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Sweet taste liking is associated with subjective response to amphetamine in women but not men

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Abstract

Rationale and Objective—Preference for sweet taste rewards has been linked to the propensity for drug use in both animals and humans. Here we tested the association between sweet taste liking and sensitivity to amphetamine reward in healthy adults. We hypothesized that sweet likers would report greater euphoria and stimulation following d-amphetamine (20mg) compared to sweet dislikers.

Methods—Men (n=36) and women (n=34) completed a sweet taste test in which they rated their liking of various concentrations of sucrose and filtered water (0.05, 0.10, 0.21, 0.42, and 0.83M). Participants who preferred the highest concentration were classified as ‘sweet likers’. All others were classified as ‘sweet dislikers’. They then completed four sessions in which they received d-amphetamine (20mg) and placebo in alternating order, providing self-report measures of euphoria and stimulation on the Addiction Research Center Inventory (ARCI) at regular intervals. We conducted linear mixed effects models to examine relationships between sweet liking and drug-induced euphoria and stimulation.

Results—Sweet likers reported significantly greater amphetamine-induced euphoria than did sweet dislikers among women. By contrast, sweet liking was not associated with amphetamine response in men. No associations with stimulation were observed.

Conclusion—The association between sweet preference and amphetamine response in women is consistent with animal studies linking sweet taste preference and drug reward, and also fits with observations that individuals who use drugs show a preference for sweet tastes. Whether the sex difference is related to circulating hormones, or other variables, remains to be determined.

Keywords

sweet taste; amphetamine; sex differences; subjective response; drug reward

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Introduction

Preference for sweet taste rewards has been linked to the propensity for drug use. Animals genetically bred to prefer sweet tastes also self-administer greater amounts of ethanol and stimulant drugs than non sweet-preferring animals, and individuals who abuse alcohol and stimulant drugs are more likely to prefer sweet tastes than are healthy controls. Thus preference for sweet taste may be an early biological predictor for drug use and abuse. Identifying shared neurobiological substrates for drug rewards and natural rewards (such as sweet taste) may suggest novel approaches to prevent and treat drug abuse.

The association between sweet preference and consumption of ethanol and cocaine was first observed in animals. Rats and mice selected for high consumption of ethanol also consume more of a saccharin solution (Forgie et al. 1988; Ramirez and Sprott 1978; Sinclair et al. 1992; Stewart et al. 1994). Conversely, rats selected for high saccharin preference also consume more ethanol (Avena et al. 2004; Dess et al. 1998) and cocaine (Carroll et al. 2002) than non-saccharin-preferring rats. The preference for drugs in saccharin-preferring animals extends beyond consumption to a range of other addiction-related measures, including speed of acquisition (Carroll et al. 2002; Perry et al. 2007), escalation of drug use over time (Holtz and Carroll 2011; Perry et al. 2006), reinstatement after a period of extinction (Anker and Carroll 2011; Perry et al. 2006), and cross-sensitization of locomotor response to amphetamine (Avena and Hoebel 2003) and cocaine (Gosnell 2005). Importantly, the high and low saccharin preferring animals in these studies did not differ in food or water consumption, suggesting that the group differences were specific to drug intake (e.g., Carroll et al. 2002; Dess et al. 1998; Forgie et al. 1988; Perry et al. 2006; 2007). In sum, there is a clear reciprocal link between preference for a sweet taste and drug-taking behaviors in animals.

Sweet preference has also been linked to drug-taking in humans. In humans, sweet taste preference is typically assessed by allowing participants to taste solutions varying in sweetness and asking them to rate how sweet the tastes are and how much they like them. Participants are then classified as 'sweet likers' or 'sweet dislikers' based on their ratings. Specifically, participants who like the sweetest concentration the most are classified as 'sweet likers' and all other participants (those who prefer low to moderate sweet tastes) are classified as 'sweet dislikers' (Garbutt et al. 2016; Kampov-Polevoy et al. 2004). Importantly, sweet likers and dislikers rate the sweetness of the concentrations similarly, suggesting that they do not differ in the ability to detect sweetness, but rather in their liking of the taste (Kampov-Polevoy et al. 1999). Using this measure, individuals with alcohol use disorders are significantly more likely to be sweet likers than are healthy controls (Kampov-Polevoy et al. 1997; Kampov-Polevoy et al. 2004; Kampov-Polevoy et al. 1998), and individuals with cocaine use disorders show a stronger preference for sweet solutions than non-users (Janowsky et al. 2003). Thus, experienced drug users appear to show a preference for sweet tastes. However, in these individuals it is difficult to determine whether the differences pre-dated the drug use or developed as a consequence of using drugs.

It has been suggested that the association between sweet taste liking and drug taking reflects common underlying neurobiological mechanisms. Both sweet tastes and drugs of abuse

activate mesolimbic dopaminergic and opioidergic reward pathways, and this activation is thought to be directly related to the subjective rewarding effects of both substances (Berridge et al. 2010; Volkow et al. 2008). Specifically, neuroimaging studies indicate that both sweet taste and administration of a stimulant drug increase activity in the ventral striatum (Drevets et al. 2001; Kareken et al. 2013; Oswald et al. 2005; Volkow et al. 1999b). Additionally, D2 receptor availability predicts both subjective response to stimulant drugs (Volkow et al. 1999a; Volkow et al. 2002) and sucrose preference (Pepino et al. 2016), such that fewer striatal D2 receptors are associated with greater stimulant drug reward and greater preference for sweet tastes. Given this overlap in reward pathways underlying both sweet taste and stimulant drug reward, it is possible that individuals who are more sensitive to sweet reward are also more sensitive to drug reward. However, no studies to date have tested the degree to which sweet taste preference predicts sensitivity to the acute rewarding effects of drugs in humans.

