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# Effects of d- and l-Amphetamine on Food Intake: Evidence for a Dopaminergic Substrate

KENNETH R. EVANS AND FRANCO J. VACCARINO[1]

*Department of Psychology, University of Toronto, 100 St. George St. Toronto, Ontario, Canada M5S 1A1*

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EVANS, K. R. AND F. J. VACCARINO. *Effects of d- and l-amphetamine on food intake: Evidence for a dopaminergic substrate.* PHARMACOL BIOCHEM BEHAV 27(4) 649–652, 1987.—The present experiment examined the effects of d- and l-amphetamine on the intake of sugar, sweetened rat chow and unsweetened rat chow in free feeding rats. Rats were injected IP with 4 doses of d- or l-amphetamine (0.0, 0.125, 0.50 and 2.00 mg/kg). Regardless of drug condition, animals were found to prefer sugar over sweetened or unsweetened chow. d-Amphetamine significantly increased food intake at 0.125 and 0.50 mg/kg doses but not at 2.00 mg/kg. l-Amphetamine had no significant effects at any dose. Further, d-amphetamine significantly increased sugar intake but not sweetened or unsweetened chow. Since d- and l-amphetamine are equipotent at releasing noradrenaline, while d-amphetamine is 2 to 5 times more potent at releasing dopamine, the results suggest that d-amphetamine-induced feeding is associated with activation of a dopaminergic substrate.

d-Amphetamine l-Amphetamine Noradrenaline Dopamine Feeding

SEVERAL studies have implicated dopamine (DA) in feeding behaviour. Peripheral administration of low doses of the catecholamine agonist amphetamine increases food intake in rats and mice [2, 6, 14, 29]. Intracerebroventricular administration of either the post-synaptic DA agonist bromocriptine or amphetamine produce similar increases in food intake while having no effect on other observed behaviours or locomotor activation [7,23]. Similar effects have been found following direct administration of amphetamine into terminal DA regions [8,29]. While these studies provide support for the hypothesis that DA has an excitatory role in feeding behaviour, it is difficult to be conclusive regarding DAergic involvement in the systemic effects of amphetamine since amphetamine increases release and blocks re-uptake of noradrenaline (NA) as well as DA [4, 21, 28] and is an inhibitor of monoamine oxidase, the enzyme necessary for the breakdown of monoamines [4]. NA is also thought to have a role in feeding behaviour [20]. Amphetamine also has excitatory effects on serotonin, though increased cortical serotonin levels and utilization occurs only at doses above 10 mg/kg [18].

In order to further examine the extent to which amphetamine-induced facilitation in food intake is associated with DAergic or NAergic activation, the present study compares the effects of d- and l-amphetamine on food intake. Although an initial study of these amphetamine isomers suggested that d- and l-amphetamine were equipotent at blocking re-uptake of DA, while d- was more potent than l-amphetamine at blocking re-uptake of NA [5], subsequent work has revealed the opposite. That is, d- and l- are actually equipotent at releasing and blocking uptake of NA, while d- is 2 to 5 times more potent than l-amphetamine at releasing and blocking uptake of DA [9, 15, 16, 18, 25, 26]. Increased responsiveness to d-amphetamine would, therefore, suggest involvement of a DAergic substrate while equal responsiveness to the two isomers would suggest involvement of a NAergic substrate in amphetamine-induced feeding. In addition, in order to investigate the extent to which changes in food intake following amphetamine treatment are associated with different sensory properties of the food, rats were given the choice of 3 different food types with varying sugar concentrations.

## METHOD

### *Subjects*

Twelve male Wistar rats weighing 400–450 g were maintained on an ad lib rat chow pellets and water diet and a 12 hr light/dark schedule (lights on: 5:00; off: 17:00).

### *Drugs*

The 4 doses of d-amphetamine (d-AMP) and l-amphetamine (l-AMP) were: 0.125, 0.50, 2.00 mg/kg and a 0.9% saline vehicle.

### *Procedure*

For 5 days prior to testing animals were presented with three 5×5×3 cm stainless steel dishes, each filled with pre-

[1]Requests for reprints should be addressed to Franco J. Vaccarino.

