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Intra-Nucleus Accumbens Amphetamine: Dose-Dependent Effects on Food Intake

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EVANS, K. R. AND F. J. VACCARINO. *Intra-nucleus accumbens amphetamine: Dose-dependent effects on food intake.* PHARMACOL BIOCHEM BEHAV **25**(6) 1149–1151, 1986.—The effects of microinjections into the nucleus accumbens (N.ACC.) of 0.0, 2.0 or 8.0 μg of (+)-amphetamine sulphate (AMPH) on food intake and running wheel activity were examined. The 2.0 μg dose of AMPH produced increased food intake while 8.0 μg significantly decreased food intake. No effect was found on running wheel activity with the 2.0 μg dose, though 8.0 μg significantly increased the number of wheel revolutions with respect to the saline group. Results were interpreted to suggest that the N.ACC. may be an important site in the mediation of the increased food intake noted with low doses of psychomotor stimulants.

Amphetamine Nucleus accumbens Feeding Locomotor activity

ALTHOUGH systemically administered amphetamine (AMPH) is known to produce depressant effects on food intake [5], recent experiments have demonstrated that low doses of this catecholamine agonist or other dopamine agonists, injected centrally or peripherally, can produce increased feeding [7,13]. This facilitatory effect is unlikely to be a result of non-specific behavioural activation since low doses of AMPH appear to have little effect on locomotor activity [1].

The nucleus accumbens (N.ACC.) has been shown to be a critical site for the mediation of reward and locomotor-activating properties of catecholamine agonists [2–4, 6, 9–12]. In order to examine the possibility that the N.ACC. is a site of action for AMPH on feeding, the effects of bilateral microinjections of AMPH into the N.ACC. on food intake were investigated. In addition, since AMPH is known to have behaviourally activating properties, the extent to which any feeding effects were associated with changes in locomotor activity were also investigated.

METHOD

Sixteen male Wistar rats, weighing 275–325 g were individually housed on a 12 hr light/dark cycle (lights on from 2:00–14:00) with ad lib access to powdered rat chow and water. Rats had unlimited access to a running wheel mounted on the side of their home cage.

Rats were anaesthetized with 60 mg/kg sodium pentobarbitol and bilateral 23 gauge stainless steel guide cannulae were stereotaxically implanted such that the tips were 3.0 mm dorsal to the N.ACC.; the coordinates were 3.2 mm anterior to bregma, +1.7 mm lateral to the midline and 4.8 mm ventral to the skull surface with the incisor bar set at 5 mm above the interaural line [8]. Cannulae were kept sealed with stainless steel obturator pins. N.ACC. injections were made over a 30 sec period through 30 gauge injection cannulae which extended 3.0 mm beyond the tip of the guide cannulae. Animals were randomly assigned to 3 groups such that rats were tested with either vehicle (n=5), 2.0 μg AMPH (n=6) or 8.0 μg AMPH (n=5). Injections were made in a 1.0 μl volume 0.9% saline vehicle (0.5 μl/side). The pH of the 8 μg AMPH dose was 6.5.

Testing began after 5 days of post-operative recovery. Following 3 hr of food deprivation (24:00–3:00) animals were injected with either vehicle or one of the doses of AMPH and returned to their home cages. A metal plate separated them from their food dish and a new dish with pre-weighed powdered rat chow was placed on the floor of the cage. Food was re-weighed and running wheel revolutions were recorded 1.5 hr later.

To verify cannulae placements, rats were sacrificed with overdoses of sodium pentobarbitol, exsanguinated with 0.9% saline and fixed with 10.0% formalin. Brains were removed, sectioned at 40 μm and stained with thionine.

RESULTS

Histologies of 3 animals showed cannulae placements to be outside the N.ACC. and were therefore not included in the analyses. This left 4 animals in the saline group, 4 animals in the 2.0 μg AMPH group and 5 animals in the 8.0 μg AMPH group.

An analysis of variance of the feeding data demonstrated a significant effect of dose of AMPH on feeding, $F(2,10)=19.02, p<0.01$. Post hoc Dunnett's test comparisons with saline controls revealed significant increases at the 2.0

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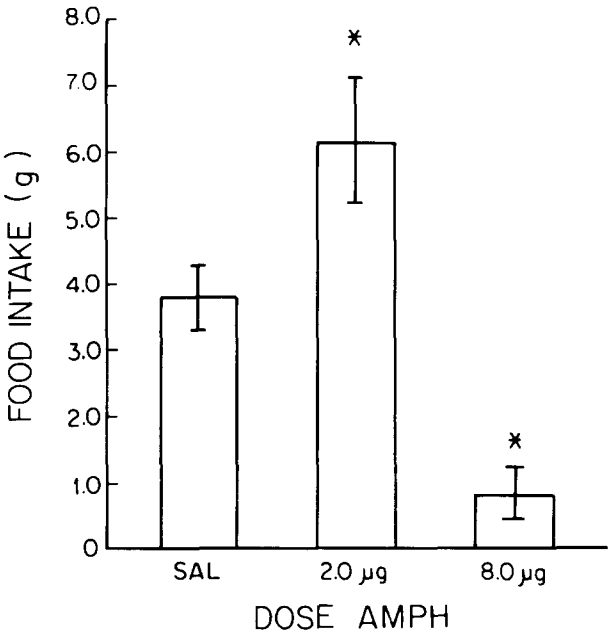

FIG. 1. Bar graph showing the amount of food eaten (g) ±S.E.M. following intra-nucleus accumbens injections of 0.0, 2.0 and 8.0 μg of (+)-amphetamine sulphate. *Significantly different from saline treated animals.

