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ORIGINAL INVESTIGATION

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# Self-administration of intravenous amphetamine is predicted by individual differences in sucrose feeding in rats

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**Abstract** *Rationale:* Previous studies have shown that individual differences in oral sucrose consumption are predictive of the psychomotor and dopamine (DA) stimulant properties of amphetamine in rats. *Objectives:* The present experiment was designed to examine the relationship between sucrose feeding and the reinforcing properties of amphetamine using the intravenous (i.v.) drug self-administration paradigm. *Methods:* Based on a median split of sucrose intake during a final 1-h feeding test session, male Wistar rats were designated as either low (LSF) or high sucrose feeders (HSF). Acquisition of i.v.-amphetamine self-administration across ten daily 30-min sessions was then assessed. Following acquisition, i.v. self-administration of several doses of amphetamine was similarly tested across daily 30-min sessions. *Results:* Data from this experiment revealed augmented responding in HSF compared with LSF during acquisition of amphetamine self-administration. Correspondingly, when given access to different doses of amphetamine, responding was greater in HSF than in LSF across several doses (3 µg and 10 µg per infusion). *Conclusions:* These data support the notion that individual differences in oral sucrose consumption are predictive of the reinforcing properties of psychostimulant drugs.

**Key words** Individual difference · Sucrose · Amphetamine · Self-administration · Reinforcement · Feeding

## Introduction

Over the past several decades, a wealth of converging evidence has critically implicated the mesolimbic dopamine (DA) system in mediating both the activating and reinforcing properties of addictive drugs. Indeed, several authors have proposed that these drugs act as chemical surrogates, activating a mesolimbic DA system which evolved subserving behaviours (e.g. exploration) associated with more conventional reinforcers (e.g. food) (Vaccarino et al. 1989; Koob 1992; Di Chiara 1995). Accordingly, research supports the notion that individual differences in DA-dependent behaviours associated with conventional reinforcement may be useful predictors of behavioural and neurochemical reactivity to drugs of abuse.

Recent studies in rodents have shown that individual differences in exploration of a novel environment predict the effects of abused drugs. In one of the first such studies, individuals from a random population of rats were designated as either low (LR) or high (HR) responders, based on a median split of their exploratory locomotor response during exposure to a novel environment (Piazza et al. 1989). It was shown that an acute systemic injection of amphetamine produced greater locomotor activation in HR than in LR. Other studies have confirmed the relationship between novel exploration and the psychomotor-stimulant properties of drugs of abuse, including amphetamine (Hooks et al. 1991a) and cocaine (Hooks et al. 1991b). Of particular interest for this study, Piazza and colleagues (1989) further demonstrated that when allowed to self-administer i.v. amphetamine, HR more readily acquired drug-seeking behaviour relative to LR. Additional studies suggest that these behavioural differences are associated with variability in the activation of mesolimbic DA projections that terminate within the nucleus accumbens (NAcc). For example, post-mortem tissue homogenate studies have reported that following exposure to a novel environment HR have a higher 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratio than LR (Piazza et al. 1991). In vivo microdialysis studies support these findings and show a positive relationship between response to novelty and extracellular DA release within the NAcc during both basal and psychostimulant-induced test conditions (Bradberry et al. 1991; Hooks et

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al. 1992). Thus, individual differences in novelty-induced responding are predictive of the reinforcing, psychomotor-stimulating, and mesolimbic-DA-activating effects of psychostimulant drugs.

Rats exhibit considerable individual variability in their consumption of granulated sucrose (Sills and Vaccarino 1991; DeSousa et al. 1998). A number of studies suggest that individual differences in sucrose feeding, like individual differences in novel exploration, are predictive of the behavioural and neurochemical effects of abused drugs (Vaccarino 1994). Based on a median split of sucrose intake in sucrose-habituated rats, Sills and Vaccarino (1996) categorized animals as either low (LSF) or high (HSF) sucrose feeders. Following administration of various doses of amphetamine, these researchers showed that HSF were more sensitive than LSF to the inhibitory effects of amphetamine on sucrose intake. In a study designed to examine exploratory locomotor activity, Sills and Vaccarino (1994) further showed that HSF displayed higher levels of exploratory activity than LSF following an acute injection of amphetamine. Additional research suggests a role for the mesolimbic DA system in the mediation of these effects. Specifically, results from microdialysis studies showed that HSF exhibited greater NAcc-DA release than LSF during access to sucrose and following acute treatment with amphetamine (Sills and Crawley 1996; Sills et al. 1998). Taken together, these data show that individual differences in sucrose consumption predict the feeding, psychomotor stimulant and DA-activational effects of amphetamine. However, it remains unknown whether individual differences in sucrose feeding are associated with the abuse potential of psychostimulant drugs.

