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Individual Differences in Sugar Consumption Following Systemic or Intraaccumbens Administration of Low Doses of Amphetamine in Nondeprived Rats

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SILLS, T. L. AND F. J. VACCARINO. *Individual differences in sugar consumption following systemic or intraaccumbens administration of low doses of amphetamine in nondeprived rats.* PHARMACOL BIOCHEM BEHAV **54**(4) 665–670, 1996.—Rats exhibit individual differences in their propensity to ingest sucrose and in their feeding response to low doses of amphetamine (AMP). Rats with high baseline sugar intake (HIGH) show a decrease in sugar consumption in response to AMP, while rats with low baseline sugar intake (LOW) show an increase in consumption (33,34). At present, it is not known whether LOW and HIGH rats would be differentially responsive to higher, anorexigenic doses of AMP. Thus, the present study was developed to further determine the dose–response curve for AMP's effects on sugar consumption in LOW and HIGH rats. One group of rats received IP injections of 0.05, 0.1, and 0.2 mg/kg AMP, while a second group was administered 0.25, 0.5, and 1.0 mg/kg AMP. A third group of rats received intranucleus accumbens (Acc) microinjections of low to moderate (2.0–8.0 μg) doses of AMP, because evidence indicates that this may be an important site of action for AMP's effects on feeding in LOW and HIGH rats. Results showed that at low doses (≤ 0.25 mg/kg), AMP stimulated sugar consumption in LOW rats and either had no effect or inhibited consumption in HIGH rats. At doses greater than 0.25 mg/kg, AMP inhibited sugar consumption in both LOW and HIGH rats. Furthermore, intra-Acc administration of AMP stimulated sugar intake in LOW rats and produced a slight, but nonsignificant, decrease in consumption in HIGH rats. Taken together, these results show that LOW and HIGH rats exhibit individual differences in their feeding response to low but not moderate to high doses of AMP. Furthermore, the evidence indicates that the Acc is an important site for AMP's facilitatory effect on sugar consumption in LOW rats.

Amphetamine Individual differences Feeding Sugar Nucleus accumbens Rat

AMPHETAMINE (AMP) has complex effects on food intake. It is well established that in moderate to high doses (≥ 1.0 mg/kg) AMP inhibits food consumption (1,22–24). At lower doses (< 1.0 mg/kg), however, results are equivocal with regard to AMP's effect on food intake. While some studies show that low doses of AMP suppress food intake (8,26), other studies have shown that similar doses of AMP actually facilitate feeding (5–7,9,14,36).

The effects on food consumption of low doses of AMP may be influenced by a number of factors, including palatability of diet, deprivation condition, and circadian period. One important factor that has been shown to influence AMP's effect on food consumption is the amount of food consumed by an animal under baseline conditions. For example, Dobrzanski and Doggett (1976) reported that AMP (1.0, 2.0, and 4.0 mg/kg) depressed food intake in mice adapted to feed between 1200–1500 each day (i.e., deprived rats), and in nondeprived mice tested at night. In contrast, AMP stimulated intake in nondeprived rats tested during the daytime. It is significant that the deprived mice and the mice tested in the dark photoperiod ate significantly more food under baseline conditions than the nondeprived mice tested in the light photoperiod.

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These results suggest that there are conditions under which animals are sensitive to the orexic effect of AMP and other conditions under which animals are sensitive to the anorexic effect of AMP. More specifically, the feeding facilitatory effect of AMP is evident under conditions where baseline intake is low. The anorexic effect of AMP, on the other hand, is prevalent under conditions where baseline intake is elevated.

Recently, it has been demonstrated that differences in baseline food consumption across animals may also be a critical determinant of the effects of low doses of AMP on food consumption. Rats that consumed low amounts of sugar under baseline conditions (LOW) showed an increase in sugar intake when challenged with 0.125 mg/kg AMP. In contrast, rats with high baseline sugar intake (HIGH) showed a decrease in sugar intake when treated with the same dose (33,34). These findings highlight the importance of considering individual differences when examining the effects of AMP on food consumption.

