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Genetic Variance Contributes to Dopamine Receptor Antagonist-Induced Inhibition of Sucrose Intake in Inbred and Outbred Mouse Strains

Cheryl T. Dym^{1,3}, Alexander Pinhas¹, Magdalena Robak¹, Anthony Sclafani^{2,3,4}, and Richard J. Bodnar^{1,3,*}

¹ Department of Psychology Queens College, The Graduate Center, City University of New York, Flushing NY 11367

² Department of Psychology Brooklyn College, The Graduate Center, City University of New York, Flushing NY 11367

³ Department of Neuropsychology and Cognition, The Graduate Center, City University of New York, Flushing NY 11367

⁴ Department of Brain and Behavior, Doctoral Sub-Programs, The Graduate Center, City University of New York, Flushing NY 11367

Abstract

Preference and intake of sucrose varies across inbred and outbred strains of mice. Pharmacological analyses revealed that the greatest sensitivity to naltrexone-induced inhibition of sucrose (10%) intake was observed in C57BL/10J and C57BL/6J strains, whereas 129P3/J, SWR/J and SJL/J strains displayed far less sensitivity to naltrexone-induced inhibition of sucrose intake. Given that dopamine D1 (SCH23390) and D2 (raclopride) receptor antagonism potently reduce sucrose intake in outbred rat and mouse strains, the present study examined the possibility of genetic variance in the dose-dependent (50–1600 nmol/kg) and time-dependent (5–120 min) effects of these antagonists upon sucrose (10%) intake in the eight inbred (BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, SJL/J, SWR/J, 129P3/J) and one outbred (CD-1) mouse strains previously tested with naltrexone. SCH23390 significantly reduced sucrose intake across all five doses in 129P3/J and SJL/J mice, across four doses in C57BL/6J and BALB/cJ mice, across three doses in DBA/2J, SWR/J, C3H/HeJ and C57BL/10J mice, but only at the two highest doses in CD-1 mice. SCH23390 was 2–3-fold more potent in inhibiting sucrose intake in 129P3/J and SJL/J mice relative to CD-1 mice. In contrast, only the highest equimolar 1600 nmol/kg dose of raclopride significantly reduced sucrose intake in the BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, SJL/J and 129P3/J, but not the SWR/J and CD-1 strains. The present and previous data demonstrate specific and differential patterns of genetic variability in inhibition of sucrose intake by dopamine and opioid antagonists, suggesting that distinct neurochemical mechanisms control sucrose intake across different mouse strains.

Keywords

Dopamine D1 receptor; Dopamine D2 receptor; SCH23390; Raclopride; Sweet Intake

*Corresponding author: Telephone: 718-997-3543; FAX: 718-997-3257; e-mail: richard.bodnar@qc.cuny.edu.

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1. Introduction

The precise role for dopamine in reward has been a consistent source of debate since the proposal of the “anhedonia hypothesis” over a quarter-century ago (e.g., 75,76), and continues unabated in recent reviews (e.g., 12,13,16,61). In place of the anhedonia hypothesis, Berridge (15,17) proposed a role for brain dopamine in ‘wanting’, that is, the attribution of incentive salience to reward-related stimuli. An alternative role for brain opioids was proposed in ‘liking’, that is, the hedonic impact of reward. Differential involvement for opioids and dopamine were found for reinforcement processes related to food and water intake (e.g., 1,2). Sucrose and saccharin intake were significantly reduced by systemic pretreatment with opioid (e.g., 3,22,38,41) and dopamine D1 and D2 (e.g., 14,46,73; but see 45,53) antagonists in rats. Using the sham-feeding procedure (74) in which ingested fluid drains out of an open gastric fistula thereby minimizing postingestive nutritive effects (69), sugar intake is also reduced following pretreatment with opioid (36,37,59) and dopamine D1 and D2 (29,62) antagonists. However, opioid and dopamine antagonists differed in their effects upon sugar-conditioned flavor preferences. Whereas the opioid antagonist, naltrexone failed to reduce sucrose-conditioned flavor preferences in sham-feeding rats (78), fructose-conditioned flavor preferences in real-feeding rats (10) or sucrose-conditioned flavor-nutrient preferences induced by intragastric sucrose (6), dopamine D1 and/or D2 receptor antagonism significantly reduced sucrose-conditioned flavor preferences in these conditioning paradigms (7,11,33,79,80).

Through the use of inbred mouse strains, genetic variation has been observed for sucrose and saccharin intake (8,9,18,21,27,34,39,40,47,52,54,58,70,72), accounting for 78% and 83% of the genetic variation associated with consumption of 0.1% saccharin and 3% sucrose, respectively (56). The genetic variation in the response to saccharin and dilute sucrose solutions is largely explained by polymorphisms in the *Tas1r3* gene that encodes for the T1R3 sweet receptor (58). In studies examining pairs of strains, C57BL/6J mice displayed greater intake of five (0.005–1 M) glucose and sucrose concentrations than 101Bag/R1 mice (70), of a 0.1% saccharin solution than DBA/2J mice (27), and of low sucrose concentrations than 129P3/J mice (8,9,65,67,68,72). Examination of 12 mouse strains across a range of nine sucrose concentrations revealed profound genetic variation in the sensitivity and magnitude of intake as well as alterations in corresponding chow intake (39). Intakes of dilute (0.1%) but not concentrated (10%) sucrose correlated with *Tas1r3* polymorphisms indicating that sweet taste sensitivity does not completely explain the consumption of calorically dense sugar solutions (34). Moreover, profound genetic variance was also observed in naltrexone’s ability to reduce intake of a 10% sucrose solution in eight inbred and one outbred mouse strains (24).