The current study tested the association between sweet taste liking and sensitivity to amphetamine reward in a sample of healthy adults. Healthy volunteers completed the sweet taste test and then received an oral dose of d-amphetamine to assess their drug-induced euphoria. We hypothesized that sweet likers would report greater euphoria and stimulation following amphetamine compared to sweet dislikers. Given evidence from animal studies that the association between saccharin preference and increased drug-taking tends to be strongest in female rats (Carroll et al. 2008), we also hypothesized that sweet taste liking would be a stronger predictor of amphetamine reward in women compared to men.

Methods

Design

These data were collected as part of an ongoing study assessing d-amphetamine response in healthy adults. Healthy young adults first completed a measure of sweet taste reward in a drug free state. Participants then completed a four-session drug challenge to assess their subjective responses to d-amphetamine (20mg) or placebo. This dose was chosen because it has reliably produced rewarding effects in similar samples of healthy young adults in our previous studies (e.g., Childs and de Wit 2009; Childs and de Wit 2013; Weafer and de Wit 2013; Weafer et al. 2014b). Participants received amphetamine on two days and placebo on two days, in alternating order, with drug administered first (amphetamine or placebo) randomly assigned. The Institutional Review Board of the University of Chicago approved the study, and it was carried out in accordance with the Declaration of Helsinki.

Participants

Volunteers were recruited from the community through online and printed advertisements. Inclusion criteria were as follows: age 21–35, BMI between 19 and 26, at least a high school education, fluency in English, no current or past year DSM-IV diagnosis, no lifetime history of substance dependence or ADHD, no serious medical conditions, and no night shift work. Participants were excluded if they reported smoking more than 5 cigarettes per day or daily use of any medications other than birth control, or if they were pregnant, lactating, or planning to become pregnant in the next 3 months. Females who were not on hormonal

contraception completed drug administration sessions only in the follicular phase of their menstrual cycle, as subjective response to amphetamine is dampened during the luteal phase (White et al. 2002).

Measures

Sweet Taste Test. Participants rated five solutions of different concentrations of sucrose and filtered water (0.05, 0.10, 0.21, 0.42, and 0.83 M) on perceived sweetness intensity and liking (Kampov-Polevoy et al. 1997; Weafer et al. 2014a). The test consisted of five blocks, in which each of the five solutions were presented in random order, for a total of 25 taste trials. For each trial, subjects received a 2ml serving in a small opaque cup. They were instructed to swish the solution in their mouths for 5 seconds, and then expectorate into a second cup. Participants rated the sweetness of the taste (from 'not sweet at all' to 'extremely sweet') and their liking of the taste (from 'disliked very much' to 'liked very much') on two 100-mm visual analogue scales. Between trials, subjects rinsed and expectorated a small amount of water. Mean sweetness and liking ratings were calculated by averaging the ratings for each solution across the five presentations.

Addiction Research Center Inventory (ARCI; Martin et al. 1971). The 49-item true/false ARCI was used to measure subjective responses to amphetamine. We focused our analyses on the MBG (Morphine-Benzedrine Group, euphoric effects) and A (Amphetamine-like, stimulant effects) scales, as these represent the typical positive, rewarding effects of amphetamine (for reviews summarizing evidence that these scales are sensitive to the acute effects of amphetamine and that they are predictive of amphetamine choice, see de Wit and Phillips 2012; Fischman and Foltin 1991; Jasinski 1991).

Procedure

All sessions took place in the Human Behavioral Pharmacology Laboratory at the University of Chicago. Participants were required to abstain from drugs, including alcohol, for 24 hours prior to each session. Compliance with drug abstinence was verified by both self-report and breath alcohol and urine drug screens at the beginning of each session.

Participants first attended an orientation session in which they provided informed consent and were familiarized with laboratory procedures and study protocol. They completed the sweet taste test during this session. The sweet taste test was conducted at least 1.5 hours after the session began to ensure that participants had not eaten or brushed their teeth in the last 1.5 hours.

The drug administration procedure is described in detail in Weafer et al. (in press). Sessions took place from 9am to 1pm, and were separated by at least 24 hours. Participants were tested individually. They were instructed not to eat after midnight before each session, and were given a light snack upon arrival to the lab. To minimize drug expectancies, participants were told that they could receive one of the following at each session: stimulant, sedative, or placebo. They completed a baseline (pre-drug) ARCI measure, and blood pressure and heart rate were measured using a portable digital blood pressure monitor (AND Medical/Life Source, San Jose, CA). At 9:20am, amphetamine (20mg) or placebo was administered in opaque capsules under double blind conditions, in alternating order across sessions.

Participants completed the ARCI at 30, 60, 90, 120, 150, 180, and 210 minutes after capsule administration. Participants left the lab at 1:00pm, after confirmation that blood pressure and heart rate had returned to baseline. Upon completion of all sessions, participants were debriefed and compensated for their time.