The purpose of the present study was to examine the relationship between sucrose intake and the response-reinforcing properties of psychostimulant drugs. Given the literature reviewed above, it was hypothesised that psychostimulants should function as more powerful reinforcers in HSF than in LSF. This hypothesis is based on two facts. First, the novel exploration measure has shown remarkable predictive utility with regard to the self-administration of i.v. amphetamine by rodents. Second, there are obvious parallels between LR/LSF and HR/HSF with respect to their reactivity to the psychomotor and mesolimbic-DA-activating properties of psychostimulant drugs. To test the hypothesis, sucrose-habituated animals were designated as LSF or HSF based on a median split of their sucrose intake in the initial phase of this study. In the second phase, acquisition of i.v.-amphetamine self-administration was assessed under a continuous reinforcement schedule in both LSF and HSF. Given that self-administration of drugs under such a schedule of reinforcement typically yields an "inverted-U" dose–response function, it is difficult to interpret differences in response levels when only a single dose is tested (Pickens and Thompson 1968; Yokel 1987; DeSousa and Vaccarino 1998). Accordingly, in the final phase we examined responding in LSF and HSF during self-administration of several doses of amphetamine.

## Materials and methods

This research was conducted with due regard for the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care and relevant University of Toronto policy.

### Subjects

Male Wistar rats ($n$=27) purchased from Charles River, Canada, were used in this study. At the time of arrival, rats weighed 250–275 g and were housed individually in Plexiglas cages in a temperature-controlled (21±1°C) colony room maintained on a 12 h light/dark cycle (lights off at 0700 hours). Water and Purina lab pellets were freely available in the home cages except as noted.

### Surgery

Animals were treated with 0.1 ml atropine (0.6 mg/ml) and anaesthetized with sodium pentobarbital (50 mg/kg) via the intraperitoneal (i.p.) route. A chronic i.v. catheter (45 µl internal volume) was then implanted into the external jugular vein using a procedure adapted from Caine and colleagues (1993). Briefly, a catheter constructed from silastic tubing was inserted into the right jugular vein and anchored via a series of non-absorbable sutures. The portion of tubing exiting the jugular vein, constructed from polyethylene tubing, was tunnelled subcutaneously and connected to a threaded guide cannula (C313G/Spc, Plastics Products, Roanoke, Va.) resting in a dental acrylic base. This assembly, secured between the skin and fascia via polypropylene mesh, emerged from the back at the mid-scapular region. To prevent clogging and to maintain a closed system, a cap constructed from microbore tubing, heat-fused at one end, was fitted to the outer part of the catheter assembly. Following surgery, animals were given an intramuscular injection of penicillin-*G*-benzathine (100,000 units/kg) to prevent infection and allowed at least 7 days recovery. To maintain patency, catheters were flushed daily with 0.1 ml saline containing heparin (30 U/ml) to inhibit blood clotting and streptokinase (2000 U/ml) to dissolve fibrinogen, plasminogen and thrombin clots. Testing was discontinued in animals whose catheters showed evidence of blockage and/or leakage.

### Drugs

D-Amphetamine (Bureau of Drug Surveillance, Ottawa, Canada) was dissolved in sterile physiological saline (0.9% NaCl) prior to each daily testing session. Amphetamine or saline solutions were infused via the i.v. route at a volume of 20 µl during all test sessions.

### Apparatus

Self-administration testing was conducted in eight ventilated and sound-attenuating operant chambers measuring 22 $cm^3$ (Med Associates Inc., Georgia, Vt.). Within the chambers, mounted 7 cm above a steel-rod floor, were two retractable response levers measuring 4.5 cm wide. Stimulus lights were positioned 5 cm above each lever and on the opposite wall a dim house light was centred 2 cm from the top of the chamber. Each chamber was additionally outfitted with a liquid infusion assembly that was connected to an infusion pump. A single microcomputer, running Med PC software (version 2.08), was programmed to activate the infusion pump following depression of the active lever.