To examine potential genetic variance in the dopaminergic receptor modulation of sucrose intake, the present study tested eight inbred (BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, SJL/J, SWR/J, 129P3/J) and one outbred (CD-1) mouse strains for differences in the ability of systemic administration of D1 (SCH23390) and D2 (raclopride) dopamine receptor antagonists to dose-dependently (50–1600 nmol/kg) and time-dependently (5–120 min) decrease intake of a 10% sucrose solution.

2. Results

2.1. Strain differences in sucrose intake following vehicle baseline injections

Evaluation of sucrose intake following vehicle baseline injections revealed significant differences among strains ($F(8,88) = 8.53$, $P < 0.0001$) and for the interaction between strains and test times ($F(40,440) = 8.83$, $P < 0.0001$). The rank-order of the cumulative 2 h baseline vehicle sucrose intake among the nine strains was: SWR/J (1.7 ml), BALB/cJ (1.7 ml), 129P3/J (1.6 ml), CD1 (1.4 ml), C3H/HeJ (1.4 ml), C57BL/10J (1.3 ml), SJL/J (1.2 ml), C57BL/6J

(1.2 ml), DBA/2J (1.2 ml). Thus, to adjust for baseline differences in sucrose intake across strains, the effects of SCH23390 and raclopride across doses and times were evaluated within each strain as well as an evaluation of the percent vehicle baseline values across strains, doses and times.

2.2. Strain differences in dopamine antagonist-induced inhibition of sucrose intake

2.2.1. SCH23390 effects—Overall significant differences in sucrose intake following SCH23390 were observed among the nine mouse strains ($F(8,86)=5.54$, $P<0.0001$), among doses ($F(5,430)=115.76$, $P<0.0001$), across test times ($F(5,430)=590.04$, $P<0.0001$), and for all two-way and three-way interactions ($P<0.0001$). Figure 1 displays the marked strain-specific differences in the dose-dependent and time-dependent ability of SCH23390 to significantly reduce sucrose intake. The 129P3/J mice displayed significant reductions across all five SCH23390 doses (Figure 1I), whereas the C57BL/6J and SJL/J mice displayed significant reductions following the four highest SCH23390 doses (Figures 1C and G). The C3H/HeJ, C57BL/10J and SWR/J mice displayed significant reductions following the three highest SCH23390 doses (Figures 1B, D and H), whereas the BALB/cJ, DBA/2J and the outbred CD-1 mice displayed significant reductions following only the two highest SCH23390 doses (Figures 1A, E and F). Moreover, significant enhancements of sucrose intake occurred following the lowest SCH23390 dose in CD-1 (15–60 min, Figure 1E), DBA/2J (5–30 min, Figure 1F) and SWR/J (15 min, Figure 1H) mice.

Significant differences in percent vehicle baseline values of sucrose intake following SCH23390 were also observed among strains ($F(8,91)=2.84$, $P<0.007$), among doses ($F(4,364)=97.55$, $P<0.0001$), across times ($F(5,455)=9.41$, $P<0.0001$), and for all two-way and three-way interactions ($P<0.0001$). Table 1 summarizes the SCH23390-induced changes in sucrose intake as the percentage of baseline vehicle intake for each strain, and indicates those instances in which one strain produced greater inhibitory effects relative to another strain. To summarize some of the major differences, 129P3/J mice displayed significantly greater magnitudes of SCH23390-induced inhibition than BALB/cJ, CD-1 and SWR/J mice. SJL/J and C57BL/6J mice also displayed significantly greater magnitudes of inhibition than BALB/cJ, CD-1 and SWR/J mice, but to a lesser degree than the 129P3/J strain.

2.2.2. Raclopride effects—Overall significant differences in sucrose intake following raclopride were observed among strains ($F(8,84)=5.67$, $P<0.0001$), among doses ($F(5,420)=20.87$, $P<0.0001$), across times ($F(5,420)=699.57$, $P<0.0001$), and for all two-way and three-way interactions ($P<0.0001$), except between strains and doses ($F(40,420)=1.24$, n.s). Figure 2 displays the markedly lesser ability of raclopride to dose-dependently and time-dependently reduce sucrose intake in terms of and the magnitude of the antagonist-induced inhibition. Seven strains (inbred BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA2/J, SJL/J, 129P3/J: Figures 2A–D,F,I) displayed raclopride-induced reductions in sucrose intake only at the highest 1600 nmol/kg dose, and two strains (inbred SWR/J and outbred CD-1: Figures 2E and H) failed to display any raclopride-induced reductions in sucrose intake. Indeed, raclopride significantly increased sucrose intake in DBA/2J mice following the 50 (15–90 min) and 400 (5–30 min) nmol/kg doses (Figure 2F), in C3H/HeJ mice following the 50 (60–90 min) nmol/kg dose (Figure 2B), in SWR/J mice following the 400 (60–120 min) nmol/kg dose (Figure 2H), and in outbred CD-1 mice following the 200 (15–120 min) nmol/kg dose (Figure 2E). Analysis of the percent of vehicle baseline values of sucrose intake following raclopride also failed to show any genetic variability (data not shown).