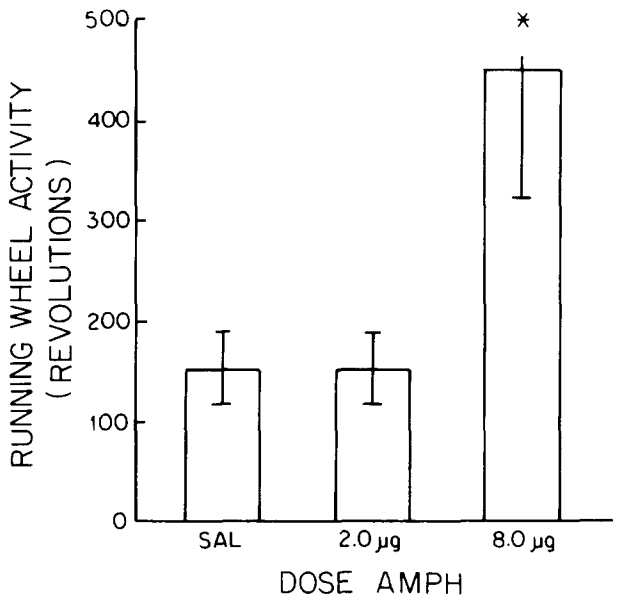

FIG. 2. Bar graph showing the number of running wheel revolutions ±S.E.M. following intra-nucleus accumbens injections of 0.0, 2.0 and 8.0 μg of (+)-amphetamine sulphate. *Significantly different from saline treated animals.

μg AMPH dose, $d(10)=2.54$, $p<0.05$, and significant decreases at the 8.0 μg dose, $d(10)=3.43$, $p<0.01$ (see Fig. 1).

An analysis of variance of the running wheel data was significant with a 1-tail test, $F(2,10)=3.85$, $p<0.05$. Post hoc Dunnett's test comparisons revealed that the 2.0 μg AMPH dose had no significant effect on activity whereas the 8.0 μg AMPH dose significantly increased activity, $d(10)=13.02$, $p<0.01$ (see Fig. 2).

DISCUSSION

It can be seen in Fig. 1 that 2.0 μg AMPH had a stimulatory effect on feeding. This raises the possibility that the N.ACC. is an important site in mediating the stimulatory effects on feeding previously observed with AMPH and other dopaminergic agonists [7,13]. Since the present study tested for total 1.5 hr food intake, it cannot be determined from these data whether the increased eating observed following 2 μg AMPH occurred early or late in the session. If the increased eating were occurring late in the session this raises the further possibility that the increased intake may be due to diffusion of AMPH (later in the session) to sites outside the N.ACC. Although this possibility cannot be entirely ruled out, the following points support a N.ACC.-specific effect. Firstly, of the 2 rats which received 2 μg AMPH outside the N.ACC., one had cannulae tips located dorsal to the N.ACC. and the other had tips located ventral to the N.ACC. Neither of these rats showed any significant change in food intake following AMPH. Secondly, the increases in wheel running observed at the 8 μg dose are consistent with the behavioural activation observed following DAergic stimulation in the N.ACC.

While the present results suggest the involvement of the N.ACC. in the AMPH effect on feeding, it should be noted that other dopaminergic terminal areas have also been implicated in AMPH-induced feeding. Winn, Williams and Herberg [13] reported that microinjections of AMPH into the striatum produced significant increases in food intake. This suggests that AMPH can act in both the N.ACC. and striatum to stimulate food intake. The extent to which AMPH injections into these two sites stimulate food intake by the same or different mechanisms remains to be investigated.

In contrast to the effects of 2.0 μg AMPH, 8.0 μg caused clear decreases in food intake. This is unlikely to reflect a motor deficit since increases in wheel running were observed following this dose of AMPH. The increased wheel running observed at the 8.0 μg dose is consistent with numerous studies indicating that the N.ACC. is an important structure in the mediation of the locomotor activation observed with moderate doses of AMPH [2–4, 11]. Since wheel running and feeding are, to some extent, mutually exclusive, the decreased food intake observed with 8.0 μg AMPH may be associated with increased wheel running and, therefore, the recruitment of behaviours which are incompatible with feeding.

It is important to note that in the present study no effect was found on running wheel activity at the 2.0 μg dose. This is consistent with previous reports demonstrating that at very low doses, AMPH does not produce behavioural activation [1]. That 2.0 μg AMPH stimulated feeding without influencing wheel running demonstrates that it is exerting a relatively selective effect on feeding at this dose. In light of the importance of N.ACC. DA transmission in the mediation of psychomotor stimulant reward [6, 9, 10, 12], the present data raise the possibility that at low doses, intra-N.ACC. AMPH may be exerting its stimulatory effects on feeding by increasing the rewarding properties of some element of the feeding process. This is consistent with the notion that the decreased feeding observed following interference with DA function reflects a motivational deficit [14].

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