### Procedure

#### *Feeding phase*

Before the sucrose feeding test, animals were habituated to sucrose across seven daily sessions. During these habituation ses-

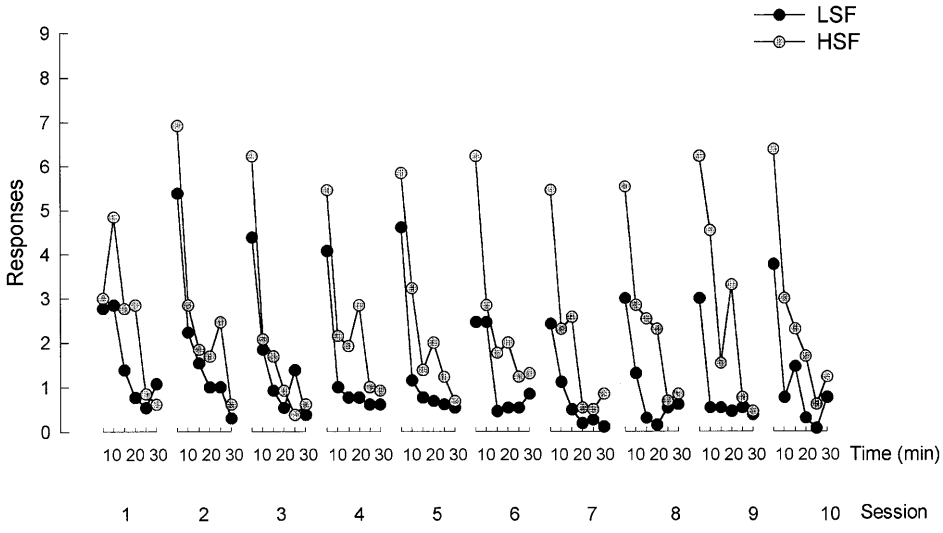


**Fig. 1** Mean intra-session (5-min time bins) active-lever response totals across ten daily i.v.-amphetamine (10 µg per infusion) self-administration acquisition sessions for low sucrose feeders (LSF) and high sucrose feeders (HSF)

sions, food pellets were removed from the home cage, and rats were presented with two stainless-steel cups (8 cm diameter by 4 cm deep), one containing granulated sucrose and the other containing powdered chow, for a period of 1 h. Between habituation sessions, food cups were removed and animals were allowed free access to fresh chow pellets. Following this habituation period, animals were implanted with i.v. catheters as described above, allowed to recover and then tested for their sucrose intake. This test session was identical to the habituation sessions with the exception that animals received an i.p. injection of saline (1 ml/kg) immediately before the presentation of the pre-weighed sucrose and chow containers. Following this test, the feeding cups were removed and re-weighed. Animals were separated into LSF and HSF on the basis of a median split of sucrose intake during this test (Sills and Vaccarino 1991).

*Acquisition of i.v.-amphetamine self-administration*

Following the feeding assay, rats were tested for acquisition of i.v.-amphetamine self-administration across ten daily 30-min sessions. At the start of each session, the house light was activated and a priming infusion of amphetamine (10 µg) was delivered. Like all subsequent infusions, this infusion was simultaneously paired with the activation of the stimulus light located above the active lever. Following the priming infusion, both levers were extended into the operant chambers. Depression of the active lever resulted in the delivery of amphetamine (10 µg/20 µl/1.16 s per infusion) on a continuous reinforcement schedule. However, active lever responses were not reinforced when they occurred during a period of drug infusion. Depression of the inactive lever had no programmed consequences. At the end of each session, both levers were retracted and the house light was turned off.

*Dose–response to i.v.-amphetamine self-administration*

Dose–response testing commenced on the day after the final-acquisition test session. In this test phase, animals were allowed to self-administer different doses of amphetamine (0, 1, 3, 30 and 100 µg per infusion) across 19 daily sessions. Following two sessions of stable responding at a specific dose, animals were allowed to self-administer a new dose determined in randomized order until all doses were tested or catheter failure occurred. Given that response levels were stable across the final two sessions of the acquisition phase, data from these sessions were used for the 10-µg per infusion test condition. All testing variables used during the dose–response phase were identical to those used during the acquisition phase, with the exception of the amphetamine dose. The total number of animals that completed testing of each individual dose was as follows: 0 µg per infusion ($n$=18); 1 µg per infusion ($n$=18); 3 µg per infusion ($n$=23); 10 µg per infusion ($n$=26); 30 µg per infusion ($n$=23); 100 µg per infusion ($n$=17).