Data Analyses

Sweet taste reward. We first checked to ensure that participants were able to correctly discriminate between the sweetness concentrations (Kampov-Polevoy et al. 1997). Participants were then classified as sweet likers or dislikers based on their liking ratings of the five sweetness concentrations. Those who liked the highest concentration (0.83M) more than each of the other four concentrations were classified as ‘sweet likers’. All other subjects were classified as ‘sweet dislikers’ (Kampov-Polevoy et al. 2001).

Effects of sex and sweet liker status on sweet taste ratings. Two linear mixed effects models for repeated measures (Hedeker and Gibbons 2006) were conducted in SPSS 22 to test the effects of sex and sweet liker status on sweetness and liking ratings across the five concentrations, as well as potential sex $\times$ sweet liker interactions. Both models included a random intercept, and the ‘liking’ model included a random concentration effect to allow for individual differences in liking across concentrations. Sex was coded as: Female = -1, Male = 1’ and sweet liker status was coded as: Sweet Disliker = -1, Sweet Liker = 1’.

Associations between sweet taste liking, sex, and subjective response to amphetamine. We conducted linear mixed effects models to examine the degree to which sweet taste liker status and sex interacted with drug (amphetamine vs. placebo) and time (across session) to predict measures of subjective drug response: ARCI MBG (euphoria) and ARCI A (stimulation). The models included random intercept, drug, and time effects to allow for individual differences in drug response and time trends, and to account for the correlation between repeated measurements. Drug order (d-amphetamine or placebo administered first) and BMI were included as covariates. The primary effects of interest were the three- and four-way interactions among sweet liker status, sex, drug (d-amphetamine vs. placebo), and time (linear and quadratic trends). Significant 4-way interactions were probed by running the model separately for men and women, with the sex term removed.

Correlations between sweet liking ratings and amphetamine response. We also examined individual differences in sweet taste liking ratings for each of the concentrations, regardless of sweet liker status, as predictors of amphetamine response. To do this, we created area under the curve (AUC) difference scores (average amphetamine AUC minus average placebo AUC; see Weafer and de Wit 2013) to provide a summary measure of amphetamine response for each participant. We hypothesized that greater response to amphetamine (as indicated by larger AUC) would be positively associated with liking of the highest sweetness solution, suggesting an association between amphetamine reward and liking of intensely sweet tastes. Conversely, we hypothesized that greater response to amphetamine would be negatively associated with liking of the lowest sweetness solutions, suggesting that greater amphetamine response is associated with *disliking* of low sweetness concentrations.

Results

Participants. Seventy-one participants completed the study. One participant was excluded due to invalid sweet taste data (see below), for a final sample size of 70 (34 women and 36 men).

Sweet taste reward. One participant failed to generate the appropriate concentration-response curve for sweetness ratings, and thus was excluded from analyses. Thirty-six participants (21 men and 15 women) rated the highest concentration (0.83M) as most liked, and were therefore classified as 'sweet likers'. The remaining 34 participants (15 men and 19 women) were classified as 'sweet dislikers'. Demographic and substance use data for sweet likers and dislikers are provided in Table 1. The groups did not differ in terms of sex, age, education, BMI, or substance use ($ps > 0.10$).

Effects of sex and sweet liker status on sweet taste ratings. Table 2 presents results from the linear mixed effects models testing effects of sex, sweet liker status, and concentration on sweetness and liking ratings. As expected ratings of sweetness increased with concentration, confirming that participants correctly rated increasing concentrations of sweetness as more sweet, and men and women did not differ on this measure (Figure 1A and 1B). Further, liking ratings also increased with concentration, and men and women did not differ in liking ratings (Figure 1C and 1D). As expected, sweet likers rated their liking of sweeter concentrations higher than sweet dislikers (Figure 1C and 1D; significant sweet liker $\times$ concentration interaction).

Associations between sweet taste liking, sex, and subjective response to amphetamine. Tables 3 and 4 present results from the linear mixed effects models testing the degree to which sweet liker status and sex interacted with drug and time to predict responses on ARCI MBG (euphoria) and ARCI A (stimulation). As previously reported in this dataset, amphetamine increased both MBG and A ratings relative to placebo (indicated by significant drug $\times$ time interactions; Weafer et al. in press). Moreover, for euphoria ratings, the magnitude of drug effect differed according to sex and sweet liker status (i.e., significant 4-way interaction between sex, sweet taste liker status, drug, and time). There were no effects of sex or sweet liker status on ratings of stimulation (ARCI A scale).

We probed the four-way interaction for euphoria by running the same linear mixed effects model described above separately for men and women, with the sex term removed (Table 5). For women, magnitude of drug effect differed among sweet likers and dislikers (i.e., significant time $\times$ drug $\times$ sweet taste liker status interaction). Figure 2 shows the time course of ARCI MBG (euphoria) responses following placebo and amphetamine in sweet likers and dislikers, separately for women and men. Both sweet likers and dislikers reported greater euphoria following amphetamine compared to placebo. However, as hypothesized, the magnitude of the effect was significantly greater in sweet likers compared to dislikers for women. By contrast, among men there was no difference in amphetamine response between sweet likers and dislikers.