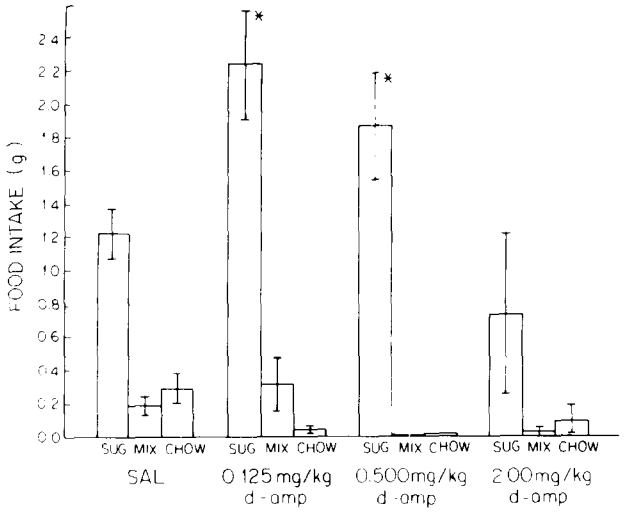


FIG. 1. Intake of sugar (SUG), sweetened chow (MIX) or unsweetened rat chow (CHOW) following systemic administration of a saline vehicle, 0.125, 0.50 or 2.00 mg/kg d-amphetamine (d-AMP). *Significantly different from saline treatment, $p<0.05$.

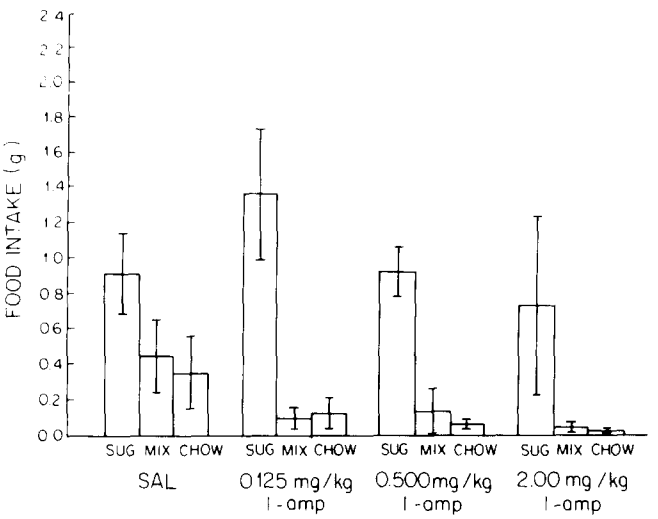


FIG. 2. Intake of sugar (SUG), sweetened chow (MIX) or unsweetened rat chow (CHOW) following systemic administration of a saline vehicle, 0.125, 0.50 or 2.00 mg/kg l-amphetamine (l-AMP). *Significantly different from saline treatment, $p<0.05$.

weighed amounts of either 100.0% sugar, unsweetened powdered chow (Purina, No. 5001) or a 5.0% sugar/chow mixture for 1.5 hr at 14:00. Thus, rats were exposed to 3 different food types simultaneously. All food types were presented in a powdered form. Food intake was recorded at the end of each session to establish baseline food intake.

Rats were matched for baseline food intake and divided into 2 groups (n=6) such that each group would receive each of the doses of d-AMP and the other would receive each of the doses of l-AMP in a counterbalanced order. On testing days each animal received one of the doses of the appropriate drug. Pre-weighed amounts of the 3 food choices used during habituation were placed in the cage for 1.5 hr after which the remaining food and spillage, which was negligible, was weighed. Rats were given two drug-free days between each of the 4 days of drug testing.

## RESULTS

A 3-way mixed-plot analysis of variance revealed that sugar was preferred over sweetened or unsweetened chow under all drug and dose conditions, $F(2,18)=96.79$, $p<0.001$. There was a significant effect of dose on food intake, $F(3,27)=3.35$, $p<0.033$, and this changed with respect to the intake of each food taste, $F(6,54)=2.86$, $p<0.017$. d-AMP increased intake of sugar but not other tastes while l-AMP produced no significant effects on food intake, $F(2,18)=5.31$, $p<0.015$ (see Figs. 1 and 2).

Dunnett's post hoc comparisons, using the 0.05 significance level, revealed that the d-AMP-induced increase in sugar intake occurred with the 0.125 and 0.50 mg/kg doses but not the 2.00 mg/kg dose. l-AMP had no significant effect on feeding at any dose.

