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Anorexigenic Effects of d-Amphetamine and l-DOPA in the Rat

I. S. SANGHVI, G. SINGER,[1] E. FRIEDMAN AND S. GERSHON

Neuropsychopharmacology Research Unit, Department of Psychiatry
New York University Medical Center, New York, New York 10016

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SANGHVI, I., G. SINGER, E. FRIEDMAN AND S. GERSHON. *Anorexigenic effects of d-amphetamine and l-dopa in the rat.* PHARMAC. BIOCHEM. BEHAV. 3(1) 81–86, 1975. – The effect of amphetamine and l-dopa was compared in 22-hr food- and water-deprived rats. Amphetamine produced marked anorexia, and l-dopa significantly reduced food intake at 200 mg/kg. Following pretreatment with RO 4-4602, a decarboxylase inhibitor, 100 mg/kg of l-dopa, a dose that did not significnatly affect eating, produced marked anorexia. The anorectic effect of both amphetamine and l-dopa was antagonized by propranolol, a β adrenergic antagonist. Phentolamine, an α-adrenergic antagonist, potentiated the anorectic effect of amphetamine and l-dopa. Haloperidol (0.1 mg/kg), a dopamine antagonist, failed to prevent the anorexia due to amphetamine but accentuated that due to l-dopa. Methysergide, a serotonin antagonist, also failed to prevent the anorexigenic effect of amphetamine. Finally, the administration of l-dopa with or without peripheral decarboxylase inhibition resulted in more than twice the increase in hypothalamic dopamine levels without significant changes in 5-HT or norepinephrine levels. The data show that the anorexigenic effect of amphetamine and l-dopa are similar and indicate a functional role for both norepinephrine and dopamine neurons in feeding behaviour in the rat.

d-Amphetamine l-Dopa Anorexia Dopamine Propranolol Phentolamine Haloperidol

AMPHETAMINE is regarded as one of the most potent anorectic agents, which has been classified as an indirectly-acting sympathomimetic amine and, as such, would be expected to produce its effect through released catecholamines. It is reported to release norepinephrine from central nervous system neurons [12] and is also known to act on dapaminergic neurons [22].

Recently, it has been shown that the lesioning of dopaminergic neurons with 6-hydroxydopamine (6-OHDA) leads to the development of aphagia and adipsia [27]. However, aphagia and adipsia have also been reported to occur follwoing lesions of the median forbrain bundle and in these animals feeding was restored through injection of norepinephrine but not dopamine. Several investigators have shown that central administration of norepinephrine into the hypothalamus or lateral ventricles results in increased food intake in the rat [3, 13, 25], but it has also been shown that norepinephrine administration may cause a decrease in food intake [19,20]. Central nervous system administration of dopamine was shown to lead to a small and delayed increase in food intake and it was suggested that the delay was the result of the conversion of dopamine to norepinephrine. However, intracerebroventricular injections of amphetamine and dopamine can produce anorexia in the rat [15]. Although there remain the paradoxical observations that these catecholamines can lead to either an increase or a decrease in eating, the findings in general suggest that both norepinephrine and dopamine may be involved in eating behavior. This is also supported by reports that clinically one of the most common side effects of l-dopa in the treatment of Parkinsonism is anorexia [26,30].

Since amphetamine is known to act on both the dopaminergic and noradrenergic neurons in the central nervous system [22], in the present study its effect on the eating behavior in the rat were compared with those of l-dopa.

METHOD

Animals

White Sprague-Dawley male rats weighing 150–200 g were individually housed in plastic cages in a continuous bright environment. To obtain a stable predrug baseline, the animals were deprived of food and water for 22 hr a day. During a 2 hour session daily, the animals had free access to a known quantity of normal rat chow pellets and water. At the end of the 2 hour period, the amount of food consumed by each animal was recorded. After a period of 2 weeks for adaptation on this schedule, the effect of drugs on eating behavior was tested. Each animal acted as its own control. A period of one week elapsed between tests. During this time, the previous drug effect had completely disappeared and the normal eating pattern was reestablished. After each test, the animals were weighed to assess the average weight of the animal before the next test, for

[1] Present address: Department of Psychology, La Trobe University, Bundoora, Victoria, Australia, 3083.

adjustment of the drug dose and to monitor its state of health.