2.3. Strain differences in the ID₅₀ of SCH23390-induced inhibition of sucrose intake

Table 2 summarizes the ID₅₀ values for the ability of SCH23390 to inhibit sucrose intake across the 120 min time course. The 129P3/J mice consistently displayed the lowest ID₅₀ values across

the first 90 min of the 2 h time course, and displayed 2–3.5-fold greater potency in SCH23390-induced inhibition of sucrose intake relative to CD-1 mice in the first hour after drug administration. In further agreement with the strain differences in SCH23390-induced inhibition in the percent of baseline sucrose intake, the SJL/J strain displayed the second highest degree of potency in inhibition of sucrose intake during the first 60 min of the time course.

2.4. Heritability estimates of SCH23390- and raclopride-induced inhibition of sucrose intake

Table 3 summarizes the narrow-sense heritability estimates for the five effective SCH23390 and one effective raclopride dose at each time point using the percent of vehicle baseline sucrose intake. Whereas moderate ($h^2 = 0.40\text{--}0.52$) heritability estimates were obtained for baseline vehicle sucrose intake across the first 30 min of the time course (data not shown), relatively meager heritability estimates were typically obtained across the time course for the different effective SCH23390 ($h^2 = 0.05\text{--}0.32$) and raclopride ($h^2 = 0.10\text{--}0.22$) doses across test times.

2.5. Sucrose intake and T1R3 sweet taste receptor status

Four inbred mouse strains (C57BL/6J, C57BL/10J, SJL/J, SWR/J) had the sweet-sensitive form of the T1R3 receptor while four strains (BALB/CJ, C3H/HeJ, DBA/2J, 129P3/J) had the sweet-sub-sensitive form of the receptor (58). Evaluation of the percent vehicle sucrose intake scores at 30 min only revealed significant differences ($F(1,78) = 6.61$, $P < 0.012$) between sensitive (25.3%) and sub-sensitive (12.3%) taster strains following the 1600 nmol/kg dose of SCH23390. Differences between sensitive (90.8%) and sub-sensitive (71%) taster strains in inhibition of sucrose intake following the 200 nmol/kg dose of SCH23390 approached, but did not achieve significance ($F = 3.24$, $P = 0.076$). Differences between the two groups in inhibition of sucrose intake failed to occur following the 50 ($F = 0.28$, ns; sensitive: 111%; sub-sensitive: 104%), 400 ($F = 0.13$, ns; sensitive: 61%; sub-sensitive: 64%) and 800 ($F = 1.81$, ns; sensitive: 46.7%; sub-sensitive: 34.3%) nmol/kg doses of SCH23390, and the 1600 nmol/kg dose of raclopride ($F = 0.46$, ns; sensitive: 82.1%; sub-sensitive: 75%). Thus, the sweet-sensitive strains show less suppression in sucrose intake following the highest SCH23390 dose than sweet-sub-sensitive strains.

3. Discussion

Marked murine strain differences were observed in the magnitude, time course and potency of the dopamine D1 (SCH23390), but not the D2 (raclopride), receptor antagonists to inhibit intake of a 10% sucrose solution. Whereas SCH23390 produced a heterogeneous response pattern as a function of mouse strain that differed across time course, magnitude and dose, raclopride's ability to reduce sucrose intake across strains was largely limited to effects following the 1600 nmol/kg dose for the BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, SJL/J and 129P3/J, but not for the inbred SWR/J and outbred CD-1 strains. Further, heritability estimates in the ability of particular strains to display raclopride-induced inhibition of sucrose intake at the highest dose tended to be quite low ($h^2 = 0.10\text{--}0.22$). Finally, strains that possessed the sweet-sensitive (C57BL/6J, C57BL/10J, SJL/J, SWR/J) and the sweet-sub-sensitive (BALB/CJ, C3H/HeJ, DBA/2J, 129P3/J) form of the T1R3 receptor (58) failed to differ in the degree of inhibition of sucrose intake following the highest dose of raclopride. These antagonist effects are in agreement with previously-observed significant dopamine antagonist-induced reductions in sucrose intake in sham-feeding rats (29,33,62,63,79,80) and in rat pups in independent ingestion tests (73), as well as in fructose intake in real-feeding rats (11). The present study also indicated that low and moderate doses of raclopride significantly increased sucrose intake in some mouse strains (C3H/HeJ, DBA/2J, SWR/J, and CD-1). These latter antagonist-induced facilitatory effects upon sucrose intake have also been observed previously in rats (45,46,53). Thus, these data thereby suggest that raclopride is quite

ineffective in reducing sucrose intake in mice, and that any interpretation regarding genetic variability in D2 antagonist-induced suppression of sucrose intake is limited by the overall ineffectiveness of this response.