Correlations between sweet liking ratings and amphetamine response. Table 6 presents correlations between sweet liking ratings for each sweetness concentration and AUC

difference scores for MBG and A, separately for women and men. For women, greater euphoria and stimulation following amphetamine were associated with greater liking of the highest sweetness concentration (Supplemental Figure 1), and less liking of the lowest sweetness concentrations. By contrast, liking ratings were not correlated with amphetamine response in men (Supplemental Figure 1).

Discussion

This study examined associations between preference for a sweet taste and subjective response to d-amphetamine in healthy men and women. We found that preference for a higher concentration of a sweet solution was related to greater euphoria following amphetamine in women, but not among men. The association and the sex differences are consistent with animal studies linking sweet taste preference and drug reward, and also fit with observations that drug users show a preference for sweet tastes. The finding that the association was present only in women raises questions about the role of ovarian hormones, or other sex-specific risk factors related to drug use in men and women.

The association between sweet taste liking and amphetamine reward in women is consistent with reports of animal studies showing a more pronounced association between sweet preference and drug-taking behaviors in female rats. For example, Carroll et al. (2002) found that saccharin preference predicted greater cocaine self-administration in female rats, but not males. Similarly, in a study of locomotor sensitization to cocaine, high saccharin preference predicted greater locomotor sensitization in female rats, but not in males (Carroll et al. 2007). Finally, high-saccharin preferring female rats were more resistant to extinction of cocaine self-administration than high-saccharin preferring male rats, but no sex differences in extinction rates were observed among low-saccharin preferring rats (Carroll et al. 2008). When our results are considered in the context of these animal studies, the findings suggest that sweet preference and drug-taking behaviors are more strongly linked in females compared to males across species.

There have been few reports of sex differences in preference for sweet taste among individuals who use drugs, and so it is not clear whether the sex differences in our findings generalize to drug abusing populations. Initial studies showing greater sweet liking in individuals with alcohol use disorders included men only (Kampov-Polevoy et al. 1997; Kampov-Polevoy et al. 1998). Of the studies that tested both men and women, one reported no sex differences in associations between sweet liking and alcoholic status (Kampov-Polevoy et al. 2004), and one did not have a large enough sample to test sex differences (Janowsky et al. 2003). Thus, it will be important for future studies to examine possible sex differences in sweet liking among individuals who use drugs.

One possible explanation for the stronger association between sweet preference and stimulant drug reward in females could be the influence of circulating sex hormones. Both sweet preference and sensitivity to drug reward vary across the menstrual cycle, and are influenced in part by the ovarian hormones estradiol and progesterone. For example, sweet taste liking is greatest in the luteal phase, when both estradiol and progesterone levels are relatively high (Bowen and Grunberg 1990; Pliner and Fleming 1983). By contrast,

stimulant drug effects are more pronounced in the follicular phase, when estradiol levels are rising and progesterone levels are low (Evans et al. 2002; Sofuoglu et al. 1999; White et al. 2002). In the present study women completed their drug administration sessions during the follicular phase but cycle phase during the sweet taste test was not controlled. It is possible that the association between sweet preference and drug reward is strongest when sweet liking is assessed during the luteal phase (when sweet liking peaks) and drug reward is tested in the follicular phase (when drug liking peaks). However, additional studies are needed to directly test this possibility.

These findings have implications for understanding risk for drug abuse in women. On the one hand, sweet preference may be a risk factor for amphetamine abuse in women, given that sweet likers reported greater amphetamine-induced euphoria, and greater subjective response to amphetamine is associated with greater risk for drug abuse (de Wit and Phillips 2012). On the other hand, it is possible that sensitivity to sweet rewards could be a protective factor against drug abuse in females. A recent animal study tested this possibility by assessing consumption of a saccharine cue that signaled subsequent access to cocaine (Cason and Grigson 2013). The authors found that females consumed more of the saccharine cue and less subsequent cocaine, whereas males avoided the saccharin cue and consumed greater amounts of cocaine. These findings suggest that greater sensitivity to alternate reinforcers could protect against drug-taking behavior in females, leading them to choose the alternate reinforcer over cocaine. This idea is further supported by the lack of a robust association between obesity and drug addiction (Sansone and Sansone, 2013), which has been theorized to be due to competition between food and drugs for the same reward pathways (Warren and Gold, 2007). Although speculative, it is possible that preference for natural sweet rewards may similarly influence women to avoid drug reward in favor of sweet taste reinforcement.

This study had some limitations. As mentioned above, we did not control for menstrual cycle phase at the time of the sweet taste test. Given the influence of sex hormone levels on sweet liking and drug reward, it will be important for future studies to directly assess the role of menstrual cycle and hormone levels on the association between the two. Additionally, we administered a single dose of amphetamine. It is possible that different associations with sweet taste liking would be observed with higher or lower doses of amphetamine. For this, it would be valuable to test sensitivity to a range of doses of amphetamine in sweet likers and dislikers. Similarly, the fixed dose of amphetamine resulted in a slight variation in dosage among participants based on weight, and so it is possible that the effectively higher doses in women (because of lower body weight) led to the stronger associations between amphetamine response and sweet liking. However, we believe this is unlikely because we recruited participants within a narrow range of BMI and there were no detectable sex differences in any subjective or physiological response to amphetamine. Another future direction might be to investigate associations between ‘wanting’, rather than ‘liking’, of sweet rewards and amphetamine, perhaps via assessments of craving or willingness to work to receive these rewards (Berridge et al., 2010). Finally, we did not collect any measures of family history of alcoholism, self-assessed sweet-liking, or preferences for sweet vs. savory foods.

