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Facilitation of Feeding by Nucleus Accumbens Amphetamine Injections: Latency and Speed Measures

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WISE, R. A., M. FOTUHI AND L. M. COLLE. *Facilitation of feeding by nucleus accumbens amphetamine injections: Latency and speed measures.* PHARMACOL BIOCHEM BEHAV **32**(3) 769–772, 1989.—Food-deprived rats were offered food in small meal segments, and latency to initiate feeding and time to complete it were recorded for each segment. Bilateral microinjections of *d*-amphetamine into nucleus accumbens dramatically increased the mean speed with which meal segments were eaten, but had no reliable effect on mean latency to initiate eating of new segments; *l*-amphetamine had similar but weaker effects. While mean eating speed was increased, this increase resulted from a decrease in the frequency of slow trials and not from an increase in the absolute speed of the fastest trials. These data suggest that amphetamine facilitates feeding by some other means than simple improvement of the motoric capacity of the animal, and they indicate that nucleus accumbens is an important site for amphetamine's established but not widely appreciated facilitory effects on feeding.

Amphetamine Appetite Nucleus accumbens Feeding

AMPHETAMINE is well known as an anorexic agent (3,10). It can also have reliable facilitory effects on feeding; the facilitory effects are generally seen with lower amphetamine doses (3). Facilitory and inhibitory effects can each be seen with microinjections into nucleus accumbens; again, facilitory effects are seen with lower doses and inhibitory effects are seen with higher doses (6–8).

The facilitory effects are of particular interest in that they represent an effect opposite to the dominant effect of neuroleptics, which normally suppress feeding and normally antagonize the effects of amphetamine (5,12). Since neuroleptics pharmacologically block the system that is damaged in Parkinson's disease, the inhibition of feeding and food-rewarded lever-pressing by neuroleptics has often (1, 19, 22, 26) been attributed to some form of parkinsonian side-effect such as inability to initiate voluntary movement (2,15). From this perspective, the facilitation of feeding by amphetamine might be thought to involve an improvement in the ability to initiate or coordinate food-related responses. However, direct observations of latency to initiate feeding (27,29) question the view that neuroleptics limit the capacity for normal response initiation. Rats treated with moderate doses of neuroleptics initiate feeding with normal latencies but slow their rates of feeding more quickly over the course of a session than do untreated animals (27,29). Even when speed of eating is slowed, normally fast trials are interdigitated with an increasing number of slow trials that are disrupted by locomotion and grooming (27,29). Thus, neuroleptics seem to alter the ability of food to sustain interest rather than to alter the absolute capacity of the animal to respond with normal latency or speed.

Such consideration of the trial-by-trial effects of neuroleptics suggests the possibility that amphetamine should not decrease latency to initiate feeding, but should rather accelerate feeding and attenuate the slowing that is normally seen as the animal satiates; moreover, if it has truly opposite effects to neuroleptics, it should accelerate feeding by reducing the number of trials in which eating is slow because of disruption by locomotion or grooming rather than by increasing the absolute limits of best performance. The present study was designed to test these a priori hypotheses.

METHOD

Seven adult (350–400 g) male Long-Evans rats were implanted with bilateral stainless-steel hypodermic guide cannulae (o.d. = 0.4 mm, i.d. = 0.3 mm) aimed at a site just dorsal to the caudal nucleus accumbens (target coordinates, with the incisor bar 5.0 mm dorsal to the interaural line, were 3.2 mm anterior to bregma, 2.5 mm lateral to the midline, and 3.9 mm ventral to the dural surface). The animals were given ad lib access to food for seven

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days and then placed on a 22-hr deprivation schedule. After five days on the deprivation schedule, the animals were trained to obtain a major portion of their daily food ration in test boxes where 18 meal segments, each consisting of five 45-mg food pellets, were presented for 36-sec periods at 72-sec intervals. Testing began after 18 days of such training.

The meal segments were introduced into a 25 × 25-cm test box by an automatic dispensing apparatus involving 36 food cups (1.3 cm dia. × 0.8 cm deep) drilled into a 25-cm (dia.) aluminum disc which extended 5 cm into the test box. Every second food cup contained a meal segment; the alternate cups were empty. At any given time, only one of the cups was exposed, through an aluminum mask, to the animal. The platters were indexed by one position every 36 sec; a solenoid pulled a rubber drive wheel on a continuously running motor against the circumference of the disc to index it when signalled by a timer. A microswitch opened the solenoid circuit when the new food cup reached its intended position. Solenoid noise was clearly audible but not loud; it could just be heard over normal conversation. The aluminum food platters were cleaned by scraping between tests; the platters were washed with distilled water and dried immediately before the experiment as minerals in tap water can interact with aluminum to alter the taste of the cup surface. Each test box was dimly lighted; the test room was otherwise dark.

Amphetamine was dissolved in sterile physiological saline and was injected bilaterally into nucleus accumbens through injector cannulae (o.d. = 0.28 mm, i.d. = 0.18 mm) that extended 2.9 mm below the tip of the guide cannulae, to a depth of 6.8 mm ventral to the dural surface. Injection volume was 0.5 μl; it was infused over a 1-min period. Three doses of *d*-amphetamine (2.5, 10, and 20 μg) and one dose of *l*-amphetamine (10 μg) were tested in counterbalanced order, with two days of drug-free testing between drug tests.