## Results

### Feeding phase

Based on a median split of their sucrose intake levels over a 1-h test period, rats were separated into LSF ($n$=13; 2.24±0.31 g) and HSF ($n$=13; 4.80±0.38 g). Statistical analysis showed that sucrose feeding was significantly greater in HSF than LSF ($F_{1,24}$=23.78, $P$<0.0001). There were no significant differences in chow intake or body weight amongst these groups.

### Acquisition of i.v.-amphetamine self-administration

Visual inspection of Fig. 1 reveals that intra-session active-lever responding is greater in HSF than in LSF across the ten acquisition test sessions. This effect is most evident in the initial 10-min "loading phase" of each session. Further examination of the loading phase totals (data not presented) showed elevated response totals for HSF, compared with LSF, on both active and inactive levers during the initial few days of testing. However, during the final test sessions responding by HSF became most pronounced on the active amphetamine lever. Statistical analyses supported this description of the data. To reduce heterogeneity of variance, response scores were subjected to a square root transformation (Kirk 1995). A mixed three-factor analysis of variance (ANOVA; group × lever × session) was conducted to examine lever-press responding during the loading phase in both LSF and HSF. This analysis revealed significant main effects of group, $F_{1,24}$=6.11, $P$<0.05, and lever, $F_{1,24}$=10.43, $P$<0.01. Additionally, there was a significant lever × day interaction, $F_{9,216}$=2.08, $P$<0.05, and

