Effects of Drugs, Sex, and Age on Preference to Sweet Taste in Rats

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Abstract

The preference of sweet taste in rats is a phenomenon that is influenced by many factors. Drugs, sex, and age are three important aspects to consider when determining the underlying mechanisms that influence increased intake in the presence of sweet taste. Research has shown that drugs acting on receptors and neurotransmitters of brain mechanisms relevant to hedonic and reinforcement effects can alter the preference for sweet taste. Particularly important are drugs that act on benzodiazepine, dopamine, and serotonin receptors. When drugs facilitate their effects, sweet intake is increased and conversely, antagonists to these drugs decrease intake. Sex-defining hormones also play a role in preference to sweet taste; females tend to have higher preference for sweet solutions. The female hormone, estrogen, is said to increase the threshold for responding to sweet solutions. Studies on age have found that increase to preference of a sweet solution increases with age, but innate tendencies to prefer sweet tastants are also present from birth. These findings together can determine under what circumstances preference for sweet tastes are the greatest. This information can be used to work towards a cure for food-related epidemics, such as obesity by modifying the underlying systems of this phenomenon.
Introduction

Through changes in gustatory signals, we are able to regulate what we put into our mouths and what becomes preferred for feeding. Stimuli are detected through receptors on the tongue and dissolved in saliva. There are four main categories of taste: sweet, salty, bitter, and sour. Each type of taste has specific receptors that code for that taste. This has an evolutionary advantage in that, detection of sweet and salty foods are determined as safe; whereas, we tend to avoid tastes of sour and bitter.

There are over 10,000 taste buds on the tongue, palate, pharynx, and larynx. Papillae cover the tongue and contain the taste buds. Taste buds contain receptor cells, which have cilia protruding from their ends into the saliva. When taste molecules make contact with the taste buds, they bind to the receptors and signal transduction occurs. In sweet gustatory reactions, sweet substances bind to the receptor cell of the tongue, and gustducin, a G protein, is activated. Gustducin activates an enzyme to produce cyclic AMP, causing calcium channels to open and initiate signal transmission by release of neurotransmitter.

Taste signals are then sent to the brain through cranial nerves 7, 9 and 10. Signals are sent through these nerves to the nucleus of the solitary tract, found in the medulla. Here, information is relayed to other parts of the brain including the thalamus, where signals are then sent to the primary gustatory cortex, then to the secondary gustatory cortex, where taste is processed. Gustatory signals also travel to the amygdala and the hypothalamus. Research indicates that this hypothalamic pathway accounts for the reinforcing effects of sweet and salty tastes. Research has also shown that neurons respond to all tastes, but have differential responding to certain tastes. Clusters of
neurons for sweet and salty tastes were found in abundance; more groups were found than for sour or bitter tastes (Carlson, 2001). These concepts, in which feeding behavior is regulated by taste mechanisms, will be further explored in this paper.

I. Drug Effects on Sweet Taste

Before examining the neurochemical components of ingestive behavior, it is important to understand the behavioral mechanisms that underlie these mechanisms. Behaviorally, the decision to increase or decrease intake of sweet solutions can be determined on the basis of reinforcement magnitude. In a study done by Czachowski, et al. (2002), reinforcement magnitude was assessed by determining the breakpoint for sucrose comparable to ethanol. Rats were trained to respond to a 3% sucrose solution, where completion of a response results in 20 minute access to the solution. Baseline breakpoints were taken according to this concentration. The breakpoint, or the last response requirement that was successfully completed, was then measured for 1, 3, 5, and 10% sucrose concentrations. The same procedure was repeated using ethanol. Results showed that the breakpoints for sucrose were highly correlated with sucrose concentrations, and were significantly greater than that of the ethanol procedure.

Based on the linear relationship between increase in sucrose and increase in breakpoint, it can be assumed that consummatory behaviors vary based on hedonic value of sweet taste. Taste factors of sweet solutions are a reliable determinant of seeking and intake behaviors. Therefore, the greater the sweeter the solution, the more rats respond in order to ingest the solution (Czachowski et al., 2006).
Many mechanisms are involved in taste and ingestion of sweet solutions. By manipulating certain factors such as receptor activity or neurotransmitter pathways through administration of various drugs, these mechanisms can be identified and attributed to playing a role in preference of sweet taste. Two systems of particular importance to regulating eating behavior are the opioid and GABA-benzodiazepine systems. When benzodiazepine and opioid receptors are stimulated, an increase in food consumption has been shown to occur in rodent species. These systems appear to share a hedonic mechanism, which enhances taste and provides reward value to the species. By administering drugs that act as agonists as well as antagonists to these receptor types, Richardson, et al. (2005) tested the hypothesis that the opioid and benzo systems are activated upon presence of sweet taste and control intake of sweet solutions (Richardson, et al., 2005).