In conclusion, this study was the first to examine associations between sweet taste preference and subjective response to a stimulant drug in non-drug-using humans. Similar to the animal literature, we found that sweet preference predicted greater stimulant drug reward, and that this effect was specific to females. The observed association between sweet taste preference and drug reward suggests that the two may share common neurobiological mechanisms, as has been previously suggested (Berridge et al. 2010; Volkow et al. 2008). Further, the finding that the association was specific to females suggests that circulating sex hormones may modulate this association. It will be important for future studies to assess the potentially overlapping neural and hormonal correlates of sweet taste and drug reward, in order to better understand the link between the two. It will also be important to determine the degree to which the association between sweet liking and drug reward generalizes to other drugs of abuse, including alcohol, or to other maladaptive, reward-seeking behaviors such as problem gambling. It is possible that sweet taste sensitivity is a marker for a general increased sensitivity to reward, and therefore could predispose individuals to increased risk for a range of addictive behaviors. Finally, future studies should examine whether sweet liking serves as a risk or protective factor for drug abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Anker JJ, Carroll ME. Adolescent nicotine exposure sensitizes cue-induced reinstatement of cocaine seeking in rats bred for high and low saccharin intake. *Drug Alcohol Depend.* 2011; 118:68–72. [PubMed: 21439737]
- Avena NM, Carrillo CA, Needham L, Leibowitz SF, Hoebel BG. Sugar dependent-rats show enhanced intake of unsweetened ethanol. *Alcohol.* 2004; 34:203–209. [PubMed: 15902914]
- Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience.* 2003; 122:17–20. [PubMed: 14596845]
- Berridge KC, Ho CY, Richard JM, DiFeliceantonio AG. The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Res.* 2010; 1350:43–64. [PubMed: 20388498]
- Bowen DJ, Grunberg NE. Variations in food preference and consumption across the menstrual-cycle. *Physiol Behav.* 1990; 47:287–291. [PubMed: 2333344]
- Carroll ME, Anderson MM, Morgan AD. Higher locomotor response to cocaine in female (vs. male) rats selectively bred for high (HiS) and low (LoS) saccharin intake. *Pharmacol Biochem Behav.* 2007; 88:94–104. [PubMed: 17707494]
- Carroll ME, Morgan AD, Anker JJ, Perry JL, Dess NK. Selective breeding for differential saccharin intake as an animal model of drug abuse. *Behav Pharmacol.* 2008; 19:435–460. [PubMed: 18690102]
- Carroll ME, Morgan AD, Lynch WJ, Campbell UC, Dess NK. Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. *Psychopharmacology.* 2002; 161:304–313. [PubMed: 12021834]
- Cason AM, Grigson PS. Prior access to a sweet is more protective against cocaine self-administration in female rats than in male rats. *Physiol Behav.* 2013; 112:96–103. [PubMed: 23474135]