The present study was developed to further examine the expression of individual differences in the feeding response to AMP. At present, it is not known whether LOW and HIGH rats would be differentially responsive to anorexigenic doses of AMP. Therefore, it was of interest to delineate a dose–response curve for AMP's effects on sugar consumption in LOW and HIGH rats. To this end, LOW and HIGH rats were tested for their sugar intake in response to low (< 0.25 mg/kg) and moderate to high (≥ 0.25 mg/kg) doses of AMP. A third group of rats was tested for their sugar consumption in response to AMP (2.0–8.0 μg) microinjected into the nucleus accumbens (Acc). Evidence indicates that the Acc is an important site for AMP's effects on food intake (2,5,7), and there is some indication that intrinsic differences in Acc-DA function may underlie the expression of individual differences in sugar consumption and responsiveness to AMP treatments (33–35).

METHOD

Systemic Amphetamine

For 7 days prior to testing, male Wistar rats (Charles River, Quebec) weighing approximately 275–300 at the start of the experiment, were habituated to the test diet for 1 h (1500–1600 h) each day; for the remaining 23 h of each day rats had ad lib access to standard Purina lab pellets. The test diet consisted of a choice of granulated sugar and powdered Purina lab chow. Animals were administered 0.05, 0.1, and 0.2 mg/kg AMP or 0.25, 0.5, 1.0 mg/kg AMP in a counterbalanced order; AMP was administered IP in a volume of 1 ml/kg. Animals had two drug-free days between each test session. On tests days, animals were removed from their home cages and were injected (IP) with the predetermined dose of AMP. After injection, animals were returned to their home cages where two $5 \times 5 \times 3$ cm stainless steel containers of preweighed amounts of sugar and powdered chow had replaced the standard lab diet. Animals were allowed to feed on the test diets for a period of 1 h (1500–1600 h), after which the remaining food (including spillage) was reweighed.

Intraaccumbens Amphetamine

Sixteen male Wistar rats (Charles River, Quebec), weighing approximately 260–320 g presurgery, were anesthetized with sodium pentobarbital (60 mg/kg IP) and stereotaxically implanted with bilateral 10 mm (long) 23 gauge guide cannulae aimed 3 mm dorsal to the Acc; the coordinates were 2.2 mm anterior to bregma, 1.2 mm lateral to the midline, 5.0 mm ventral to the surface of the skull, with the mouthbar set at −3.5 mm (27). Cannulae were sealed with stainless steel obturators.

The procedure was identical to the previous two groups with the following exceptions. Rats received microinjections of AMP (0.0, 2.0, 4.0, and 8.0 μg) into the Acc. Bilateral intra-Acc AMP was delivered via a Stoelting microsyringe over a period of 1 min at a rate of 0.25 μl per min per side; injectors were kept in place for a further 30 s. Following injections, animals were returned to their home cages and provided access to the test diets for 1.5 h. At the conclusion of all testing, animals were given sodium pentobarbital overdose. The animals were exsanguinated and then perfused with 0.9% saline, followed by 10% formalin. Brains were removed and 40 μm slices were obtained using a cryostat. The slices were stained with thionin and histological verification of cannulae placements and injection sites were ascertained with a microscope.

Analyses

Analyses were carried out using Pearson Product Moment Correlation, and Repeated Measures Analysis of Variance (ANOVA), followed by post hoc comparisons using the least significant difference test.

RESULTS

In all cases animals consumed primarily sugar and, thus, only the sugar intake data were analyzed. Animals were divided into LOW and HIGH feeders based on a median split of their sugar intake in response to saline administration.