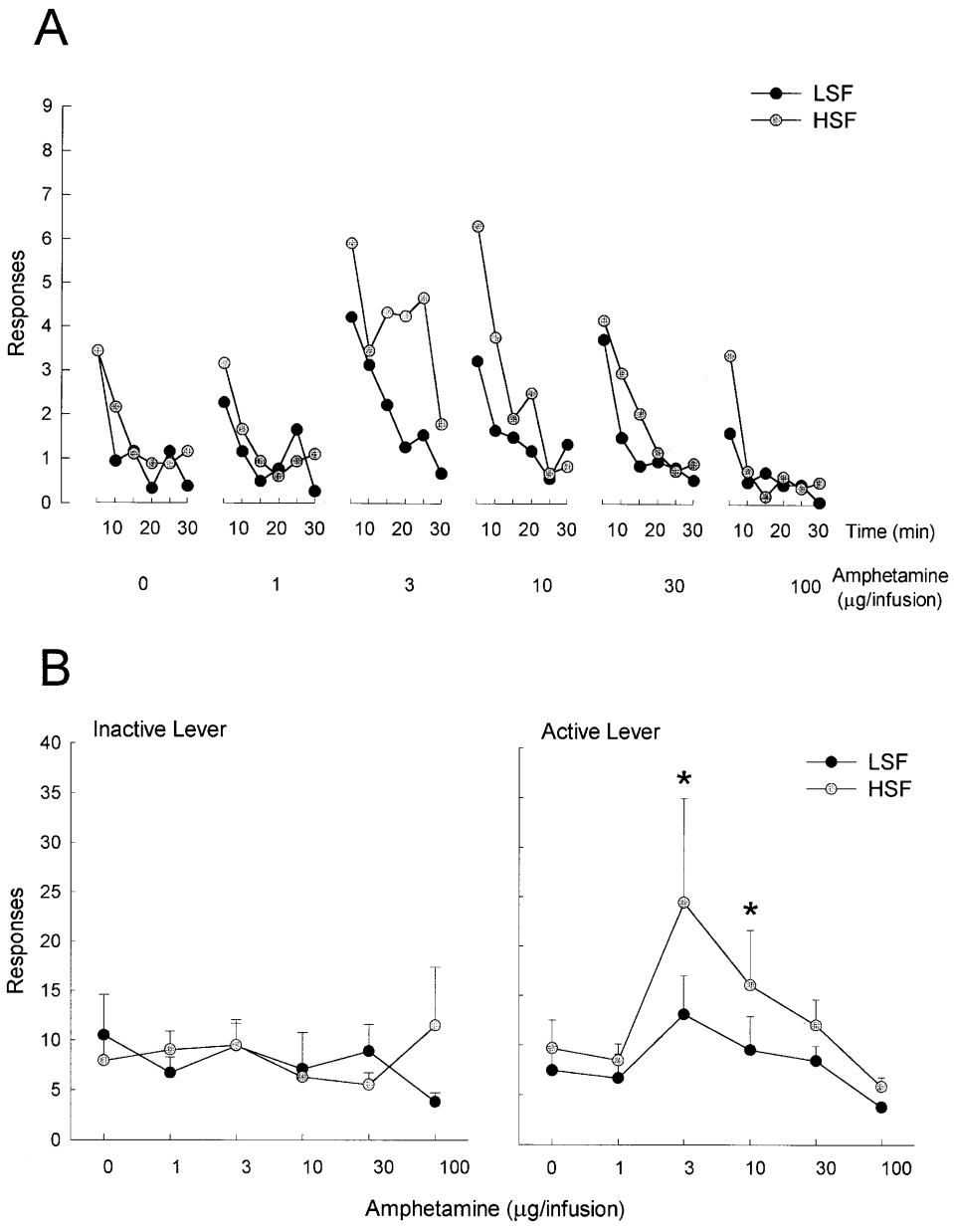


**Fig. 2** **A** Mean 2-day block intra-session (5-min time bins) active-lever response totals during i.v. self-administration of several doses of amphetamine (0, 1, 3, 10, 30 and 100 µg per infusion) for low sucrose feeders (LSF) and high sucrose feeders (HSF). **B** Mean (±SEM) 2-day-block 30-min session inactive- and active-lever response totals during i.v. self-administration of several amphetamine doses for LSF and HSF. **P*<0.05, different from LSF, *t*-test

post-hoc analyses using the Newman-Keuls test revealed that active-lever responding was significantly greater than inactive-lever responding on days 6–10 of acquisition testing ($P<0.05$). To further examine the relationship between sucrose feeding and the acquisition of i.v.-amphetamine self-administration, *t*-tests were conducted comparing LSF and HSF across days. These analyses showed that responding during the loading phase on the inactive lever was greater in HSF than LSF for sessions 1, 5 and 10 ($P<0.05$). In contrast, responding on the active amphetamine lever was higher in HSF than LSF across all test sessions ($P<0.05$), except session 8.

## Dose–response to i.v.-amphetamine self-administration

Examination of Fig. 2A indicates that intra-session active-lever responding is most pronounced for HSF during the 3-µg and 10-µg amphetamine self-administration test conditions. Figure 2B demonstrates a clear amphetamine dose–response function for HSF responding on the active lever. In comparison, LSF show only a blunted amphetamine dose–response. Results from statistical analyses are consistent with this description of the data. Again, response scores were subjected to a square root transformation prior to analyses (Kirk 1995). Due to unequal numbers of animals tested across each of the different doses, each individual dose condition was subjected to a two-factor ANOVA (group × lever) of the 2-day-block mean-response totals for active and inactive levers in LSF and HSF. These analyses revealed significant main effects of lever, showing that active-lever responding was significantly greater than inactive-lever responding for the 3-µg, $F_{1,21}=4.94$, $P<0.05$, and 10-µg, $F_{1,24}=8.38$, $P<0.01$, amphetamine test conditions. To fur-

ther analyse these results, *t*-tests were conducted comparing responding of LSF with HSF during the 3-µg and 10-µg amphetamine conditions. Results from these analyses showed significantly greater levels of active-, but not inactive-, lever responding in HSF than LSF at the 3-µg and 10-µg amphetamine dose conditions ($P<0.05$).

## Discussion

In the present study, we examined the relationship between sucrose feeding and the reinforcing properties of amphetamine using the i.v.-amphetamine self-administration paradigm. Based on a median split of their sucrose intake, animals were designated as LSF or HSF. Results showed that during acquisition of self-administration behaviour, responding for i.v. amphetamine was greater in HSF than in LSF across each of ten daily sessions. Further, in a subsequent phase, it was found that when animals were given access to different doses of i.v. amphetamine, responding on the active lever was greater in HSF than LSF across all doses tested. This effect reached statistical significance at the doses supporting the highest levels of responding (3 µg and 10 µg per infusion). Taken together, these results suggest that the reinforcing value of amphetamine may be augmented in HSF compared with LSF.

