothalamus in relation to feeding inhibition. Brain Res. 201:315–345; 1980.
26. Leibowitz, S. F.; Miller, N. Unspected adrenergic effect of chlorpromazine: eating elicited by injection into the rat hypothalamus. Science 156:609–611; 1969.
27. Leibowitz, S. F.; Rossakis, C. Mapping study of brain dopamine- and epinephrine-sensitive sites which cause feeding suppression in the rat. Brain Res. 172:101–113; 1979.
28. Leibowitz, S. F.; Rossakis, C. Pharmacological characterization of perifornical hypothalamic dopamine receptors mediating feeding inhibition in the rat. Brain Res. 172:115–130; 1979.
29. Lindvall, O.; Björklund, A. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol. Scand. (Suppl.) 367:1–48; 1971.
30. Lloyd, K. G.; Bartholini, G. The effect of drugs on the release of endogenous catecholamines into the perfusate of discrete brain areas of the cat in vivo. Experientia 31:560–562; 1975.
31. Lyon, M.; Robbins, T. W. The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In: Essman, W.; Valzelli, R., eds. Current developments in psychopharmacology. New York: Spectrum Publications; 1975:79–163.
32. Markstein, R. Pharmacological characterization of central dopamine receptors using functional criteria. In: Winlow, W.; Markstein, R., eds. Neurobiology of dopamine systems. Manchester: Manchester University Press; 1984:40–52.
33. Morgenstern, R.; Fink, H. Sulpiride blocks postsynaptic dopamine receptors in the nucleus accumbens. J. Neural Transm. 61:152–160; 1985.
34. O'Connor, S. E.; Brown, R. A. The pharmacology of sulpiride—A dopamine receptor antagonist. Gen. Pharmacol. 13:185–193; 1982.
35. Palkovits, M.; Brownstein, M.; Saavedra, J. M.; Axelrod, J. Norepinephrine and dopamine content of hypothalamic nuclei of the rat. Brain Res. 77:137–149; 1974.
36. Parada, M. A.; Hernández, L. Correlación significativa entre la anorexia por anfetamina, serotonina y dopamina intrahipotalámicas. XXXII Convención anual de ASOVAC. Caracas, Venezuela, 1982.
37. Pizzi, M.; Coen, E.; Memo, M.; Missale, C.; Carruba, M. O.; Spano, P. F. Evidence for the presence of D_2 but not D_1 receptors in rat hypothalamic perifornical area. Neurosci. Lett. 67:159–162; 1986.
38. Roth, R. H. Dopamine autoreceptors: pharmacology, function and comparison with post-synaptic dopamine receptors. Commun. Psychopharmacol. 3:429–445; 1979.
39. Smith, G. P. Mesocorticolimbic dopamine functions in eating behavior. Ann. N.Y. Acad. Sci., in press, 1987.
40. Stoof, J. C.; Kebabian, J. W. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 35:2281–2296; 1984.

41. Ungerstedt, U. Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. [Suppl.] 367:1–48; 1971.
42. Versteeg, D. H. G.; Van der Gugten, J.; de Jong, W.; Palkovits, M. Regional concentration of noradrenaline and dopamine in rat brain. Brain Res. 113:563–574; 1976.
43. Willis, G. L.; Smith, G. C. Catecholamine-blocking drugs injected at sites of amine accumulation reverse catecholamine degeneration associated deficits. Behav. Brain Res. 15:101–106; 1985.
44. Wise, R. A.; Spinder, J.; De Wit, H.; Gerber, G. J. Neuroleptics induced "anhedonia" in rats: pimozide blocks reward quality of food. Science 201:262–264; 1978.