Animals were tested singly, 10 minutes after injection. Latency to make oral contact with the first pellet and time to complete the eating of all five pellets were timed with electronic stopwatches for each meal segment. Pellets left uneaten were noted. Incidents of grooming, freezing, and exploration were noted when they occurred prior to completion of a meal segment.

RESULTS

There was only one trial in which an animal failed to eat all five food pellets; this was the last trial in the control condition for one animal. A cutoff score of 36 sec was assigned in this case for the purpose of estimating average duration score. Every animal ate every pellet in the amphetamine condition. Instances of grooming and exploration never occurred prior to completion of all five pellets except in the single case where the animal did not eat the fifth pellet. Instances of freezing were brief (less than two seconds) and rare; they were restricted to the few times when outside noises intruded. Such cases were treated as pauses rather than periods of true freezing.

Latency scores were as short as 0.5 sec; few scores longer than 2.5 sec were seen. The distribution of scores was skewed (Fig. 1), and amphetamine decreased, to some extent, the number of extremely long scores and increased the number of short scores; this trend was statistically reliable for the highest dose [binomial sign test, $p<0.001$ (23)], but not for either of the lower doses. Median latency under 20 μg of *d*-amphetamine was 0.52 sec and median latency in the control condition was 0.97 sec. Aside from a tendency for long latencies on the first one or two trials, there were no obvious trends over time in either the *d*-amphetamine (Fig. 2) or the *l*-amphetamine (Fig. 3) data.

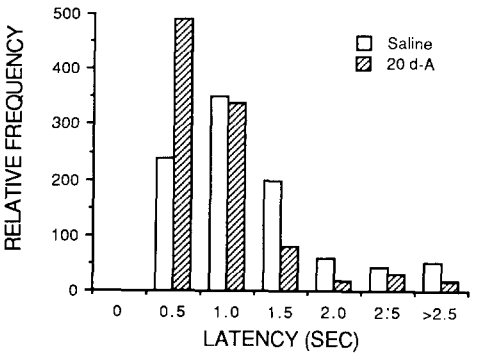

FIG. 1. Distribution of latency scores following saline or 20 micrograms of *d*-amphetamine (d-A) injected into nucleus accumbens.

The distribution of duration scores was also skewed, at least in the amphetamine condition (Fig. 4). At the 20 μg dose, *d*-amphetamine shifted the distribution toward shorter values, reducing the number of long durations and increasing the number of short ones. Median duration under 20 μg of *d*-amphetamine was 12.3 sec; and median duration under the control condition was 20.7 sec. The effects of the three doses of *d*-amphetamine were dose-orderly (Fig. 5) and statistically reliable (low dose, $p<0.02$; medium and high doses, $p<0.001$). At the 10 μg doses, *d*-amphetamine accelerated feeding significantly ($p<0.001$) more

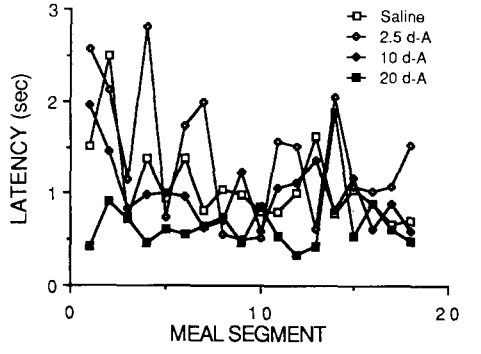

FIG. 2. Mean latency to initiate feeding following saline, 2.5, 10, or 20 microgram injections of *d*-amphetamine (d-A).

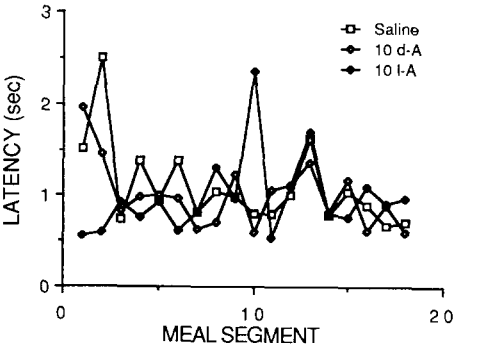

FIG. 3. Mean latency to initiate feeding following saline, 10 micrograms of *d*-amphetamine (d-A) or 10 micrograms of *l*-amphetamine (l-A).

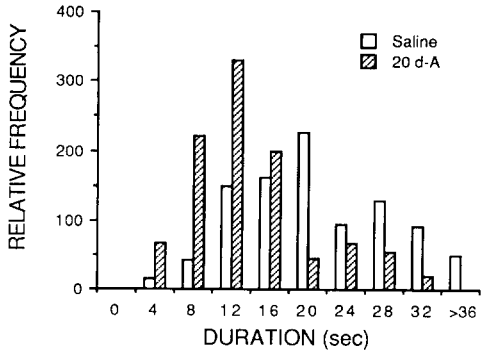

FIG. 4. Distribution of duration scores following saline or 20 micrograms of *d*-amphetamine (d-A) injected into nucleus accumbens.