These results are supported by previous studies in which individual differences in sucrose feeding were found to predict the psychomotor response to amphetamine. For example, Sills and Vaccarino (1994) have shown that HSF demonstrate significantly greater levels of locomotor activation than LSF following acute treatment with 1.75 mg/kg, but not 1.0 mg/kg, amphetamine. Further, repeated treatment with the 1.0-mg/kg dose of amphetamine revealed greater levels of locomotor sensitisation in HSF when compared with LSF. Results from microdialysis studies suggest that these differences are mediated via the mesolimbic DA system. For example, Sills and Crawley (1996) demonstrated that acute systemic treatment with 1.75 mg/kg amphetamine resulted in significantly greater DA overflow in the terminal region of the medial-posterior NAcc in HSF than in LSF. The present self-administration data extend these findings by demonstrating that individual differences in sucrose feeding are also predictive of amphetamine's reinforcing properties. Additionally, these data are consistent with findings from studies examining the relationship between individual differences in other DA-dependent behaviours and psychostimulant drug reactivity (Piazza et al. 1989; Bradberry et al. 1991; Hooks et al. 1991a, 1991b, 1992; Piazza et al. 1991).

Glickman and Schiff (1967) proposed that a common feature of all natural reinforcers is their ability to facilitate approach-related behaviour. This facilitation was thought to be critically mediated by the medial forebrain bundle (MFB) system. More recently, a number of authors have extended this idea and suggested that the capacity of drugs of abuse to serve as positive reinforcers is intimately associated with their locomotor-activating properties (Wise and Bozarth 1987; Vaccarino et al. 1989; Vaccarino 1994, 1995). Activation of the mesolimbic DA system, a component of the MFB, is proposed as a critical element in such processes. The sucrose-feeding/self-administration data presented here fit nicely within such a framework, as do the results from the behavioural and neurochemical studies described above.

In contrast to the results reported here, a recent study has shown no relationship between acquisition of i.v.-cocaine self-administration and the voluntary intake of a solution containing the non-caloric sweetener, saccharin (Gahtan et al. 1996). Similarly, in a study examining individual differences in saccharin avidity, defined as the ratio of weight-adjusted fluid intake during availability of solutions containing both water and saccharin to intake during availability of water alone, no relationship was observed between saccharin intake and acquisition of i.v.-cocaine self-administration during a single 18-h session (Gosnell et al. 1998). Interestingly, further examination of a subgroup of animals whose self-administration levels did not approach a predetermined limit revealed evidence of an "inverted-U" relationship between saccharin avidity and i.v.-cocaine intake. However, as pointed out by these authors, conclusions drawn following the elimination of selected data points should be regarded tentatively.

The apparent discrepancy between the findings presented here and those from studies exploring the link between saccharin intake and cocaine self-administration are very likely related to a number of important methodological differences. For example, granulated sucrose feeding was assayed in the present study, whereas previous studies have measured drinking of saccharin-sweetened solutions. This raises a number of potentially important qualitative differences. First, it is unclear whether the form (solid or liquid) of the sweetener used during the assessment of individual differences is critical to the present findings. To our knowledge, no one has yet directly investigated whether results from studies measuring sucrose feeding generalize to those measuring sucrose drinking in the context of individual differences. Second, in contrast to saccharin, sucrose has nutritive value and its intake is influenced by factors regulating energy balance. This is shown by behavioural studies demonstrating differences in sucrose intake between control and sham-drinking preparations (Mook 1963; Mook et al. 1983). Third, sucrose and saccharin differ significantly with respect to taste. In humans, the hedonic properties of saccharin are rated less positively than are those of sucrose (Schiffman and Erickson 1971). Further, multidimensional scaling analyses have shown that, unlike sucrose, the taste of saccharin is associated with taste stimuli possessing "bitter" and "metallic" properties (Schiffman et al. 1979). Indeed, Dess (1993) has reviewed numerous animal studies that have delineated the aversive properties of saccharin. It is likely that nutritive and taste parameters together account for results from conditioned place-preference studies showing

that saccharin, unlike sucrose, fails to produce a place preference even at concentrations that support robust intake (White and Carr 1985; Agmo and Marroquin 1997). The latter findings indicate that saccharin does not reinforce behaviour to the same degree as sucrose. Thus, it is likely that both nutritive and taste characteristics, as well as differences in reinforcing potential, contribute to the apparent discrepancies between sucrose- and saccharin-based results.