- Childs E, de Wit H. Amphetamine-induced place preference in humans. *Biol Psychiatry*. 2009; 15:900–904.
- Childs E, de Wit H. Contextual conditioning enhances the psychostimulant and incentive properties of d-amphetamine in humans. *Addict Biol*. 2013; 18:985–992. [PubMed: 22129527]
- de Wit H, Phillips TJ. Do initial responses to drugs predict future use or abuse? *Neurosci Biobehav Rev*. 2012; 36:1565–76. [PubMed: 22542906]
- Dess NK, Badia-Elder NE, Thiele TE, Kiefer SW, Blizard DA. Ethanol consumption in rats selectively bred for differential saccharin intake. *Alcohol*. 1998; 16:275–278. [PubMed: 9818978]
- Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry*. 2001; 49:81–96. [PubMed: 11164755]
- Evans SM, Haney M, Foltin RW. The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. *Psychopharmacology*. 2002; 159:397–406. [PubMed: 11823892]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *Br J Addict*. 1991; 86:1563–70. [PubMed: 1786488]
- Forgie ML, Beyerstein BL, Alexander BK. Contributions of taste factors and gender to opioid preference in C57BL and DBA mice. *Psychopharmacology*. 1988; 95:237–244. [PubMed: 3137604]
- Garbutt JC, Kampov-Polevoy AB, Kalka-Juhl LS, Gallop RJ. Association of the sweet-liking phenotype and craving for alcohol with the response to naltrexone treatment in alcohol dependence: A randomized clinical trial. *JAMA Psychiatry*. 2016; 73:1056–1063. [PubMed: 27627782]
- Gosnell BA. Sucrose intake enhances behavioral sensitization produced by cocaine. *Brian Research*. 2005; 1031:194–201.
- Hedeker, D., Gibbons, RD. *Longitudinal data analysis*. Wiley; New Jersey: 2006.
- Holtz NA, Carroll ME. Baclofen has opposite effects on escalation of cocaine self-administration: Increased intake in rats selectively bred for high (HiS) saccharin intake and decreased intake in those selected for low (LoS) saccharin intake. *Pharmacol Biochem Behav*. 2011; 100:275–283. [PubMed: 21924281]
- Janowsky D, Pucilowski O, Buyinza M. Preference for higher sucrose concentrations in cocaine abusing-dependent patients. *J Psychiatr Res*. 2003; 37:35–41. [PubMed: 12482468]
- Jasinski DR. History of abuse liability testing in humans. *Br J Addict*. 1991; 86:1559–62. [PubMed: 1786487]
- Kampov-Polevoy A, Garbutt JC, Janowsky D. Evidence of preference for a high-concentration sucrose solution in alcoholic men. *Am J Psychiatry*. 1997; 154:269–270. [PubMed: 9016281]
- Kampov-Polevoy AB, Eick C, Boland G, Khalitov E, Crews FT. Sweet liking, novelty seeking, and gender predict alcoholic status. *Alcohol Clin Exp Res*. 2004; 28:1291–1298. [PubMed: 15365298]
- Kampov-Polevoy AB, Garbutt JC, Davis CE, Janowsky DS. Preference for higher sugar concentrations and tridimensional personality questionnaire scores in alcoholic and nonalcoholic men. *Alcohol Clin Exp Res*. 1998; 22:610–614. [PubMed: 9622439]
- Kampov-Polevoy AB, Garbutt JC, Janowsky DS. Association between preference for sweets and excessive alcohol intake: A review of animal and human studies. *Alcohol Alcohol*. 1999; 34:386–395. [PubMed: 10414615]
- Kampov-Polevoy AB, Tsoi MV, Zvartau EE, Neznanov NG, Khalitov E. Sweet liking and family history of alcoholism in hospitalized alcoholic and non-alcoholic patients. *Alcohol Alcohol*. 2001; 36:165–170. [PubMed: 11259214]
- Kareken DA, Dzemidzic M, Oberlin BG, Eiler WJA. A preliminary study of the human brain response to oral sucrose and its association with recent drinking. *Alcohol Clin Exp Res*. 2013; 37:2058–2065. [PubMed: 23841808]
- Martin WR, Sloan JW, Sapira JD, Jasinski DR. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther*. 1971; 12:245–258. [PubMed: 5554941]

- Oswald LM, Wong DF, McCaul M, Zhou Y, Kuwabara H, Choi L, Brasic J, Wand GS. Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. *Neuropsychopharmacology*. 2005; 30:821–832. [PubMed: 15702139]
- Pepino MY, Eisenstein SA, Bischoff AN, Klein S, Moerlein SM, Perlmutter JS, Black KJ, Hershey T. Sweet dopamine: sucrose preferences relate differentially to striatal D2 receptor binding and age in obesity. *Diabetes*. 2016; 65:2618–2623. [PubMed: 27307220]
- Perry JL, Anderson MM, Nelson SE, Carroll ME. Acquisition of i.v. cocaine self-administration in adolescent and adult male rats selectively bred for high and low saccharin intake. *Physiol Behav*. 2007; 91:126–133. [PubMed: 17360010]
- Perry JL, Morgan AD, Anker JJ, Dess NK, Carroll ME. Escalation of i.v. cocaine self-administration and reinstatement of cocaine-seeking behavior in rats bred for high and low saccharin intake. *Psychopharmacology*. 2006; 186:235–245. [PubMed: 16596398]
- Pliner P, Fleming AS. Food-intake, body-weight, and sweetness preferences over the menstrual-cycle in humans. *Physiol Behav*. 1983; 30:663–666. [PubMed: 6878471]
- Ramirez I, Sprott RL. Genetic mechanisms of drinking and feeding. *Neurosci Biobehav Rev*. 1978; 2:15–26.
- Sansone RA, Sansone LA. Obesity and substance misuse: is there a relationship? *Innov Clin Neurosci*. 2013; 10:30–35.
- Sinclair JD, Kampovpoleyov A, Stewart R, Li TK. Taste preferences in rat lines selected for low and high alcohol-consumption. *Alcohol*. 1992; 9:155–160. [PubMed: 1599627]
- Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, Hatsukami DK. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. *Exp Clin Psychopharmacol*. 1999; 7:274–283. [PubMed: 10472516]
- Stewart RB, Russell RN, Lumeng L, Li TK, Murphy JM. Consumption of sweet, salty, sour, and bitter solutions by selectively bred alcohol-preferring and alcohol-nonpreferring lines of rats. *Alcohol Clin Exp Res*. 1994; 18:375–381. [PubMed: 8048741]
- Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Gifford A, Hitzemann R, Ding YS, Pappas N. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D-2 receptor levels. *Am J Psychiatry*. 1999a; 156:1440–1443. [PubMed: 10484959]
- Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J Pharmacol Exp Ther*. 1999b; 291:409–15. [PubMed: 10490931]
- Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci*. 2008; 363:3191–3200. [PubMed: 18640912]
- Volkow ND, Wang GJ, Fowler JS, Thanos P, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas N. Brain DA D2 receptors predict reinforcing effects of stimulants in humans: Replication study. *Synapse*. 2002; 46:79–82. [PubMed: 12211085]
- Warren MW, Gold MS. The relationship between obesity and drug use. *Am J Psychiatry*. 2007; 164:1268. [PubMed: 17671293]
- Weafer J, Burkhardt A, de Wit H. Sweet taste liking is associated with impulsive behaviors in humans. *Front Behav Neurosci*. 2014a; 8:228. [PubMed: 24987343]
- Weafer J, de Wit H. Inattention, impulsive action, and subjective response to d- amphetamine. *Drug Alcohol Depend*. 2013; 133:127–33. [PubMed: 23790566]
- Weafer J, Gallo DA, de Wit H. Amphetamine fails to alter cued recollection of emotional images: study of encoding, retrieval, and state-dependency. *PLoS One*. 2014b; 9:e90423. [PubMed: 24587355]
- Weafer J, Gorka SM, Hedeker D, Dzemidzic M, Kareken DA, Phan KL, de Wit H. Associations between behavioral and neural correlates of inhibitory control and amphetamine reward sensitivity. *Neuropsychopharmacology*. in press.
- White TL, Justice AJ, de Wit H. Differential subjective effects of d-amphetamine by gender, hormone levels and menstrual cycle phase. *Pharmacol Biochem Behav*. 2002; 73:729–41. [PubMed: 12213517]