## DISCUSSION

The findings of this study indicate that sugar is preferred to sweetened and unsweetened chow. It is interesting to note that d-AMP selectively stimulated sugar intake while having no significant effect on sweetened or unsweetened chow intake. This suggests that amphetamine is not causing general excitatory effects on food intake but rather is acting to selectively enhance the intake of sugar. Thus, it may be that amphetamine is most effective at increasing the intake of foods associated with preferred sensory or post-ingestional hedonic properties. It is important to note, however, that even in the presence of only chow, amphetamine increases intake [29]. Thus, the selective increase of sugar found in the present study indicates that, faced with a choice, amphetamine will selectively increase sugar intake over chow intake.

It is clear from the present results that d-AMP is more potent than l-AMP at stimulating food intake. Since d-AMP is more potent than l-AMP at releasing DA, these results suggest that d-AMP-induced increases are associated with DAergic stimulation. The greater responsiveness of DA-mediated behaviours to d-AMP over l-AMP has been demonstrated with other behavioural paradigms [3, 10, 13, 17, 25]. The notion that d-AMP is mediating its stimulatory effects via DAergic activation is consistent with the finding that direct amphetamine microinjections into DAergic terminal regions also stimulate feeding [8,29]. It should be noted that there is behavioural evidence for the presence of DA neuron subtypes which may show similar sensitivities to d- and l-AMP [11]. The present results, then, would suggest that DA involvement in feeding is associated with DA neurons showing an increased sensitivity to d-AMP.

The lack of stimulatory effect of d-AMP at the 2.00 mg/kg dose is consistent with previous reports of no change or decreased food intake following moderate to high doses of this drug [1,21]. At high doses d-AMP produces behaviours such as increased locomotion and stereotyped behaviours [21] which could interfere with the expression of feeding behaviour. Thus, higher doses of d-AMP could be recruiting behavioural systems incompatible with feeding. Interestingly, the NA beta-blocker l-propranolol or receptor blocker thymoxamine attenuate AMP-induced anorexia, suggesting NA involvement in the effect [19,27]. Though in the present study the 2.00 mg/kg dose of l-AMP might have been expected to increase feeding due to similar excitation of DA neurons to that found with lower doses of d-AMP, the

level of stimulation of NA neurons would be much greater. Thus, given the possible involvement of NA in amphetamine anorexia, the lack of effect on food intake of 2.00 mg/kg l-AMP might be due to increased NA activity overriding the DA effect. In addition to influencing NAergic systems, AMP also has excitatory effects on serotonin [21]. However, since the stimulatory effects of systemically administered AMP on serotonin levels occur only at high doses [18,24], it is unlikely that there is a significant serotonin contribution to the present effects.

Since amphetamine exerts excitatory influences on NA and serotonin transmission as well as DA transmission, it is not surprising that studies examining the effects of intracranial microinjections of AMP demonstrate both increases and decreases in feeding. For example, microinjections of AMP into the paraventricular nucleus of the hypothalamus (PVN) produce increased food intake [20] while injections into the perifornical region attenuate feeding [22]. The facilitatory effects of AMP in the PVN have been suggested to be mediated by activation of alpha-adrenergic receptors [20]. The inhibitory effects of AMP in the perifornical region are likely associated with increased activation of DA and beta-adrenergic receptors in that region [20]. AMP can also stimulate feeding in DA terminal regions outside the hypothalamus [8,29]. Taken together, these results make it clear that the effects of AMP vary as a function of brain site. The present results, however, indicate that, in low doses, the net effect of d-AMP on these brain regions in the expression of feeding is a facilitatory one. Moreover, the fact that d- is more potent than l-AMP suggests that activation of DA transmission is contributing to the expression of this facilitatory effect on feeding.

The present findings confirm those of earlier reports [2, 6, 14, 29] indicating that, in low doses, systemic d-AMP can stimulate food intake and further support the notion that this effect is DA-dependant. The present results are also consistent with recent studies which utilized the neuroleptic pimozide. Wise [30–32] has suggested from operant studies that, at the doses tested, pimozide acts to attenuate the rewarding properties of food while having no effect on non-specific behaviours. Consistent with this, pimozide preferentially decreases intake of a sucrose solution in both sham-fed and free-feeding animals at doses which produce no motor impairment and have no sedative effect [12,33]. The sham feeding data suggest that the proposed specific excitatory role for DA in feeding is likely associated with taste factors rather than post-ingestional factors [12]. Further, since the decreases in drinking rate following pimozide were similar to decreases produced by lowering the sucrose concentration, it was suggested that DA may specificially mediate the reinforcing component of sweet taste. The present study suggests that this may also be true of solid food intake.

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