Since opioid peptides play a role in the production of pleasurable feelings by acting on the nucleus accumbens in the brain, opioid receptor antagonists can decrease feeding by decreasing the reward value of food intake. Evidence suggests that the opioid system interacts with the benzo system in their hedonic effects. By using opioid receptor antagonists, the actions of benzos can be blocked. In a study by Richardson, et al. (2005), the drug naltrexone, an opioid receptor antagonist, was administered in combination with diazepam, a benzo agonist, to determine its effects on benzodiazepine-induced enhancement of taste. Rats were also given a vehicle injection, diazepam alone, and naltexone alone. Then, rats were given a sucrose/quinine solution to determine benzo’s effect on taste enhancement. Measurements of “liking” were based on orofacial expressions in the rat.
When diazepam was administered alone, it increased liking to the solution, and decreased aversion to the quinine, compared to the control. Naltrexone administered alone had no effect. When the combination of diazepam and naltrexone was given, no hedonic expressions were present in the rats, and results were similar to that of the control group. It was found that naltrexone blocks the action of diazepam, and “liking” reactions to a sucrose/quinine solution decrease significantly while aversive “disliking” reactions increase. Therefore, benzodiazepines increase intake of the sweet solution, but this reaction can be altered by eliminating its interaction with opioid peptides. (Richardson, et al., 2005).

The role of opioid peptides on ingestion can be further determined by looking at its effects on motivation. Opioid antagonists can produce changes in taste, taste perception, and taste palatability by blocking receptor activity in a variety of central and peripheral processes. Previous studies have found that that naloxone, an additional opioid receptor antagonist acts on natural reward systems because in previous studies the drug decreases intake of high-fat foods. In a study by Cleary, et al. (1996), rats were tested for breakpoint on three concentrations of sucrose, 2, 5, and 10% after being injected with 0.3, 1, 3, and 10 mg/kg naloxone. Breakpoint was defined as the maximum amount of work the subject would expend for 0.1 ml of a given sucrose solution. It was found that breakpoint was significantly reduced compared to control groups under 2% and 5% sucrose reinforcement, but not under the 10% sucrose solution. Furthermore, the effect of naloxone was inversely related to the concentration of sucrose. Highest concentrations were least suppressed by naloxone. Also, naloxone reduced breakpoint, dependent on the dose, with the highest dose reducing breakpoint the greatest. Because
responding depended on the strength of the reinforcer, there is a considerable motivational effect of opioid peptides in the role of feeding (Cleary et al, 1996).

Benzodiazepine agonists have shown to increase intake of palatable foods by producing enhanced hedonic effects. However, Petry & Heyman (1996) demonstrated a bidirectional modulation of sweet and bitter tastes by the benzo agonist chloradiazepoxide. Rats were injected with the drugs, and then tested on an operant response to sucrose and quinine solutions. When chloradiazepoxide was administered alone, sucrose responding increased significantly from baseline, suggesting that the sucrose solution provided more hedonic value with pre-testing drug administration. Rats were also given a combination injection of chloradiazepoxide and flumazenil, a benzo antagonist. The antagonist blocked the action of the agonist and produced no effect different from the baseline responding, demonstrating that the benzo receptor is involved in taste palatability (Petry and Heyman, 1996).

Neurotransmitters, such as dopamine and serotonin are also involved in the regulation of ingestive behaviors in rats. A general hypothesis was proposed in 1989 by Wise and Rompre, stating that central dopaminergic mechanisms are involved in the mediation of food reward. Dopamine (DA) antagonists decrease intake of sucrose and sweet solutions. This occurs not by decreasing perceived sensory intensity, but by decreasing the reinforcing potency of the solutions. The DA antagonist, raclopride, was used in an experiment by Hsiao and Smith (1994). Rats were given a flavored solution paired with a pretreatment IP injection of raclopride, which caused a 55% decrease in intake from baseline intake of the same flavored solution. In a later two-bottle test, preference for the same flavored solution was decreased, without the drug being present.
Therefore, the flavor provided less reinforcement due to the effect of the drug in the first test. This suggests that DA mechanisms that were suppressed by the DA antagonist are responsible for reward of ingesting sucrose solutions (Hsiao and Smith, 1994).