In contrast, genetic variability in SCH23390-induced inhibition of sucrose intake was clearly demonstrated in two independent measures in the present study: magnitude of effect, and sensitivity to lower doses of the antagonist. SCH23390 significantly reduced sucrose intake across all five doses (50–1600 nmol/kg) in 129P3/J and SJL/J mice, across four doses (200–1600 nmol/kg) in C57BL/6J and BALB/cJ mice, across three doses (400–1600 nmol/kg) in SWR/J, C3H/HeJ and C57BL/10J mice, across three different doses (200, 800, 1600 nmol/kg) in DBA/2J mice, but only at the two highest doses (800, 1600 nmol/kg) in CD-1 mice. A similar pattern of SCH23390-induced inhibitory actions were observed in assessing antagonist ID₅₀ potency across strains with the 129P3/J and SJL/J inbred strains showing the greatest sensitivity consistently across the time course. A 2–3-fold difference was observed between the most (129P3/J) and least (CD-1) sensitive strains in the first hour following SCH23390 treatment. The strain-specific inhibition of SCH23390 sometimes occurred at different doses and time point measurement intervals of the drug. It is unclear from the present data as to whether different and distinct multiple genetic mechanisms are responsible for individual SCH23390 dose and time effects, or whether a single genetic mechanism explains all effects. Interestingly, however, there also appeared to be some degree of genetic variance in SCH23390-induced inhibition of sucrose intake in evaluating strains with the sweet-sensitive (C57BL/6J, C57BL/10J, SJL/J, SWR/J) and the sweet-sub-sensitive (BALB/cJ, C3H/HeJ, DBA/2J, 129P3/J) form of the T1R3 receptor (58) with significant differences following the 1600 nmol/kg dose for the sensitive (25.3%) and sub-sensitive (12.3%) taster strains, and approaching significance following the 200 nmol/kg dose for the sensitive (90.8%) and sub-sensitive (71%) taster strains. Thus, the sweet-sensitive strains appear to display less suppression in sucrose intake following SCH23390 than sweet-sub-sensitive strains; potential implications of these results will be discussed subsequently. Whereas a number of these previous criteria appear to support genetic variance of the percent of vehicle intake in SCH23390-induced inhibition of sucrose intake, narrow-sense heritability estimates as a measure of genetic variance were quite meager ($h^2 = 0.05–0.32$) across each of the time points and each of the SCH23390 doses that produced significant inhibition of sucrose intake. A previous study (24) examining opioid inhibition of sucrose intake indicated more consistent heritability estimates for effective naltrexone doses to produce genetic variance in the inhibition of sucrose intake ($h^2 = 0.38–0.51$). Thus, whereas measures of magnitude of effect, potency of effect and sensitive vs. sub-sensitive strains revealed genetic variance in SCH23390-induced inhibition of sucrose intake, this interpretation should be tempered by the meager heritability data.

It is possible that these strain-specific effects of SCH23390 could be due to other factors such as pharmacokinetic actions, actions at sites outside of the central nervous system, or actions upon activity or motor behavior. Although pharmacodynamic effects of SCH23390 acting at the D1 receptor were initially reported in rat studies (e.g., 19,31,57,64), the strain-specific effects of SCH23390 could alternatively be due to pharmacokinetics with SCH23390 acting as a poor D1 antagonist in some murine strains and a strong D1 antagonist in others. For instance, SCH23390 binding is significantly reduced in homozygous mice for the recessive gene weaver (55, but see 50), dopamine D(1A) receptor knockout mice (43,44), and diabetic mice (60), but is increased in Purkinje Cell Degeneration mutant mice (23). In contrast, SCH23390 binding is unchanged in hypoxic mice (5), MPTP-treated mice (4), methamphetamine-treated mice (77), 6-hydroxydopamine and iron-deficient mice (81), mu-opioid receptor knock-out mice (71), and cannabinoid CB1 receptor knockout mice (32). In assessing whether inbred strains display similar or different SCH23390 binding characteristics, although restraint stress increased D1 receptor density in the nucleus accumbens of DBA/2 mice, while it reduced D1 receptor density in the striatum of C57BL/6 mice (20), no differences

were observed in mesocorticolimbic and striatal SCH23390 binding in normal DBA/2 and C57BL/6 mice (25). BALB/c and DBA/1 mice made aggressive by clonidine treatment displayed reduced SCH23390 binding in the limbic forebrain, an effect not observed in clonidine-treated C57BL/6J mice (48). Kanos and co-workers (35) did perhaps the most extensive strain survey in examining D1 receptor binding with [3H]SCH23390, using eight strains of which four (BALB/c, C3H/He, C57BL/6 and DBA/2) were evaluated in the present study. Although they failed to find any strain differences in [3H]SCH23390 uptake into the caudate or cerebellum, BALB/cJ mice displayed higher [3H]SCH23390 binding in the nucleus accumbens (19%), lateral caudate-putamen (15%) and substantia nigra, pars reticulata (27%) than C57BL/6 mice with DBA/2 and C3H/He mice intermediate to the other strains. C3H/He mice displayed higher [3H]SCH23390 binding in the dorsal caudate-putamen (23%) than C57BL/6 mice with DBA/2 and BALB/c mice intermediate to the other strains. Our behavioral data indicated that C57BL/6J and C3H/HeJ inbred strains showed moderate sensitivity, and BALB/cJ and DBA/2J inbred strains showed lesser sensitivity to SCH23390-inhibition of sucrose intake. [3H]SCH23390 binding data on strains (e.g., 129P3/J and SJL/J) highly sensitive to SCH23390-induced inhibition of sucrose intake are not available, so it may be premature to describe these effects as D1-receptor specific, but more appropriately to ascribe these effects as SCH23390-sensitive or -subsensitive. A second caveat is that both D1 and D2 antagonists were administered subcutaneously, and any systemic effects, particularly for SCH23390, could be due to D1 receptor blockade in relevant sites outside of the central nervous system. Relevant candidate sites displaying D1 receptor binding as measured by SCH23390 include gastric (30,49) and intestinal (26,42) areas. Further studies using ventricular or intracerebral administration of D1 antagonists are needed to confirm whether central sites of action are involved. A third and final caveat is to determine whether the genetic variance in SCH23390-induced inhibition of sucrose intake is an epiphenomenon of a generalized effect on activity and/or motor behavior. Although this factor was not directly studied in this paradigm, it is important to note that the same animals in each strain were assessed for both SCH23390-induced and raclopride-induced inhibition of sucrose intake using equimolar concentrations of each drug. Whereas D1 antagonism produced both strain-specific and dose-dependent reductions in sucrose intake, raclopride only produced reductions at the highest dose. Yet D1 antagonism with SCH23390 and D2 antagonism with related antagonists to raclopride produced equal reductions in hyperlocomotion induced by caffeine, cocaine and amphetamine (28,51), albeit at doses higher than those employed in the present study. Therefore, it does not appear that deficits in motor activity produced the differential strain-specific and dose-dependent reductions in sucrose intake induced by SCH23390.