Systemic Amphetamine (0.05–0.2 mg/kg)

A two-way ANOVA, with group and day as factors, was carried out to examine the amount of sugar consumed by LOW ($n = 17$) and HIGH ($n = 15$) rats across the 7-day adaptation period. There were significant main effects of group, $F(1, 30) = 7.913$, $p < 0.01$, and day, $F(6, 180) = 2.986$, $p < 0.01$. As can be seen in Fig. 1a, HIGH rats consumed more sugar than LOW rats during the adaptation phase, suggesting a stable difference between the two groups of rats. A two-way ANOVA was carried out to investigate the effects of the three doses of AMP on sugar intake in LOW and HIGH feeders. There were significant main effects of dose, $F(3, 90) = 4.74$, $p < 0.01$, and group, $F(1, 30) = 32.54$, $p < 0.001$. However, the group × dose interaction was only marginally significant, $F(3, 90) = 2.54$, $p = 0.06$. As is shown in Fig. 1b, sugar intake was stimulated in LOW rats by AMP at all doses. In HIGH rats, on the other hand, there was a slight but nonsignificant increase at the lowest dose and slight but nonsignificant decreases at the medium and high doses.

Systemic Amphetamine (0.25–1.0 mg/kg)

Figure 2a shows that HIGH ($n = 15$) animals consumed more sugar than LOW ($n = 15$) animals across the 7-day adaptation period, $F(1, 28) = 16.383$, $p < 0.01$. A two-way ANOVA investigated the effects of the three doses of AMP on sugar consumption in LOW and HIGH rats. This analysis revealed significant main effects of group, $F(1, 28) = 56.886$, dose, $F(3, 84) = 740.711$, and a significant two-way interaction of group × drug, $F(3, 84) = 12.939$, $p < 0.01$. As can be seen in Fig. 2b, AMP inhibited sugar intake at all doses in HIGH animals. In LOW animals, on the other hand, AMP significantly inhibited sugar consumption only at the two highest doses tested.

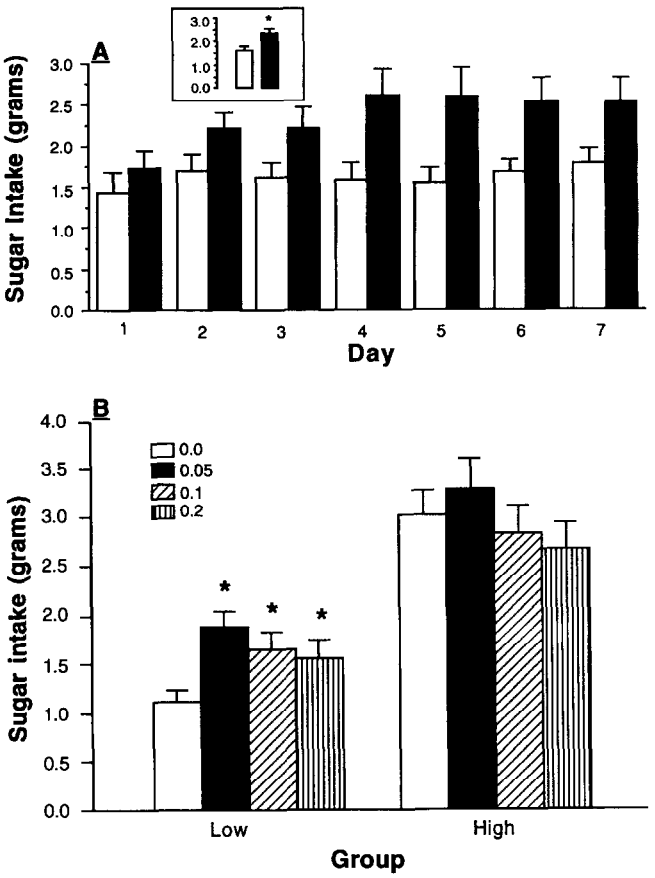

FIG. 1. (A) The average (± SEM) amount of sugar consumed by LOW (□) and HIGH (■) rats across the 7-day adaptation period. Inset: Average daily sugar intake in LOW and HIGH animals. (*$p <$ 0.05 as compared to LOW rats). (B) The average (± SEM) amount of sugar consumed by LOW and HIGH rats in response to the intraperitoneal administration of amphetamine (open column—0.0 mg/kg; filled column—0.05 mg/kg; slanted rule column—0.1 mg/kg; vertical rule column—0.2 mg/kg). (*$p < 0.05$ as compared to 0.0 mg/kg amphetamine).