Procedure

All drugs were administered intraperitoneally except propranolol, which was administered subcutaneously. All drugs were dissolved in normal saline. The following time schedule of drug administration was used. At time zero, d-amphetamine or saline was administered, and food and water were offered 10 min after the injection. Following l-dopa administration, food and water were offered 30 min later. Haloperidol, methysergide, RO 4-4602, phentolamine, propranolol, and saline were administered 15 min before either l-dopa or amphetamine injection or, when administered on their own, they were injected at time zero. Each animal was injected once with each drug dose with an interval of at least 1 week between injection days. In a separate series of experiments, effects of l-dopa on the amine contents of the hypothalamus before and after peripheral decarboxylase inhibition were determined. l-Dopa was administered peripherally in doses that produced a significnat effect on eating. 5-Hydroxytryptamine (5-HT), norepinephrine, and dopamine were determined spectrofluorometrically following extraction in butanol according to the methods described elsewhere [1,9]. The animals were sacrificed by decapitation two hours after l-dopa administration. The hypothalamus was removed according to a technique of Miller *et al.* [21].

The following drugs were used: 1-3-4-dihydroxyphenylalanine (l-dopa) (Sigma Chemical Co., St. Louis, Mo.); d,l-seryl (2,3,4 trihydroxy-benzyl)-hydrazine hydrochloride (RO 4-4602), a decarboxylase inhibitor (Hoffmann-La Roche, Inc., Nutley, New Jersey); amphetamine sulfate (Sigma Chemical Co., St. Louis, Mo.); haloperidol (Haldol), a dopamine antagonist (McNeil Laboratories, Inc., Fort Washington, Pennsylvania); methysergide maleate, a serotonin antagonist (Sandoz Pharmaceuticals, Hanover, New Jersey); phentolamine (Regitine), an α adrenergic antagonist (CIBA Pharmaceutical Company, Summit, New Jersey); and propranolol hydrochloride, a β adrenergic antagonist (Ayerst Laboratories, Montreal, Canada). All doses referred to in the text are expressed as salts, except l-dopa and haloperidol. Statistical analysis for degree of significance between various drug treatments was carried out using the Student's t test.

RESULTS

Following placebo (normal saline) injection, the normal food intake of rats for a 2 hour period was between 13 and 14.5 g. Amphetamine reduced the eating in dose-effect relationship (Fig. 1). Thus, in a dose of 0.25 mg/kg, amphetamine failed to reduce the eating significantly, whereas 1 mg/kg produced a moderate effect ($p<0.01$) and, at 3 mg/kg, it severely reduced the eating ($p<0.001$). Water intake generally followed the food intake so that, when less food was eaten by the animals, less water was drunk.

l-Dopa had a much weaker effect on eating compared to amphetamine. At doses of 50 and 100 mg/kg, l-dopa failed to reduce eating; however, at a dose of 200 mg/kg, l-dopa produced a marked reduction in eating ($p<0.005$) (Fig. 2) without any observable significant effect on other behavior of the animals.

In order to understand the mechanism underlying anorexia by amphetamine and l-dopa, their effects were compared in the presence of various drugs.

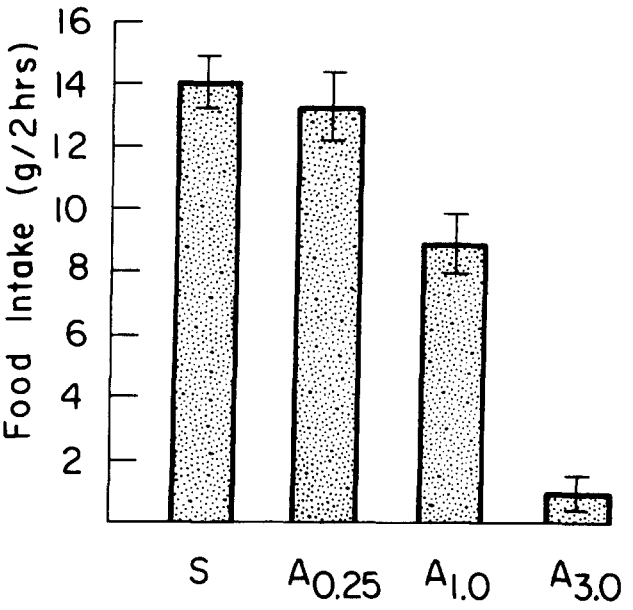

FIG. 1. Dose-response relationship of amphetamine on the food intake of the rats. S, saline control; $A_{0.25}$, $A_{1.0}$, and $A_{3.0}$, amphetamine sulfate 0.25 mg/kg, 1.00 mg/kg, and 3.00 mg/kg, respectively. All injections were given intraperitoneally. Each bar represents mean and S.E. of 15 observations.