The studies at issue also differed methodologically with respect to their self-administration components. In addition to significant procedural differences between studies, animals in the present study were assessed for self-administration of amphetamine, as opposed to cocaine. While the psychomotor-activating and reinforcing properties of amphetamine and cocaine appear to be mediated via the same mesolimbic circuitry, their rate of onset and metabolism differ. Other differences include their mechanisms of action. For example, amphetamine acts primarily by releasing stored pools of DA, while cocaine blocks the re-uptake of released DA (Carboni et al. 1989). As such, the DA-stimulating actions of amphetamine, unlike cocaine, are impulse independent. Additionally, amphetamine and cocaine have differential effects on non-DAergic transmitter systems. For example, amphetamine inhibits re-uptake of norepinephrine, while cocaine inhibits serotonin re-uptake (Taylor and Ho 1978). Not surprisingly, behavioural studies have also shown that the profile of reinforcement differs for i.v.-amphetamine and cocaine self-administration (Shannon and Risner 1984). So, it is possible that discrepant findings between the present study and previous studies are due to the use of different psychostimulants.

In summary, the present study examined the relationship between individual differences in oral sucrose intake and i.v.-amphetamine self-administration. Results indicated that responding for amphetamine was significantly greater in HSF than in LSF across ten daily acquisition sessions. Further, examination of responding for different doses of amphetamine showed that lever-pressing was significantly augmented in HSF versus LSF at doses of 3 µg and 10 µg per infusion. These data are consistent with reports that demonstrate greater sensitivity of HSF than LSF, to the psychomotor-activating and DA-releasing effects of amphetamine. More generally, these results are also consistent with studies showing that individual differences in other DA-dependent behaviours are predictive of the activational and reinforcing effects of psychostimulant drugs. The present study highlights the utility of experimental designs examining individual differences and, more importantly, has implications for future studies directed at examining the link between behaviours associated with conventional reinforcers and the acquisition and maintenance of psychostimulant drug abuse.

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## References

Agmo A, Marroquin E (1997) Role of gustatory and postingestive actions of sweeteners in the generation of positive affect as evaluated by place preference conditioning. Appetite 29:269–289

Bradberry CW, Gruen RJ, Berridge CW, Roth RH (1991) Individual differences in behavioral measures: correlations with nucleus accumbens dopamine measured by microdialysis. Pharmacol Biochem Behav 39:877–882

Caine SB, Lintz R, Koob GF (1993) Intravenous drug self-administration techniques in animals. In: Sahgal A (ed) Behavioural neuroscience: a practical approach, vol 2. Oxford University Press, Oxford, pp 117–142

Carboni E, Imperato A, Perezzani L, Di Chiara G (1989) Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in nucleus accumbens of freely moving rats. Neuroscience 28:653–661

DeSousa NJ, Vaccarino FJ (1998) Preclinincal behavioral approaches for assessing the reinforcing properties of drugs of abuse. In: Boulton AA, Baker GB, Bateson AN (eds) In vivo neuromethods (Neuromethods, vol 32). Humana Press, New Jersey, pp 227–252

DeSousa NJ, Wunderlich GR, de Cabo C, Vaccarino FJ (1998) Individual differences in sucrose intake predict behavioural reactivity in rodent models of anxiety. Pharmacol Biochem Behav 60:841–846

Dess NK (1993) Saccharin's aversive taste in rats: evidence and implications. Neurosci Biobehav Rev 17:359–372

Di Chiara G (1995) The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend 38:95–137

Gahtan E, Labounty LP, Wyvell C, Carroll ME (1996) The relationships among saccharin consumption, oral ethanol, and i.v. cocaine self-administration. Pharmacol Biochem Behav 53:919–925

Glickman SE, Schiff BB (1967) A biological theory of reinforcement. Psychol Rev 74:81–109