Genetic variability has also been previously observed in the ability of the opioid antagonist naltrexone to suppress sucrose intake (24). Sucrose intake of SWR/J mice failed to decrease significantly following a wide range (0.01–5 mg/kg) of naltrexone doses. Naltrexone's maximal magnitude of inhibitory effects was small (35–40%, (ID_{50} = 7.5–10 mg/kg at 60 min)) in 129P3/J and SJL/J mice, moderate (~50%) in BALB/cJ, C3H/HeJ, CD-1 and DBA/2J mice, and profound (70–80%, (ID_{50} = 0.5–1.5 mg/kg at 60 min)) in C57BL/6J and C57BL/10J mice. Thus, there was a marked 37-fold difference across strains in naltrexone's effectiveness to reduce sucrose intake (24) which compares with the much smaller 2–3 fold difference observed with SCH23390 in the present study. To directly assess the relationship between the respective abilities of naltrexone and SCH23390 to inhibit sucrose intake, we derived the ID_{50} value of each antagonist for each of the nine common strains tested, and the correlation between the ID_{50} values for each antagonist across the nine strains was calculated. There was a weak, negative correlation between the ID_{50} of naltrexone and SCH23390 to inhibit sucrose intake 30 min following drug administration (r = -0.32; r^2 = 0.11, ns). This particular data point produced the most consistent inhibition across drugs, doses and times. Figure 3 illustrates differences in each drug's effects in the various strains. For instance, whereas the 129P3/J and SJL/J were among the least responsive strains to naltrexone, they were among the most

responsive strains to SCH23390. In contrast, the C57BL/10J and C57BL/6J strains were the most responsive strains to naltrexone, but were only moderately sensitive to SCH23390. The dichotomy between dopaminergic (SCH23390) and opioid (naltrexone) antagonist modulation of sucrose intake has been observed in other paradigms. Thus, although significant reductions in sucrose and saccharin intake have been observed in sham-feeding and real-feeding rats following dopamine (SCH23390: e.g., 14,29,46,62,63,73) and opioid (naltrexone: e.g., 3,22, 36–38,41,59) antagonists, these antagonists have different effects on the hedonic response to sweet taste (13,17) and flavor conditioning effects of sugars (6,7,10,11,33,78–80).

Berridge's (15,17) proposed involvement of brain dopamine in food 'wanting' and brain opioid systems in food hedonics ('liking') provides one widely-discussed framework to explain the differential effects of dopamine and opioid drugs on food-motivated behavior and reward in general. Whereas dopamine and especially D1 receptor antagonism decreases sucrose intake in rats (e.g., 13,17) and indeed all mouse strains tested in the present study, the magnitude and potency of the effects were strain-specific. Dopamine D1 antagonism is also particularly effective in blocking the acquisition of flavor-nutrient conditioning of simple carbohydrates (7), the acquisition of flavor-flavor conditioning of sucrose in sham-feeding rats (80) and of fructose in real-feeding rats (11), as well as the expression of flavor-flavor conditioning (11, 79,80). All of these studies implicate the D1 dopamine receptor in reward mediated by simple carbohydrates. The mechanism by which this mediation of reward acts is still unclear. The present and previous (24) study demonstrating differences in the pattern and effectiveness of dopaminergic and opioid antagonism of sucrose intake across different inbred mouse strains may provide yet another form of converging evidence for separation of these two pharmacological systems, although our knowledge of the ability of a wide variety of mouse strains to display these specific attributes of food seeking is presently limited to the eight inbred strains evaluated. Other studies of the 129P3/J and C57BL/6J inbred strains provide some intriguing information relevant to this issue. These two strains differ in their sweet taste sensitivity with C57BL/6J mice possessing the sweet-sensitive form of the Tas1R3 receptor, and 129P3/J possessing the sweet-sub-sensitive form of the receptor (58). Consistent with this finding, 129P3/J mice underconsumed a variety of natural and artificial sweeteners compared to C57BL/6J mice (9,58). However, after experience with concentrated sugar solutions, the difference in the sucrose preferences of the two strains disappeared, an effect attributed to the postingestive conditioning actions of the sugar (66). Indeed 129P3/J mice showed a flavor conditioning response to intragastric sucrose infusions that was as strong, if not more so, as that displayed by C57BL/6J mice when the sweetness of the cue flavors were equated for the two strains (68). Furthermore, sucrose-experienced 129P3/J mice licked more on a progressive ratio schedule for sucrose rewards than did C57BL/6J mice (65). The respective strong and weak sensitivity of 129P3/J mice to SCH23390- and naltrexone-induced inhibition of sucrose intake may reflect their greater reliance on the postingestive conditioning of sweet rewards than the activity of their subsensitive sweet taste receptors. Supporting this interpretation are the findings that SCH23390, but not naltrexone, blocks the postingestive conditioning actions of sugars (6,7). Further limited support for this concept is the present finding that the highest dose of SCH23390 produced significantly greater inhibition of sucrose in the sweet-sub-sensitive strains (BALB/cJ, C3H/HeJ, DBA/2J, 129P3/J) relative to the sweet-sensitive strains (C57BL/6J, C57BL/10J, SJL/J, SWR/J), and is consistent with Berridge's proposals (15,17) that brain dopamine may be less involved in 'liking' relative to 'wanting'. Therefore, such data suggest that inbred genetic differences among mouse strains may provide a viable model for differentiating among the multiple processes involved in food reward.