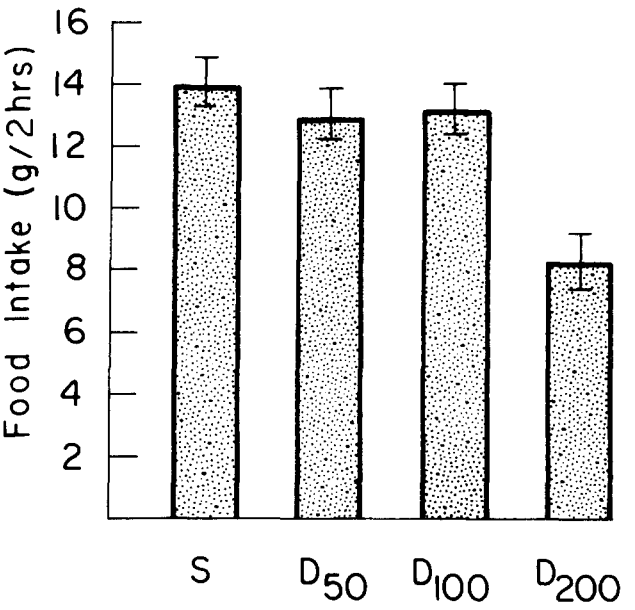

FIG. 2. Dose-response relationship of l-dopa on the food intake of the rats. S, saline control; D_{50}, D_{100}, and D_{200}, l-dopa 50 mg/kg, 100 mg/kg, and 200 mg/kg, respectively. All injections were given intraperitoneally. Each bar represents mean and S.E. of 15 observations.

In order to establish a dose-effect relationship, various doses of adrenergic blocking agents were employed. Propranolol, a β adrenergic antagonist, in a dose of 5 mg/kg (s.c.), failed to modify the anorectic effect of amphetamine; however, in doses of 10 and 20 mg/kg (s.c.),

TABLE 1

EFFECT OF d-AMPHETAMINE AND ITS INTERACTION WITH ANTAGONISTS ON FOOD INTAKE IN RATS

Treatment		N	Food Intake (g/2 hr) Mean ± S.E.	p Value
Saline		20	14.51 ± 0.75	–
Amphetamine	1	20	8.94 ± 0.84	<0.01*
Propranolol	5 + Saline	10	14.31 ± 0.65	N.S.
Propranolol	10 + Saline	10	12.59 ± 0.93	N.S.
Propranolol	20 + Saline	10	11.27 ± 0.59	<0.05*
Phentolamine	5 + Saline	10	14.57 ± 0.46	N.S.
Phentolamine	10 + Saline	10	13.22 ± 0.53	N.S.
Phentolamine	20 + Saline	10	12.82 ± 0.82	N.S.
Haloperidol	0.1 + Saline	10	16.57 ± 0.68	N.S.
Methysergide	5 + Saline	10	15.66 ± 0.85	N.S.
Propranolol	5 + Amphetamine 1	10	9.84 ± 0.35	N.S.
Propranolol	10 + Amphetamine 1	10	11.58 ± 0.33	<0.05†
Propranolol	20 + Amphetamine 1	10	13.72 ± 0.42	<0.01†
Phentolamine	5 + Amphetamine 1	10	5.50 ± 0.78	<0.001†
Phentolamine	10 + Amphetamine 1	10	5.10 ± 0.65	<0.001†
Phentolamine	20 + Amphetamine 1	10	4.80 ± 0.85	<0.001†
Haloperidol	0.1 + Amphetamine 1	10	8.98 ± 0.84	N.S.
Methysergide	5 + Amphetamine 1	10	9.91 ± 0.40	N.S.

Number following each drug refers to mg/kg.
N.S.: Not significantly different from saline or amphetamine.
*Compared with saline control.
†Compared with amphetamine.

propranolol almost completely prevented the effect of amphetamine ($p<0.01$). This effect of propranolol and other drugs on amphetamine-induced anorexia is shown in Table 1. Phentolamine, an α adrenergic blocking agent, in doses of 5 to 20 mg/kg, further augmented the anorexigenic effect of amphetamine ($p<0.01$) in a dose-dependent manner. The effect of various doses of antagonists by themselves on eating was not significant, except that propranolol at the highest dose used in this study (20 mg/kg) did produce mild anorexia (Table 1). Haloperidol, a dopamine antagonist (0.1 mg/kg), and methysergide (5 mg/kg), a serotonin antagonist, failed to antagonize the effect of amphetamine on eating. Higher doses of haloperidol were not employed, as they produced sedation. Doses of l-dopa of up to 100 mg/kg had no anorexigenic effect, hence its effects on eating were examined following pretreatment with RO 4-4602 (50 mg/kg), a decarboxylase inhibitor. This dose of RO 4-4602 is reported to inhibit mainly the peripheral decarboxylase activity [2]. l-Dopa in a dose of 100 mg/kg, which had had no anorectic effect before, now produced a very marked anorexia ($p<0.001$). This effect of RO 4-4602 and other drugs on the l-dopa effect on eating is shown in Table 2. Propranolol, a β adrenergic antagonist, in a dose of 5–10 mg/kg, failed to produce any effect on eating after l-dopa administration. However, when given in a large dose (20 mg/kg), propranolol caused a marked increase in eating after l-dopa ($p<0.01$). On the other hand, when the animals were pretreated with phentolamine, an α adrenergic antagonist, l-dopa administration resulted in marked anorexia ($p<0.01$). This effect of phentolamine was dose-dependent (Table 2). Haloperidol, a dopamine receptor blocker, in a dose of 0.1 mg/kg, appeared to promote the anorectic effect of l-dopa.