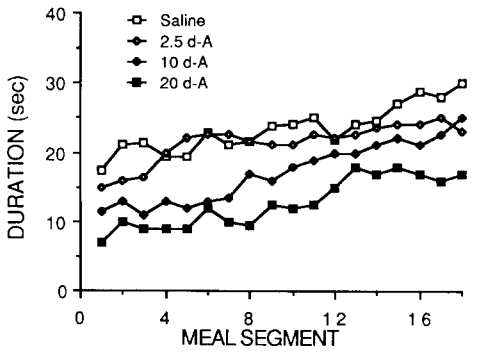

FIG. 5. Mean time to eat five food pellets following saline, 2.5, 10, or 20 microgram injections of *d*-amphetamine (d-A).

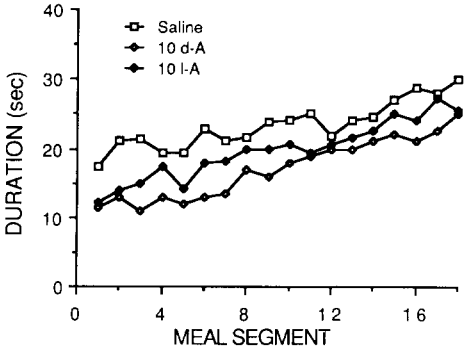

FIG. 6. Mean time to eat five food pellets following saline, 10 micrograms of *d*-amphetamine (d-A) or 10 micrograms of *l*-amphetamine (l-A).

than *l*-amphetamine, which accelerated feeding significantly ($p<0.001$) relative to saline conditions (Fig. 6). The effects of each isomer were uniform throughout the 18 meal segments (Figs. 5 and 6).

DISCUSSION

Nucleus accumbens injections of amphetamine improved both latency and speed measures of feeding. The improvement of speed measures was more dramatic, but this may have been due to floor effects; that is, latency scores were so short under saline conditions that it may have been difficult to detect much amphetamine-induced tendency toward improvement. The improvement that was seen, however, resulted from a decrease in the frequency and extremity of worst scores, and not from an increase in the absolute values of best scores. That is to say, the distributions of scores under amphetamine appeared to be anchored to the same absolute limits of performance capacity (0.5-sec latency scores and 4-sec duration scores) as the distributions of scores under saline. Thus, amphetamine increased the frequency of trials when animals performed near the limits of their capacity, but did not alter the absolute levels of such performance. Disruption of performance by locomotion and grooming was observed in trials where scores were particularly long; thus, long scores reflected conflicting behaviors or attentional distraction rather than motoric inability.

The effect of neuroleptics in this paradigm is to cause a progressively greater decrease in eating speed as the test progresses; this has been interpreted as reflecting decreased interest in food as a result of experience in the early moments of the test (27,29). There was no analogous experience-dependent component to the effects of amphetamine in the present study. Thus, if the interpretation of the neuroleptic data is correct, and the animal must taste the food under drug conditions before performance will be altered, then much less experience of this type must be required to alter performance under amphetamine than is required under pimozide. Indeed, under pimozide conditions, learning appears to be spaced over the first two test days (27,29); in the present experiment any learning as to amphetamine-altered stimulus effectiveness of food must have taken place within the very first meal segment. This possibility is not counterintuitive; if neuroleptics reduce the rewarding impact of food and amphetamine increases them, one might expect it to take longer for the animals to become discouraged under neuroleptics than to become encouraged under amphetamine. If this speculation has merit, then more sensitive tests will be required to demonstrate an interaction of amphetamine with taste experience in the testing situation. Offering a single pellet per meal segment or offering pellets with minimal palatability might be effective.

The *d*-isomer of amphetamine was more effective than the *l*-isomer, which confirms that the nucleus accumbens injections facilitated feeding through pharmacological rather than physicochemical actions. While the two isomers are equally effective in their effects on peripheral (4, 20, 21, 24) and central noradrenergic (9, 11, 13, 14, 25, 28) mechanisms, they are differentially effective in their influence on the dopamine system (9, 11, 13, 14, 25). The differential effectiveness in the present paradigm thus not only confirms pharmacological actions, it suggests pharmacological actions involving dopaminergic function. That dopaminergic function in the nucleus accumbens itself is involved is suggested by studies in which injections dorsal to the nucleus accumbens have been examined; such injections are less effective than nucleus accumbens injections in facilitating feeding (6,7). This does not, however, rule out the possibility that amphetamine has similar actions at other brain sites, including other dopamine terminal fields. Frontal cortex injections were not tested, and we have not thoroughly explored the caudate in our neuroleptic studies. To do so would involve a major study, as subregions of the caudate are thought to serve different behavioral functions, and subregions of nucleus accumbens may do so as well.

The present study thus confirms earlier work suggesting that dopaminergic actions of amphetamine in nucleus accumbens can facilitate feeding (6–8). This action of amphetamine on feeding appears to involve a mechanism independent of the hypothalamic mechanisms that have been traditionally associated with amphetamine's anorectic effects (16–18).

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