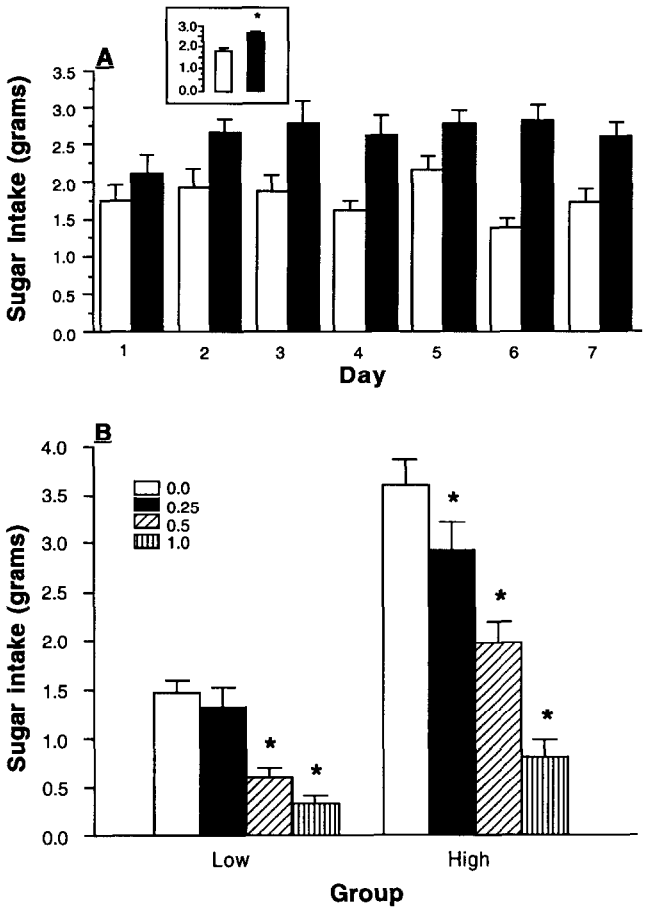

FIG. 2. (A) The average (± SEM) amount of sugar consumed by LOW (□) and HIGH (■) rats across the 7-day adaptation period. Inset: Average daily sugar intake in LOW and HIGH animals. (*$p <$ 0.05 as compared to LOW rats). (B) The average (± SEM) amount of sugar consumed by LOW and HIGH rats in response to the intraperitoneal administration of amphetamine (open column—0.0 mg/kg; filled column—0.25 mg/kg; slanted rule column—0.5 mg/kg; vertical rule column—1.0 mg/kg) (*$p < 0.05$ as compared to 0.0 mg/kg amphetamine).

Intraaccumbens Amphetamine

Thirteen of the 16 rats were found to have bilateral cannulae placements within the rostral Acc (see Fig. 3). Examination of the sugar intake data from the 10-day adaptation period revealed a significant effect of group, $F(1, 11) = 8.172$, $p < 0.05$. As is evident in Fig. 4a, HIGH animals consumed more sugar across the 10-day adaptation period than did LOW animals. A two-way ANOVA examining sugar intake at each dose for LOW and HIGH sugar feeders revealed a significant main effect of group, $F(1, 11) = 5.678$, $p < 0.05$, and a significant two-way interaction of group and dose, $F(3, 33) = 4.178$, $p < 0.05$. As can be seen in Fig. 4b, intra-Acc AMP stimulated sugar intake in LOW animals at the medium dose. In HIGH animals, on the other hand, AMP caused a slight, but nonsignificant, decrease in sugar intake at all doses.

DISCUSSION

The results of the present study show that rats exhibit individual differences in their propensity to ingest sugar and in their feeding response to low doses of AMP. Animals that consumed low amounts of sugar under baseline conditions (LOW) showed an increase in sugar intake when challenged with low ($\leq$ 0.2 mg/kg) doses of AMP. Animals that consumed high amounts of sugar under baseline conditions (HIGH), on the other hand, were either not affected or showed a decrease in sugar consumption when challenged with the same doses of AMP. In contrast to the effects of low doses of AMP, moderate to high doses ($\geq$ 0.25 mg/kg) of AMP resulted in an inhibition of sugar consumption in both groups of rats, with HIGH rats being more sensitive to the anorectic effect of AMP than LOW rats. The minimum anorectic dose of AMP was lower in HIGH rats (0.25 mg/kg) compared to LOW rats (0.5 mg/kg). Taken together, these results indicate that LOW and HIGH rats are differentially responsive to feeding effects of AMP at doses equal to or less than 0.25 mg/kg. At higher doses ($\geq$ 0.5 mg/kg) AMP inhibits sugar consumption in both groups of rats.