4. Experimental Procedure

4.1. Subjects

Outbred (CD-1, Charles River Laboratories, Wilmington, MA; $n = 11$) and eight strains of inbred BALB/cJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, SJL/J, SWR/J and 129P3/J (The Jackson Laboratory, Bar Harbor, ME) male mice (6 weeks of age) were initially acclimated to the Queens College vivarium for 1 week in group (5 per cage) housing. Ten to twelve mice of each inbred strain completed testing; variability was due to isolated deaths of animals due to unrelated factors. The animals were then housed individually in plastic cages ($30 \times 20 \times 15$ cm) with stainless steel tops throughout the entire study, and maintained on a 12 h light/12 h dark cycle (lights off at 2000 h) at a constant temperature of 22°C. All animals were provided with chow (Lab Diet Mouse Chow 5015) and water *ad libitum* throughout the experiment, except when experimental testing was conducted.

4.2. Testing apparatus

Accurate measurement (± 0.2 ml gradations) of the sucrose solution was insured by using a retrofitted testing sipper tube consisting of a leur slip tip syringe (10 ml, 0.2 ml gradations, Pharmaseal Laboratories, Glendale, CA), silicone sealant (All-Glass Aquarium Co., Inc., Franklin, WI), a rubber stopper and a straight sipper tube (63 mm in length, 8 mm in width, Lab Products, Seaford, DE) (e.g., 24). The apparatus was created by drilling a hole into the top of the syringe, inserting the stopper and sipper tube into the hole, and securing them with the sealant that also prevented leaking. The sucrose sipper tube was firmly secured to the stainless steel top of the cage by a taut metal spring (100 mm) with clips at each end that affixed to the cage top so that the gradations and meniscus were easily visible.

4.3. Sucrose intake procedure

All procedures were approved by the Queens College Institutional Animal Care and Use Committee. At the start of the testing procedure at approximately 3–7 h into the light cycle, chow and water were removed from the cage, and each animal was given access to approximately 8 ml of 10% sucrose in the sipper tube for 2 h. Sucrose intake was measured by reading the meniscus of the sucrose solutions along the gradations after 5, 15, 30, 60, 90, and 120 min, whereupon the sipper tube was removed and food and water were returned. Each animal was exposed to one sucrose session per day until a criterion minimum of 1 ml was consumed over three consecutive exposures; this criterion was employed to avoid “floor effects” of antagonist treatment. Three to five sessions were needed to reach this criterion in tests conducted approximately three times each week. All mice in all strains met the above criteria, and thereupon underwent testing. Following this initial baseline treatment, the mice received a subcutaneous (sc) vehicle (0.3 ml distilled water/30 g body weight) injection, and 30 min thereafter, sucrose intake was measured over 2 hr. Following determination that each mouse met the minimal 1 ml criterion sucrose intake following vehicle treatment, 2-hr sucrose intakes were measured 30-min after sc injection of the D1 (SCH23390) and D2 (raclopride) dopamine receptor antagonists (Sigma Chemical Co., St Louis, MO) at doses of 50, 200, 400, 800 and 1600 nmol/kg. The drugs were mixed at concentrations of 5, 20, 40, 80 and 160 nmol/ml and administered at 10 ml/kg with a minimum 72 h interval between doses. This dose range and post-injection interval were chosen on the basis of significant effects observed in rats (7, 11, 79, 80). Subgroups of animals of each strain, matched for vehicle sucrose intake, received an ascending series of SCH23390 doses followed by a descending series of raclopride doses, a descending series of SCH23390 doses followed by an ascending series of raclopride doses, an ascending series of raclopride doses followed by a descending series of SCH23390 doses, and a descending series of raclopride doses followed by an ascending series of SCH23390 doses. Orders of drug or specific dose presentation failed to produce any significant effects, insuring lack of order or carry-over effects. Following all dopamine antagonist treatments,

sucrose intake was reassessed following a second vehicle injection. Analyses of sucrose intake under baseline and the two vehicle treatments failed to reveal any differences, and therefore, these data were pooled as a representative baseline treatment for each strain. Sample size differences among strains reflected unrelated deaths of individual animals.