An additional neurotransmitter involved in regulation of ingestive behavior is serotonin (5-HT). Amperozide is a 5-HT antagonist that is expected to reduce intake of a palatable solution. A study by Biggs and Myers (1997) examined the effects of naltrexone and amperozide and their ability to alter gustatory function in the drinking of a chocolate nutrient solution, the drinking of a saccharin solution, and food intake. Amperozide reduces intake of the chocolate solution the most during injections of the drug; however, both amperozide and naltrexone had a greater effect on intake than the saline injection. Also, high doses of amperozide decrease food intake.

Amperozide is found, in separate studies, to be involved in the suppression of ingestion of alcohol. Using these, along with the previous findings, it can be assumed that separate mechanisms are involved in the reinforcing properties of different fluids. Amperozide produced an amperozide dose-dependent suppression of preference for the chocolate solution as well as a reduction in food intake. This indicates that amperozide may have an effect on the central regulation of caloric intake. The drug produced the same effect for saccharin. These findings may suggest that 5-HT antagonists may act on reinforcement, as well as ingestive properties. Since amperozide also involves dopaminergic systems, it could be that amperozide affects dopaminergic function by altering reinforcement qualities of the two solutions. It can also be concluded that naltrexone acts on the gustatory component because it decreases intake of the saccharin (non-nutrient) solution and of the nutrient chocolate solution (Biggs and Myers, 1997).
Many findings related to sweet-seeking behaviors or mechanisms of reinforcement on gustatory enhancement in rats should be considered when evaluating their implications in humans. However, certain factors relative to human behavior should also be considered. Previous studies had reported that an inverse relationship exists between nicotine and body weight because of changes in food consumption due to nicotine, especially when the foods are sweet. Parker and Doucet (1995) found that chronic exposure to nicotine decreased palatability to a sucrose solution, but palatability returns upon withdrawal of the nicotine. In a study by Grunberg et al. (1988), effects of nicotine on body weight in rats with access to “junk” foods were determined. Rats were given access to three food cups containing either chips, Oreo cookies, or laboratory chow. They were then exposed to nicotine or saline at a constant rate for 17 days. In both males and females, body weight increased less for the nicotine group than for the saline group. In examination of the amount of decrease in each food cup, less Oreo cookies were consumed than chips or chow. Based on the inverse relationship between nicotine and sweet food consumption, nicotine may act as a suppressor of reward value of appealing foods, assuming the Oreo cookies were more appealing than the chips or chow (Grunberg et al., 1988). These findings are in agreement with previous studies in which nicotine reduces intake of sweet solutions.

By demonstrating the effects of several drugs on food intake, certain mechanisms can be targeted as critical in the regulation of intake of sweet foods. By using this information, we can then alter the effects produced by sweet taste.
II. The Role of Sex on Sweet Taste

Not only should neurochemical components to sweet taste be examined, but other influences should be considered. Sex is one of these factors. There has been significant research on male versus female preferences for sweet taste. Most studies have found, that males are more sensitive to sweet taste. Research done by Ackroff and Sclafani (2004) examined the effects of different factors that alter rats’ responding to fructose. In their experiments, both male and female rats were conditioned with a 16% fructose infusion to both a sweet flavored solution and a plain solution and a water infusion to a sweet solution and a plain solution. It was found that both males and females preferred the sweet solution conditioned with fructose, but males avoided the non-sweet solution conditioned with fructose. Females, however, were indifferent to the non-sweet solution. The differential responding to sweet and non-sweet taste, when both are reinforced by fructose implicates a greater sensitivity in males to the postingestive effects of fructose: as reinforcing or non-reinforcing. Females show a much lower sensitivity, as they are less responsive to the difference between solutions, demonstrating that females may have a higher taste threshold for sweet solutions to become reinforcing. (Ackroff and Sclafani, 2004).