Previously it has been reported that 0.125 mg/kg AMP significantly inhibited sugar consumption in HIGH rats (33,34). In the present experiment, sugar consumption in HIGH rats was not significantly affected by AMP at a similar

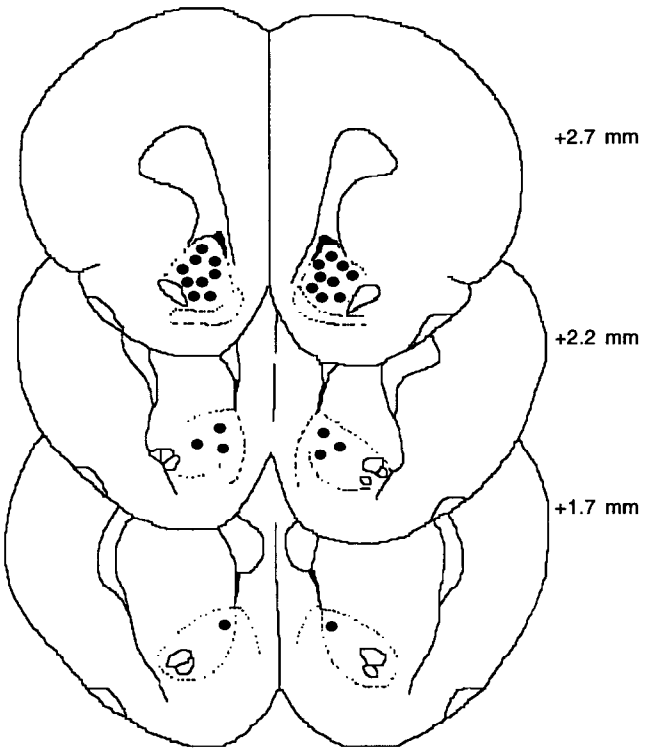

FIG. 3. Cannulae placements of all animals receiving drug treatments. Only animals with bilateral cannulae placements within the nucleus accumbens were used in the data analyses. Numbers beside each section represent the anterior location relative to bregma (mm). Abbreviations: aca, anterior commissure; Acc, nucleus accumbens; CC, corpus callosum; CPu, caudate putamen; fmi, forceps minor corpus callosum.