4.4. Statistics

Because there were no significant differences in sucrose intake following the baseline and the two vehicle injections, a pooled vehicle score comprising these sessions was assessed for each time point for each animal in each strain. The first types of analyses assessed drug-induced changes in cumulative sucrose intake across strains using two three-way randomized block analyses of variance with the nine strains as a between-subjects variable, the pooled vehicle and five SCH23390 or raclopride doses as one within-subject variable, and the six test times as the second within-subject variable. Bonferroni comparisons ($P < 0.05$) evaluated significant drug effects within groups in this and subsequent analyses. The second types of analyses evaluated individual strain-specific effects of SCH23390 or raclopride across the six dose conditions and six test times upon cumulative sucrose intake using two-way repeated-measures analyses of variance. Because the mouse strains differed in their 2 hr baseline sucrose intakes, the third types of analyses evaluated between-strain differences by transforming the intakes following drug treatments into percent intakes ($\text{intake}/\text{baseline intake} \times 100$), and performing three-way randomized-block analyses of variance with the nine strains as a between-subjects variable, the five SCH23390 or raclopride doses as one within-subject variable and the six test times as the second within-subject variable. The fourth type of analyses examined strain-specific differences in the potency of SCH23390 that produced significant dose-dependent inhibitory effects such that post-drug intake difference scores were calculated by subtracting sucrose intake following each SCH23390 dose condition from pooled baseline intake for each animal in each strain. Then linear regression analyses were performed for each time point for each strain with the SCH23390 dose as the independent variable and the difference scores for each mouse in each strain as the dependent variable to determine the dose that would inhibit sucrose intake by 50% (ID_{50}). A sensitivity ratio reflecting the potency fold shift of SCH23390-induced inhibition of sucrose intake (ID_{50}) was calculated by obtaining the quotient between the least sensitive strain at each time point relative to the most sensitive strain. The fifth type of analyses examined potential differences in narrow-sense trait heritability between strains for those drug doses (all SCH23390 doses and the highest raclopride dose) that previously produced significant inhibitory effects. A better variable for estimating heritability of drug effects would be relative sucrose intake (% of baseline) because of baseline differences in sucrose intake across strains. Heritability was determined by comparing the between-strain sum of squares to the total sum of squares for each percent vehicle baseline score for the five effective doses of SCH23390 and the high effective dose of raclopride at each time point after drug administration. Because animals are isogenic (i.e., genetically identical) within individual inbred strains, between-strain variance (measured by the sum of squares between-subjects score) provides a measure of additive genetic ('allelic') variation (VA), whereas within-strain variance ('error variance', measured by the sum of squares error score) represents environmental variability (VE). Thus, using all eight inbred strains, an estimate of narrow-sense heritability (h^2) for each trait was obtained using the formula: $h^2 = VA/(VA+VE)$. Finally, a sixth type of analysis assessed whether differences in the magnitude of dopamine D1 and D2 receptor antagonist inhibition varied as a function of strains that possessed the sweet-sensitive form of the Tas1R3 receptor (C57BL/6J, C57BL/10J, SJL/J, SWR/J) relative to the sweet-sub-sensitive form (BALB/cJ, C3H/HeJ, DBA/2J, 129P3/J) (58). Two-way analyses of variance were performed on the percentage of vehicle baseline intake score at 30 min for the five doses of SCH23390 and the high dose of raclopride, all of which displayed significant inhibition of sucrose intake. The 30 min intake point was chosen because overall baseline intakes of the sweet-sensitive and sweet-sub-sensitive strains were equal at this interval.

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Figure 1.

Alterations (mean, $\pm$ SEM) in sucrose intake following the five doses of the D1 dopamine receptor antagonist, SCH23390 in nine mouse strains. Individual analyses of variance for each strain revealed significant main dose effects and interactions between doses and times for all of the nine strains. Significant ($p < 0.05$) increases (#) and decreases (*) in sucrose intake following specific drug doses relative to corresponding vehicle intake are denoted.

Figure 2.

Alterations (mean, $\pm$ SEM) in sucrose intake following the five doses of the D2 dopamine receptor antagonist, raclopride in nine mouse strains. Significant ($p < 0.05$) increases (#) and decreases (*) in sucrose intake following specific drug doses relative to corresponding vehicle intake are denoted.

Figure 3. Scatterplot and best-fit regression line of ID₅₀ of naltrexone-induced inhibition (24) and SCH23390-induced inhibition of sucrose intake after 30 min across nine mouse strains. A weak, negative and non-significant correlation between the ID₅₀ of naltrexone and SCH23390 to inhibit sucrose intake 30 min following drug administration ($r = -0.32$; $r^2 = 0.11$, ns) was observed.

TABLE 1

SCH23390 inhibition of sucrose (10%) intake across strains, doses and test times as a measure of percent of vehicle baseline intake.