A number of factors could account for the variability in taste sensitivity between males and females. One hypothesis proposed by Curtis, et al. (2005) describes estrogen as the main effect of this sensitivity difference. Female ovariectomized rats were allowed access to a 0.2 M sucrose solution, then injected with either LiCl or a NaCl vehicle injection. The LiCl injection produced an aversive response on day 2. Rats that had been given the aversive injection, were then treated with an estrogen replacement and retested
for 0.025 M and 0.075 M sucrose solutions. It was found that rats with estrogen injections preferred the aversive solution more than did the rats without the estrogen replacement. Estrogen did not alter preference to the less concentrated sucrose solution, as occurred in the non-ovariectomized rats. They were also unable to discriminate between the 0.025 M sucrose solution and water. Therefore, intact females are less sensitive to changes in the amount of sucrose being ingested. These findings provide strong evidence that estrogen increases the threshold for gustatory detection of sucrose (Curtis et al., 2005).

Preference for sweet solutions can be modulated by a number of factors in combination with hormonal influence. Diet and exercise, for example, are factors that affect sweet intake, and allow further study into hormones involved. In a study by Eckel and Moore (2004), exercise and gender was examined for its effects on caloric intake of diet and the diet’s ability to induce hyperphagia. Rats were given a diet of either normal laboratory chow or chow plus sweet milk and allowed either running wheel access or no wheel access. Their findings showed that females preferred the chow plus milk better, regardless of wheel access, while males preferred plain chow more. Rats that had access to the running wheels, showed a decrease in overall intake of food, but females still consumed more chow plus milk than males. In comparing the overall caloric intake of the rats when switched from a diet of chow alone to the chow plus sweet milk diet, the percentage increase was much greater for females. When female rats with no wheel access were introduced to the sweeter food choice, they increased their caloric intake by 36%, while males under the same conditions increased intake by only 9%. Females with wheel access increased caloric intake by 15% when switched to the sweeter diet, and
males increased intake by only 3%. Furthermore, rats with the sweeter diet utilized the running wheel less than those on the plain chow diet.

Females are more vulnerable to diet-induced hyperphagia that is triggered by the availability of a sweeter diet. Evidence suggests that sweeter diets influence behaviors of not only overeating, but also a sedentary lifestyle. This phenomenon seems to occur with greater magnitude in females. Research suggests that it may be due to a difference in taste preference, but hormonal influence should also be considered (Eckel and Moore, 2004).

Previous studies have hypothesized that an interaction between opioid receptors and gonadal steroids may account for a difference in preference for sweet solutions in rats. Opioid antagonists significantly reduce sucrose consumption in male rats, as previously stated. Further studies examine the effects of the same opioid antagonist, naltrexone on both male and female mice. In a design by Moles and Cooper (1993), a baseline amount of 1.5% sucrose intake was measured for male and female mice. They were then injected with either naltrexone or a vehicle injection, and intake was measured again. When males were presented with the second solution of 5%, their reduction in intake was comparable to that of the 1.5% baseline solution. Females, however, showed little difference in intake of the two solutions. This finding concurs with previous findings that suggest that females have a higher threshold for detection of sucrose solutions.

A second aspect of the experiment measured intake to a 5% sucrose solution at 20 minutes after naltrexone injection and intake to a 10% sucrose solution at 30 minutes after injection. When the 5% solution was replaced with a 10% solution, suppression of
licking reversed in females, but not in males. Female intake to the 10% solution rose to
greater than intake to the 5% solution. One hypothesis to this finding is that females have
a greater number of hypothalamic µ receptor sites. Using this hypothesis, it can be
assumed that the opioid transmission is not blocked for the 10% solution, and increased
transmission occurs in the larger number of receptors. Therefore, increased intake is due
to the presence of hedonic value in the 10% solution compared to the 5% solution (Moles
and Cooper, 1993).

By looking at differences between males and females on the basis of intake of
sweet solutions, we can determine factors that lead to an overall preference for sweet
taste. Females show less sensitivity to sweet taste, which could account for females
preferring solutions greater in sweet taste more than males do.

III. Age Effects on Sweet Taste

Age is a significant factor in preference for sweet taste, as taste changes over time
with development. Research indicates that preference for sweet taste occurs as rats prefer
sweet solution more around the time of puberty. Postweaning rats prefer starch-based
diets over sugar-based diets, but adults show the opposite in preference. In a study by
Perez and Sclafani (1989), male and female rats, 4 weeks of age at the start of the
experiment were tested on amount of intake and preference between sucrose and
Polycose, a hydrolyzed starch. Both solutions yielded a greater amount of intake than
water. Sucrose did not diverge from Polycose in amount of intake until week 4, and it
continued to increase over time, while Polycose remained constant after week 4. When
rats were presented the two solutions in a two-bottle test, preference for sucrose was
apparent from the start and continued to increase with age, and by week 9, the last week of testing, rats showed almost total preference for sucrose over Polycose.