Fig 1.

Mean sweetness (A and B) and liking (C and D) ratings of each of the five sweetness concentrations for sweet likers and dislikers, separately for men and women. Men and women did not differ in sweetness or liking ratings. Capped vertical lines represent standard error of the mean (SEM)

Fig 2.

Mean euphoria change from baseline scores (MBG) at each timepoint following placebo and amphetamine (averaged across sessions) for female (panel A) and male (panel B) sweet likers and dislikers. As hypothesized, female sweet likers reported significantly greater euphoria following amphetamine compared to placebo than did female sweet dislikers. By contrast, male sweet likers and dislikers did not significantly differ in ratings of euphoria. Capped vertical lines represent standard error of the mean (SEM)

Table 1

Sample Characteristics

	Sweet Likers (n=36)	Sweet Dislikers (n=34)
Gender (M:F)	21:15	15:19
Age	24.1 (2.6)	25.0 (2.6)
Education (years)	15.3 (1.6)	15.5 (1.6)
BMI	23.0 (2.1)	23.0 (2.0)
Race		
Caucasian	19	22
African-American	6	5
More than one race	7	4
Asian	2	2
American Indian/Alaskan	0	1
Hawaiian/Pacific Islander	1	0
Not reported	1	0
Current substance use		
Alcohol (drinks/occasion)	3.0 (2.0); n=35	2.6 (1.4); n=32
Cigarettes (per day)	1.1 (1.8); n=12	1.3 (1.8); n=11
Caffeine (cups/day)	1.3 (0.8); n=32	1.7 (1.2); n=31
Marijuana (times/month)	22.2 (19.1); n=10	10.2 (15.3); n=15
Lifetime substance use (% ever used)		
Marijuana	80.6%	79.4%
Hallucinogens	33.3%	35.3%
Stimulants	25.0%	35.3%
MDMA	25.0%	23.5%
Opiates	16.7%	14.7%
Sedatives	16.7%	8.8%

Table 2

Linear mixed effects models testing effects of sex and sweet liker status on sweet taste ratings

	Estimate	SE	<i>t</i>	<i>p</i>
Sweetness Ratings				
Concentration	94.08	2.60	36.1	< 0.001
Sex	-0.14	1.38	0.11	0.917
Sweet Liker	-0.43	1.38	0.31	0.756
Sex×Concentration	-3.96	2.60	1.52	0.129
Sweet×Concentration	-1.27	2.60	0.49	0.626
Sex×Sweet	0.26	1.38	0.19	0.853
Sex×Sweet×Concentration	2.97	2.60	1.14	0.254
Liking Ratings				
Concentration	17.56	4.20	4.18	< 0.001
Sex	-1.65	1.70	0.97	0.337
Sweet Liker	-7.07	1.70	4.16	< 0.001
Sex×Concentration	3.95	4.20	0.94	0.350
Sweet Liker×Concentration	40.06	4.20	9.54	< 0.001
Sex×Sweet	2.27	1.70	1.33	0.187
Sex×Sweet×Concentration	-4.52	4.20	1.08	0.286

Note. Significant effects are indicated in a bold font.

Table 3

Linear mixed effects models testing effects of sex and sweet liker status on amphetamine-induced euphoria