Strain	5 min	15 min	30 min	60 min	90 min	120 min
A: SCH 50 nmol/kg						
BALB/cJ	167% ^{a,b,c,g,h}	160% ^{a,b,h}	129%	110%	108%	94%
C3H/HeJ	80% ^e	100% ^e	88% ^e	90%	100%	86%
C57BL/6J	125% ^d	100%	100%	100%	91%	83%
C57BL/10J	133%	140%	100%	113%	91%	85%
CD-1	180% ^{a,b,c,g,h}	186% ^{a,b,c,h}	167% ^{a,b,c,h}	145% ^{a,b}	131%	129%
DBA/2J	160% ^{a,b,c,f,g}	180% ^{abch}	183% ^{a,b,c,h}	138% ^{a,b,c}	130%	117%
SIL/J	120%	75%	78%	80%	73%	100%
SWR/J	150% ^h	163% ^{a,b}	140% ^a	125% ^{a,b}	107%	106%
129P3/J	100%	89%	80%	67%	64%	63%
B: SCH 200 nmol/kg						
BALB/cJ	133% ^{a,b,c,e,g}	100% ^{a,b,e,h}	86%	80%	85%	76%
C3H/HeJ	60%	57%	63%	70%	109% ^{a,e}	114% ^{a,d,e}
C57BL/6J	75% ^a	71%	67%	70%	73%	75%
C57BL/10J	100%	120% ^{a,b,c,e,h}	100% ^{a,b,c,e,h}	100%	100%	92%
CD-1	140% ^{a,b,c,e,g,h}	143% ^{a,b,e,h}	111% ^{a,b,c,e,h}	100%	108%	129%
DBA/2J	40%	60%	67%	50%	60%	58%
SIL/J	60%	50%	44%	80%	91%	100%
SWR/J	117% ^{a,b,c,e,g}	113% ^{a,b,h}	90%	92% ^e	113% ^{a,e}	112% ^a
129P3/J	71%	56%	60%	58%	64%	75%
C: SCH 400 nmol/kg						
BALB/cJ	67% ^b	80% ^{a,b,f}	71%	70%	77%	76%
C3H/HeJ	60% ^b	57%	50%	50%	73%	79%
C57BL/6J	75%	57%	56%	60%	73%	75%
C57BL/10J	67% ^b	60%	57%	63%	64%	69%
CD-1	80% ^b	71% ^{a,b}	78%	73%	85%	100%
DBA/2J	60% ^b	80% ^b	67%	88%	90%	92%

Strain	5 min	15 min	30 min	60 min	90 min	120 min
SJL/J	40%	38%	33%	50%	64%	83%
SWR/J	50%	38%	40%	50%	67%	82%
129P3/J	43%	44%	40%	50%	50%	69%
D: SCH 800 nmol/kg						
BALB/cJ	33%	40%	29%	50%	62%	65%
C3H/HeJ	40%	29%	38%	30%	55%	79% ^e
C57BL/6J	25%	29%	22%	30%	45%	50%
C57BL/10J	33%	20%	29%	38%	55%	54%
CD-1	40%	29%	22%	36%	31%	64%
DBA/2J	20%	20%	17%	25%	40%	42%
SJL/J	40%	38%	33%	40%	55%	67%
SWR/J	50%	38%	40%	50% ^{a,c,e}	80% ^{e,i}	94% ^{c,e}
129P3/J	29%	22%	20%	25%	43%	56%
E: SCH 1600 nmol/kg						
BALB/cJ	0%	0%	0%	10%	23%	18%
C3H/HeJ	20%	14%	25%	20%	36%	43%
C57BL/6J	25%	14%	11%	10%	45% ^{a,d,e}	50% ^e
C57BL/10J	0%	20%	14%	38% ^e	36%	38%
CD-1	40% ^{a,b,c,d,e,f,g,h}	43% ^{a,c,d,e,f,g,h}	33% ^{ac,d,e,g}	36% ^e	38%	50% ^e
DBA/2J	0%	0%	0%	0%	10%	17%
SJL/J	20%	25%	22%	20%	36%	67% ^{a,e}
SWR/J	17%	13%	20%	25%	33%	47%
129P3/J	14%	11%	10%	8%	21%	31%

NOTE: Significantly ($p < .05$) less % Vehicle inhibition than

^a 129P3/J,

^b SJL/J,

^c C57BL/6J,

^d BALB/cJ,

^e DBA/2J,

$f_{\text{SWR/1}}$,
 $^8\text{C57BL/10J}$,
 $h_{\text{C3H/HeJ}}$ or
 i_{CD1}

Linear regression values (ID₅₀) of SCH23390-induced inhibition (nmol/kg) of sucrose intake among the inbred and outbred mouse strains across the 120 min time course.

TABLE 2

Strain	Linear Regression ID ₅₀							
	5 min	15 min	30 min	60 min	90 min	120 min		
BALB/cJ	967	987	642	890	875	1165		
C3H/HeJ	628	733	622	763	1010	1465		
C57BL/6J	672	566	649	694	1478	1629		
C57BL/10J	830	888	735	998	1637	1288		
CD-1	1249	1183	1043	1059	1037	1300		
DBA/2J	713	896	751	681	814	1014		
SJL/J	521	493	414	729	945	1873		
SWR/J	1010	819	797	964	1604	1567		
129P3/J	505	410	321	513	650	1072		
Sensitivity Ratio	2.5 ^a	2.9 ^a	3.2 ^a	2.1 ^a	2.5 ^b	1.8 ^c		

Note: The sensitivity ratio reflects the potency fold shift of SCH23390-induced inhibition of sucrose intake (ID₅₀) between the least sensitive strain at each time point relative to the most sensitive strain:

^aCD-1 vs 129P3/J;

^bC57BL/10J vs 129P3/J;

^cSJL/J vs DBA/2J.

Heritability estimates for percent baseline vehicle sucrose intake scores across strains for each SCH23390 dose at each time point and for the effective raclopride dose.

Heritability Scores						
Time →	5 min	15 min	30 min	60 min	90 min	120 min
Condition ↓						
SCH23390						
50 nmol/kg	.24	.25	.32	.17	.17	.15
200 nmol/kg	.22	.24	.18	.11	.19	.24
400 nmol/kg	.07	.15	.11	.06	.06	.05
800 nmol/kg	.05	.05	.06	.11	.15	.23
1600 nmol/kg	.10	.15	.22	.15	.16	.18
Raclopride						
1600 nmol/kg	.10	.22	.15	.16	.10	.12