Gosnell BA, Krahn DD, Yracheta JM, Harasha BJ (1998) The relationship between intravenous cocaine self-administration and avidity for saccharin. Pharmacol Biochem Behav 60:229–236

Hooks MS, Jones GH, Neill DB, Justice JB Jr (1991a) Individual differences in amphetamine sensitization: dose-dependent effects. Pharmacol Biochem Behav 41:203–210

Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB Jr (1991b) Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 9:121–128

Hooks MS, Colvin AC, Juncos JL, Justice JB Jr (1992) Individual differences in basal and cocaine-stimulated extracellular dopamine in the nucleus accumbens using quantitative microdialysis. Brain Res 587:306–312

Kirk RE (1995) Experimental design: procedures for the behavioral sciences, 3rd edn. Brooks/Cole, Pacific Grove

Koob GF (1992) Neural mechanisms of drug reinforcement. In: Kalivas PW, Samson HH (eds) The neurobiology of drug and alcohol addiction, vol 654. Academic Sciences, New York, pp 171–191

Mook DG (1963) Oral and postingestional determinants of the intake of various solutions in rats with esophageal fistulas. J Comp Psychol 4:645–659

Mook DG, Culberson R, Gelbart RJ, McDonald K (1983) Oropharyngeal control of ingestion in rats: aquisition of sham-drinking patterns. Behav Neurosci 97:574–584

Piazza PV, Deminière JM, Le Moal M, Simon H (1989) Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511–1513

Piazza PV, Rogué-Pont F, Deminière JM, Kharouby M, Le Moal M, Simon H (1991) Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res 567:169–174

Pickens R, Thompson T (1968) Cocaine reinforced behaviour in rats: effects of reinforcement magnitude and fixed ratio size. J Pharmacol Exp Ther 161:122–129

Schiffman SS, Erickson RP (1971) A psychophysical model for gustatory quality. Physiol Behav 7:617–633

Schiffman SS, Reilly DA, Clark III TB (1979) Qualitative differences among sweetners. Physiol Behav 23:1–9

Shannon HE, Risner ME (1984) Comparison of behavior maintained by intravenous cocaine and d-amphetamine in dogs. J Pharmacol Exp Ther 229:422–432

Sills TL, Crawley JN (1996) Individual differences in sugar consumption predict amphetamine-induced dopamine overflow in nucleus accumbens. Eur J Pharmacol 303:177–181

Sills TL, Vaccarino FJ (1991) Facilitation and inhibition of feeding by a single dose of amphetamine: relationship to baseline intake and accumbens cholecystokinin. Psychopharmacology 105:329–334

Sills TL, Vaccarino FJ (1994) Individual differences in sugar intake predict the locomotor response to acute and repeated amphetamine administration. Psychopharmacology 116:1–8

Sills TL, Vaccarino FJ (1996) Individual differences in sugar consumption following systemic or intraccumbens administration of low doses of amphetamine in nondeprived rats. Pharmacol Biochem Behav 54:665–670

Sills TL, Onalaja AO, Crawley JN (1998) Mesolimbic dopamine mechanisms underlying individual differences in sugar consumption and amphetamine hyperlocomotion in Wistar rats. Eur J Neurosci 10:1895–1902

Taylor D, Ho BT (1978) Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. Res Commun Mol Pathol Pharmacol 21:67–75

Vaccarino FJ (1994) Nucleus accumbens dopamine-CCK interactions in psychostimulant reward and related behaviors. Neurosci Biobehav Rev 18:207–214

Vaccarino FJ (1995) CCK, addiction and anxiety. In: Bradwejn J, Vasar E (eds) Cholecystokinin and anxiety: from neuron to behavior. Springer, Berlin Heidelberg New York, pp 127–142

Vaccarino FJ, Schiff BB, Glickman SE (1989) A biological view of reinforcement. In: Klein SB, Mowrer RR (eds) Contemporary learning theories. Laurence Erlbaum, New Jersey, pp 111–142

White NM, Carr GD (1985) The conditioned place preference is affected by two independent reinforcement processes. Pharmacol Biochem Behav 23:37–42

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94:469–492

Yokel RA (1987) Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preferences. In: Bozarth MA (ed) Methods for assessing the reinforcing properties of abused drugs. Springer, Berlin Heidelberg New York, pp 1–33