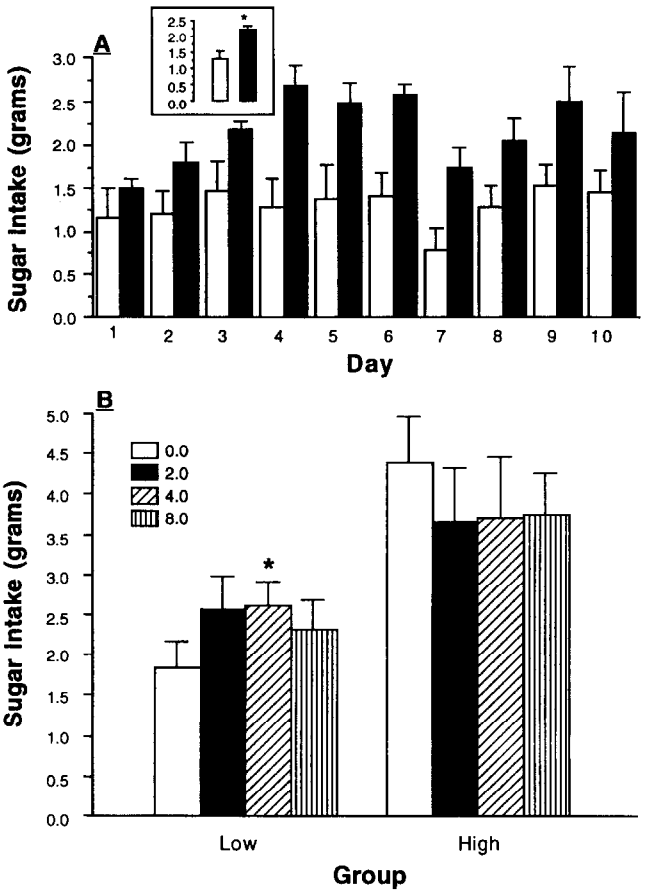

FIG. 4. (A) The average (± SEM) amount of sugar consumed by LOW (□) and HIGH (■) rats across the 7-day adaptation period. Inset: Average daily sugar intake in LOW and HIGH animals. (*$p <$ 0.05 as compared to LOW rats). (B) The average (± SEM) amount of sugar consumed by LOW and HIGH rats in response to the microinjection of amphetamine (open column—0.0 μg; filled column—2.0 μg; slanted rule column—4.0 μg; vertical rule column—8.0 μg) into the nucleus accumbens. (*$p < 0.05$ as compared to 0.0 μg amphetamine).

dose or even at a dose almost twice that used in the previous studies. The discrepancy in the results of this experiment and the previous two studies may be due to methodological differences. In the previous two studies, HIGH rats received central injections of saline in addition to systemic AMP. By necessity, rats in the previous two studies were restrained for a longer period of time than rats in the present experiment. It is possible, therefore, that animals subjected to microinjections were more stressed than animals receiving only systemic injections. The increased stress may have lead to HIGH rats exhibiting a greater sensitivity to the anorectic effect of systemically administered AMP. This notion, that restraint stress increases the susceptibility of HIGH rats to the anorectic effect of AMP, awaits further testing.

AMP affects food consumption, in part, by stimulating central DAergic systems (7,22,23,33). Heffner et al. (10) have suggested that there is an inverted-U relation between DA activity and feeding behavior. That is, there is some optimal level of DA activity for feeding, above or below which there is a decrease in feeding behavior. It has been postulated that HIGH sugar feeders are at or near this optimal level of DA activity, with LOW sugar feeders somewhere below this level (33). Increasing DA activity with low doses of AMP would be expected to produce a level of DAergic activation in LOW feeders sufficient to stimulate feeding. The same level of stimulation in HIGH feeders, on the other hand, would be expected to induce a state of DA hyperstimulation resulting in a decrease in food intake. With a higher level of DA stimulation, such as the case with moderate to high doses of AMP, it would be expected that even LOW animals would be stimulated to such a degree as to produce anorexia, as was evident in this present experiment.

Microdialysis studies have provided evidence that feeding behavior is accompanied by increased Acc-DA activity (11, 12,31). It has been suggested that intrinsic variation in Acc-DAergic function underlie the expression of individual differences in sugar consumption and responsivity to AMP treatments, such that HIGH rats express higher levels of Acc-DA activity than LOW rats (33,34). In support of this hypothesis, Sills et al. (33) reported that intra-Acc administration of the neuroleptic α-flupenthixol reduced sugar consumption in animals expressing elevated levels of sugar intake, either naturally occurring (HIGH rats) or AMP-induced (LOW rats). In the present study, microinjections of AMP into the Acc stimulated sugar consumption in LOW rats further indicating that the Acc is an important site of action for the orexigenic effect of AMP observed in LOW feeders.

The increase in sugar intake observed in LOW animals in response to intra-Acc AMP treatment is consistent with the findings that low doses of AMP stimulate the consumption of

palatable foods when microinjected into the Acc (2,5,7). Intra-Acc administration of AMP has also been found to selectively stimulate the intake of carbohydrates in animals that have been deprived of this nutrient (7). Evans and Vaccarino (7) have suggested that AMP may act to selectively stimulate the intake of foods high in carbohydrate content and that this facilitatory effect is due to increased endogenous DA transmission at Acc-DA sites. The findings reported here fit well with this interpretation.