	Estimate	SE	<i>t</i>	<i>p</i>
ARCI MBG (Euphoria)				
Order	−0.31	0.43	0.72	0.471
BMI	0.16	0.11	1.46	0.149
Sex	−0.37	0.35	1.07	0.287
Sweet Liker	−0.17	0.35	0.48	0.631
Drug	−0.11	0.39	0.28	0.777
Time (Linear)	−0.30	0.14	2.09	0.039
Time² (Quadratic)	0.04	0.02	2.08	0.039
Sex×Drug	0.59	0.39	1.52	0.132
Sex×Time	0.20	0.14	1.39	0.167
Sex×Time ²	−0.01	0.02	0.80	0.427
Sweet×Drug	−0.14	0.39	0.35	0.728
Sweet×Time	0.10	0.14	0.69	0.491
Sweet×Time ²	−0.01	0.02	0.69	0.491
Sex×Sweet	−0.41	0.35	1.18	0.242
Drug×Time	2.03	0.14	14.87	< 0.001
Drug×Time²	−0.21	0.02	10.98	< 0.001
Sweet×Drug×Time	0.12	0.14	0.88	0.379
Sweet×Drug×Time ²	−0.01	0.02	0.42	0.673
Sex×Drug×Time	−0.10	0.14	0.76	0.445
Sex×Drug×Time ²	0.02	0.02	0.93	0.354
Sex×Sweet×Drug	−0.14	0.39	0.37	0.716
Sex×Sweet×Time	0.11	0.14	0.79	0.433
Sex×Sweet×Time ²	−0.01	0.02	0.70	0.485
Sex×Sweet×Drug×Time	−0.43	0.14	3.15	0.002
Sex×Sweet×Drug×Time²	0.05	0.02	2.66	0.008

Note. Significant effects are indicated in a bold font.

Table 4

Linear mixed effects models testing effects of sex and sweet liker status on amphetamine-induced stimulation

	Estimate	SE	<i>t</i>	<i>p</i>
ARCI A (Stimulation)				
Order	0.17	0.27	0.64	0.527
BMI	0.11	0.07	1.69	0.095
Sex	-0.04	0.19	0.19	0.852
Sweet Liker	0.05	0.19	0.27	0.786
Drug	-0.12	0.24	0.48	0.629
Time (Linear)	-0.14	0.07	1.96	0.050
Time ² (Quadratic)	0.02	0.01	1.85	0.065
Sex×Drug	0.15	0.24	0.61	0.541
Sex×Time	0.08	0.07	1.19	0.234
Sex×Time ²	-0.01	0.01	0.74	0.461
Sweet×Drug	-0.02	0.24	0.09	0.926
Sweet×Time	-0.01	0.07	0.14	0.888
Sweet×Time ²	0.01	0.01	0.31	0.760
Sex×Sweet	-0.09	0.19	0.49	0.628
Drug×Time	1.39	0.09	14.79	< 0.001
Drug×Time²	-0.14	0.01	10.86	< 0.001
Sweet×Drug×Time	0.02	0.09	0.21	0.835
Sweet×Drug×Time ²	-0.01	0.01	0.12	0.903
Sex×Drug×Time	0.01	0.09	0.08	0.934
Sex×Drug×Time ²	0.01	0.01	0.38	0.702
Sex×Sweet×Drug	-0.15	0.24	0.61	0.541
Sex×Sweet×Time	0.04	0.07	0.62	0.536
Sex×Sweet×Time ²	-0.01	0.01	0.60	0.549
Sex×Sweet×Drug×Time	-0.17	0.09	1.76	0.078
Sex×Sweet×Drug×Time ²	0.02	0.01	1.37	0.171

Note. Significant effects are indicated in a bold font.

Table 5

Linear mixed effects models testing effects of sweet liker status on amphetamine-induced euphoria

	Estimate	SE	<i>t</i>	<i>p</i>
Women				
Order	−0.72	0.50	1.46	0.155
BMI	0.01	0.15	0.10	0.924
Sweet Liker	0.27	0.43	0.64	0.527
Drug	−0.70	0.55	1.28	0.206
Time (Linear)	−0.49	0.19	2.57	0.013
Time² (Quadratic)	0.05	0.02	2.15	0.035
Sweet×Drug	0.01	0.55	0.01	0.991
Sweet×Time	−0.01	0.19	0.07	0.943
Sweet×Time ²	0.01	0.02	0.01	0.994
Drug×Time	2.14	0.19	11.43	< 0.001
Drug× Time²	−0.22	0.03	8.71	< 0.001
Sweet×Drug×Time	0.55	0.19	2.95	0.003
Sweet×Drug×Time²	−0.06	0.03	2.25	0.024
Men				
Order	0.20	0.66	0.30	0.766
BMI	0.22	0.15	1.54	0.133
Sweet Liker	−0.55	0.55	0.99	0.327
Drug	0.48	0.55	0.87	0.389
Time (Linear)	−0.10	0.21	0.48	0.633
Time ² (Quadratic)	0.02	0.03	0.87	0.388
Sweet×Drug	−0.28	0.55	0.50	0.617
Sweet×Time	0.21	0.21	1.01	0.316
Sweet×Time ²	−0.03	0.03	0.94	0.350
Drug×Time	1.93	0.20	9.71	< 0.001
Drug× Time²	−0.19	0.03	6.92	< 0.001
Sweet×Drug×Time	−0.31	0.20	1.56	0.118
Sweet×Drug×Time ²	0.04	0.03	1.54	0.124

Note. Significant effects are indicated in a bold font.

Table 6

Correlations between sweet liking ratings and subjective response to amphetamine

Sweetness Concentrations (M)	Euphoria		Stimulation	
	Women	Men	Women	Men
0.05	−0.39 *	0.33	−0.37 *	0.29
0.10	−0.38 *	0.16	−0.39 *	0.18
0.21	−0.13	−0.23	−0.24	−0.08
0.42	0.33	−0.32	0.30	−0.23
0.83	0.47 **	−0.27	0.43 *	−0.23

Note.

* indicates $p < 0.05$;** indicates $p < 0.01$