Biochemical data presented in Table 3 showed a significant increase ($p<0.001$) in the hypothalamic dopamine level when l-dopa was administered with or without a prior decarboxylase inhibitor. There was no significant effect on 5-HT or norepinephrine levels. The effect of 100 mg/kg l-dopa was significantly lower compared with that of 200 mg/kg l-dopa or of the combination of RO 4-4602 and l-dopa (100 mg/kg).

DISCUSSION

The results from this study show that amphetamine and l-dopa's mechanism of action on feeding behavior may be similar. Some of our data support explanations which suggest the involvement of noradrenergic neurons or receptors [5, 17, 19, 20] in amphetamine anorexia, while other results presented in this study suggest that the anorexigenic effects of amphetamine may also be related to its effect on dopaminergic neurons. These conclusions are based on the following observations: Amphetamine shows both facilitatory and inhibitory effects on eating behavior

TABLE 2

EFFECT OF l-DOPA AND ITS INTERACTION WITH ANTAGONISTS ON FOOD INTAKE IN RATS

Treatment			N	Food Intake (g/2 hr) Mean ± S.E.	p Value
Saline			20	14.51 ± 0.75	–
l-Dopa	100		20	15.63 ± 0.78	N.S.
RO 4-4602	50	+ Saline	10	14.44 ± 0.72	N.S.
RO 4-4602	50	+ l-Dopa 100	10	3.40 ± 0.74	<0.001*
Propranolol	5	+ l-Dopa 100	10	15.50 ± 0.65	N.S.
Propranolol	10	+ l-Dopa 100	10	15.28 ± 0.60	N.S.
Propranolol	20	+ l-Dopa 100	10	20.91 ± 1.29	<0.01*
Phentolamine	5	+ l-Dopa 100	10	10.63 ± 0.82	<0.01*
Phentolamine	10	+ l-Dopa 100	10	5.64 ± 0.61	<0.01*
Phentolamine	20	+ l-Dopa 100	10	5.30 ± 0.71	<0.01*
Haloperidol	0.1	+ l-Dopa 100	10	8.39 ± 0.65	<0.01*

Number following each drug refers to mg/kg.
N.S.: Not significantly different from saline or l-dopa.
*Compared with l-dopa.

TABLE 3

EFFECT OF l-DOPA ON BIOGENIC AMINES IN THE HYPOTHALAMUS OF THE RAT*

Treatment	Dose (mg/kg)		% of Control 5HT	NE	DA	p value
Saline		(5)	100 ± 10	100 ± 14	100 ± 12	
l-Dopa	100	(5)	92.47 ± 5.50	97.89 ± 8.90	145.75 ± 12.50†	<0.01
l-Dopa	200	(5)	87.43 ± 2.10	114.20 ± 15.72	280.69 ± 25.86†	<0.001
RO 4-4602 + l-Dopa	50 + 100	(5)	87.73 ± 3.88	103.44 ± 15.29	223.66 ± 32.68†	<0.001
RO 4-4602 + Saline	50 + –	(5)	83.35 ± 5.92	99.82 ± 5.25	125 ± 11.23†	<0.05

*Animals were sacrificed 2 hr after last injection. RO 4-4602 was administered 30 min before l-dopa. All drugs were administered intraperitoneally. Saline was injected in equivalent volume.
†Compared to dopamine levels in control. No significant effect on 5 HT and NE levels between various treatments. Control levels of amines were (μg/g): 5 HT: 1.86 ± 0.32, NE: 1.42 ± 0.36 and DA: 1.53 ± 0.65. Number in parenthesis indicates number of animals.