At the time when sucrose intake exceeded Polycose intake, at approximately 8 weeks of age, females were entering puberty. This could be one factor that accounts for the difference in the amounts of intake. However, males had a greater overall intake of sucrose. The increase with age could also be dependent upon the magnitude of concentrations. At 0.06 M sucrose concentration, rats initially consumed more Polycose than sucrose, but this reversed as rats grew older. One way of analyzing this effect is to recognize the higher caloric content of the Polycose versus the lower caloric sucrose solution.

Early in the stages of development, taste systems are modulated changes in needs for nutrients to facilitate development. It could be that since Polycose has more nutrient content, its preference was higher in early development. Sex differences can also be considered, since males, overall, consumed more sucrose than Polycose. One hypothesis is that gonadal hormones alter taste preference and selection of diet, as nutrient requirements change with age. These theories account for the increase to preference for sweet solutions with age (Perez and Sclafani, 1989).

The taste preference for more nutrient solutions in rats during early development seems to be an innate quality. Rats also express a similar innate behavior at the time of birth, as they prefer both nutrient and sweet solutions over sour, bitter, or salty solutions. In a study by Nizhnikov et al. (2001), newborn rats were given solutions of sweet, sour, salty, and bitter taste through a surrogate nipple, and were tested of how these initial gustatory experiences effected subsequent responding. Results show that rats initially
preferred milk and saccharin solutions through the nipple over water and other distinct
tastes, and these fluids increased attachment to the nipple. In subsequent trials, saccharin
was preferred over the other solutions, as taste preference was influenced by initial
exposure to the solution and positive responding to the nipple containing saccharin.
These results suggest that gustatory detection is present, and further, controls later
feeding behaviors in newborn rats (Nizhnikov, et al., 2001).

Age, like sex, is a predisposition that cannot be manipulated in order to alter
preference to sweet taste. However, findings such as these can be used to learn more
about feeding behaviors, and how adults come to prefer sweet solutions over others.

Conclusion

Because there are multiple factors that contribute to the preference to sweet taste
in rats, all common theories must be considered. Neurochemical factors include a reward
system involving opioid peptides and benzodiazepines. These factors can be
manipulating through the use of drugs that act on their receptors, either increasing or
decreasing the preference for sweet taste. Similar effects are seen in dopamine and
serotonin systems as well. Such a simple manipulation can alter eating behaviors.
Females are significantly less sensitive to sweet taste than males because of the presence
of the female hormone, estrogen, and preference for sweet taste tends to increase with age
in both males and females.

Although most research in this area agrees on certain theories, there are several
that conflict, or have confounding factors that do not allow them to fit. For example,
most research concerning gender agrees that females consume more of sweet solutions
and have a higher threshold for its detection. However, Perez and Sclafani (1989) found in their experiment that males consumed more sucrose than females. Contrasting results such as these can be accounted for based on methodology and purposes of the experiments. Perez and Sclafani were not directly testing gender differences in preference of sweet taste; they were evaluating sugar and starch intake on the basis of age in rats.

Most research cited in this paper, other than papers based on effects of sex differences, use male rats as their subjects. As seen in several of the studies, differences are great among males and females. It is important to account for factors like these when using these studies in real-world applications.

Furthermore, the results of the previous studies can have many real-world implications. Taste is an area of research consistently being studied, relative to obesity and its defining characteristics. In the study by Grunberg et al. (1988), rats were given access to “junk” foods, which were similar in value to the foods humans typically over consume. It is no coincidence that sweet taste is an area highly researched based on its large consumption by humans. Since obesity is a growing epidemic, it is important to examine factors such as these in the role of taste in obesity. For example, the study by Eckel and Moore (2004), it was found that a sweet diet and sedentary lifestyle in rats led to excessive weight gains. Other important findings cited in this paper, such as drug-induced decrease in sweet taste preference, female preference to sweet taste, or sweet taste increasing with age, provide necessary knowledge in order to tackle problems like obesity in today’s society. If factors that lead to excessive ingestion of sweet foods can
be pinpointed, we can potentially alter those systems in order to slow the rising trend of obesity.
References