In the present study, intra-Acc AMP administration did not significantly reduce sugar consumption in HIGH feeders. This result is in line with the observation that intra-Acc α-flupenthixol does not block the inhibitory effect of systemically administered AMP in HIGH rats (33), indicating that stimulation of Acc-DA activity is not critical to the inhibitory effect of AMP. It is likely that DAergic mechanisms in the hypothalamus, specifically in the region of the perifornical area, mediate AMP-induced anorexia (22,23). However, it must be noted that in a previous study Evans and Vaccarino (5) reported that the intra-Acc administration of 8 μg AMP (equal to the highest dose used in the present experiment) significantly inhibited food consumption. This discrepancy may be accounted for by important methodological differences in the two studies. First, Evans and Vaccarino tested animals in the dark photoperiod. Previous evidence indicates that HIGH rats are more susceptible to the anorectic effect of AMP when tested in the dark photoperiod (33). A second important difference in the two studies is that Evans and Vaccarino (7) provided the animals with a running wheel in which they could express any behavioral activating effect of AMP treatment, which would conflict with feeding. Indeed, Evans and Vaccarino (5) reported that this dose of AMP significantly stimulated running wheel activity. It is probable that the hypothalamic site mediates AMP effect on satiety per se (22,23), while the Acc site mediates AMP's effect on behavioral activation, which competes with feeding and results in decreased food consumption (5).

The findings of the present study add to the growing body of literature on individual differences in behaviors mediated by the mesolimbic DA system (3,13,15–21,28–30). For example, animals that show high novelty-induced locomotor activity show a greater locomotor response to AMP and cocaine, and more readily self-administer AMP, than animals that exhibit low novelty-induced locomotor activity (17,28). In vivo microdialysis studies have shown that rats that show high levels of AMP-induced locomotor behavior exhibit more Acc-DA activity than rats with low levels of AMP-induced locomotor behavior under both baseline conditions and in response to psychostimulant treatments (16,17,29,30). Importantly, HIGH sugar feeders also exhibit higher AMP-induced locomotor activity than LOW sugar feeders (35), consistent with the notion that HIGH animals exhibit higher levels of Acc-DA activity than LOW animals.

There is other evidence suggesting that individual differences in food intake and responsiveness to AMP treatment are associated with intrinsic differences in Acc-DA activity. Mittleman et al. (25) showed that rats with high levels of food intake elicited by electrical stimulation of the lateral hypothalamus, a procedure known to stimulate Acc-DA activity (11,12), exhibited a greater degree of sensitization to AMP and a greater degree of Acc-DA activation in response to foot shock stress than rats with low levels of food intake elicited by stimulation of the lateral hypothalamus. Mittleman et al. (25) concluded that intrinsic differences in the action of forebrain DA systems underlie individual differences in the propensity of rats to exhibit nonregulatory ingestive behaviors, such as feeding induced by electrical stimulation of the hypothalamus. The results of the present study extend this notion to include sugar consumption exhibited by rats under nondeprived, free-feeding conditions.

The baseline-dependent feeding effects reported here may relate to the principle of rate-dependency of psychomotor stimulant action as described by Robbins (32). The principle of rate dependency has been advanced to describe the inverse relation between the control (baseline) rate of responding and the effect of psychomotor stimulant treatment observed in operant paradigms. Specifically, low doses of AMP increase low rates of operant responding and decrease high rates of operant responding. This conceptualization of AMP's actions can also describe the feeding effects of low doses of AMP (33,34). The results of this study further indicate that the Acc-DA system may be the neurobiological substrate mediating AMP's rate-dependent effects. However, caution should be exercised in applying the principle of rate-dependency to the feeding effects of AMP. The rate-dependency describes the effects of AMP on the rates of responding in operant paradigms. The measure obtained in this study was that of amount of sugar ingested. It would be of interest to determine whether LOW and HIGH sugar feeders differ in their rate of sugar consumption, and whether low doses of AMP differentially affect the rate of consumption in LOW and HIGH sugar feeders.

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