of the rat, [3,16]. l-Dopa, which presumably is acting following conversion to dapamine and norepinephrine [4,7], also appears to facilitate or inhibit the eating, as shown here. An anorexigenic effect of l-dopa is evident at higher doses (200 mg/kg) and at lower doses following a peripheral decarboxylase inhibitor. In the absence of inhibition of peripheral decarboxylase, most l-dopa is metabolized extracerebally and only about 0.1% of injected amino acid is found in the brain [29]. RO 4-4602 permits higher concentrations of dopa, and hence of dopamine, to be attained in the brain [2,6]. In the present study, it has been shown that amphetmaine increases eating following propranolol, a β adrenergic antagonist. This is consistent with the finding that centrally-induced amphetamine

anorexia is blocked by propranolol [17]. l-Dopa, which in small to medium doses does not affect the overall food intake, also produced marked increases in food intake in rats pretreated with propranolol. This increase in food intake, is presumably the result of inhibitory effects of propranolol on a β adrenergic satiety center [17]. Administration of phentolamine, an α adrenergic antagonist, resulted in anorexia when combined with either l-dopa or amphetamine. These effects of α and β blockers are in accordance with data reported elsewhere [16] and with the theory of an α adrenergic feeding system in the lateral hypothalamus and a β adrenergic satiety system in the ventromedial hypothalamus. However, our biochemical results indicate a possible functional role for dopamine in the regulation of feeding. l-Dopa administration caused a very marked increase in hypothalamic dopamine levels without significant changes in norepinephrine or 5-HT levels. A raised dopamine level would result in increased spilling over onto the receptors causing anorexia. Recent data [14] show the effect of l-dopa on hypothalamic monoamines and 5-HT levels, which is in agreement with present results, except that we did not find significnat changes in the 5-HT level. It has also been reported that the anorexigenic dose of d-amphetamine had no effect on the steadystate concentration of tel-diencephalic norepinephrine [8]. Direct comparison of the effects of l-dopa and amphetmaine on brain catecholamine levels is necessary to explore further the similarity in the effects of l-dopa and amphetamine suggested by our data and to determine whether there is a common dopamine involvement.

There are some findings in our experiments that cannot be explained readily. These are: (1). The potentiation of the anorectic effect of dopa by haloperidol and its lack of effect on amphetamine anorexia in the striatum [18]. A similar effect of haloperidol on dopaminergic neurons in the hypothalamus may explain potentiation of the l-dopa on eating. However, another dopamine antagonist, pimozide, is reported to antagonize the anorectic effect of dopamine [15]. (2) The relatively small effect (35–40% suppression of eating) of 200 mg/kg of l-dopa compared with the profound effect of amphetamine (95% suppression of eating, at 3 mg/kg) may be explained by the differential rates of penetration in the neruonal tissue and metabolism of these two substances (3). The correlation between anorexia and the increased level of dopamine is not perfect; 200 mg/kg, which shows the highest increase in hypothalamic dopamine levels, is less effective in blocking food intake than 100 mg/kg plus RO 4-4602, which shows a similar dopamine level increase. One possible explanation for this discrepancy is suggested by the observations that l-dopa, in the absence of a peripheral decarboxylase inhibitor, poorly penetrates the blood-brain barrier and that most of it is decarboxylated in cerebral capillaries. Peripheral decarboxylase inhibition would facilitate the penetration of l-dopa into the neuronal tissue to be converted to dopamine [10,11]. The concentration of dopamine measured in the absence of decarboxylase inhibition would more probably reflect extraneuronal levels, while the amine concentration measured in the presence of peripheral decarboxylase inhibition would be more indicative of neuronal levles. Such a contention could explain the smaller anorexigenic effect of 200 mg/kg l-dopa as compared with that of RO 4-4602 (50 mg/kg) and l-dopa (100 mg/kg).

The failure of methysergide to prevent anorexia due to amphetamine may be due to an inadequate dose of the serotonin antagonist. However, it is reported that another serotonin antagonist, cyproheptadine, also failed to prevent anorexia due to centrally administered dopamine in the rat [15].

The data from the present study indicate a strong similarity between l-dopa and amphetamine on eating behavior. The increase in hypothalamic dopamine levels and no change in norepinephrine levles which accompanied the l-dopa anorexia, and the fact that amphetamine can act on dopaminergic neurons in the striatum [23, 24, 28] would suggest a possible functional role of dopamine in feeding behavior. The direction of this effect is in contradiction to Ungerstedt's [27] hypothesis which suggests a facilitatory role for dopamine in the regulation of feeding.

However, the effects of α and β blockers on both amphetamine and l-dopa anorexia and the data on haloperidol support the now well established role of norepinephrine in eating behavior and further experiments are needed to clarify this problem.

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