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Chronic sucrose intake enhances nicotine-induced antinociception in female but not male Long–Evans rats

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Abstract

Previous work has demonstrated that intake of palatable foods can alter the behavioral actions of opioid drugs. To investigate whether intake of palatable fare only affects opioid-induced behaviors or more generally influences drug-induced responses, this study examined the effects of chronic intake of a palatable sucrose solution on nicotine-induced antinociception. Eight male and eight female Long–Evans rats were provided with ground chow and water (control group), while eight males and eight females were provided with chow, water and a 32% sucrose solution (sucrose group). After 3 weeks of exposure to the dietary conditions, all rats were tested for nicotine-induced antinociception using the tail flick test. Nicotine, administered using a cumulative dose regime (0.03, 0.1, 0.3 and 1.0 mg/kg sc), led to dose-dependent increases in tail flick latencies in male and female rats. Females in the sucrose group displayed significantly greater antinociceptive responses to nicotine than those in the control group. Similar results were obtained when females were retested after an additional 2 weeks. Comparison of males and females, revealed that sucrose enhanced nicotine's antinociceptive action in female but not in male rats. While previous research suggested that sweet tasting substances might affect drug action by acting on the endogenous opioid system, the present results indicate that sucrose intake could also alter the cholinergic system and possibly other systems involved in nicotine antinociception.

Keywords: Nicotine; Antinociception; Rats; Sucrose; Pain; Palatability; Tail flick; Sweet taste; Analgesia

Recent work has revealed that intake of palatable foods and fluids can significantly alter the behavioral consequences of opioid agents (e.g. D'Anci et al., 1996, 1997; Kanarek et al., 1991, 1997, 1999, 2000; Roane and Martin, 1990; Rudski et al., 1997). For example, the antinociceptive effects of morphine and other opioid agonists are greater in rats and mice chronically consuming a sucrose solution than in animals not drinking the sugar solution (e.g. D'Anci et al., 1996, 1997; Kanarek et al., 1991, 2000; Roane and Martin, 1990). Moreover, rats that have previously consumed palatable nutritive foods and fluids are more responsive to the anorectic properties of opioid antagonists than rats maintained on only a standard laboratory diet (Kanarek et al., 1997; Rudski et al., 1997; Yeomans, 1993; Yeomans and Clifton, 1997). On the basis of these data, it has been hypothesized that intake of palatable foods and fluids alters the behavioral actions of opioid drugs by directly influencing the activity of the endogenous opioid system (D'Anci et al., 1996, 1997; Kanarek et al., 1997, 2000; Rudski et al., 1997). Evidence for this hypothesis comes from findings that intake of palatable foods and fluids: (1) stimulates the release and breakdown of hypothalamic beta-endorphin (Dum et al., 1983); (2) enhances opioid receptor binding in rat brains (Marks-Kaufman et al., 1989); and (3) increases levels of prodynorphin mRNA and dynorphin, respectively, in the arcuate nucleus and paraventricular nucleus of the hypothalamus (Welch et al., 1996).

Although there is support for the preceding hypothesis, no studies have yet addressed whether chronic sucrose intake influences the behavioral consequences of nonopioid drugs. Thus, it cannot be determined if intake of palatable foods and fluids specifically alters the endogenous opioid system or more generally affects behavioral responses induced by psychoactive drugs. Nicotine is a

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drug that is particularly interesting to examine with respect to the potential effects of chronic intake of a palatable solution on its behavioral actions for two reasons. First, nicotine alters feeding behavior in both rats and humans. More specifically, administration of nicotine decreases, while the cessation of nicotine use, increases the consumption of food, particularly sweet-tasting palatable items (Grunberg, 1982; Grunberg et al., 1984, 1985, 1986, 1987). Second, the results of recent studies suggest that intake of sweet-tasting nutritive carbohydrates decreases the urge to smoke in subjects attempting to quit smoking (Helmers and Young, 1998; West et al., 1990, 1999).

Previous research has shown that nicotine induces antinociception in various animal species, including humans (e.g. Block et al., 1993; Caggiula et al., 1995; Craft and Milholland, 1998; Jamner et al., 1998; Mousa et al., 1988; Perkins et al., 1994; Pomerleau, 1986; Pomerleau et al., 1984; Sahley and Berntson, 1979; Tripathi et al., 1982; Wewers et al., 1999). It has been proposed that nicotine produces its pain relieving effects by acting directly on the central nervous system (Hamann and Martin, 1992; Molinero and Del Rio, 1987; Sahley and Berntson, 1979; Tripathi et al., 1982). In support of this proposal, Sahley and Berntson (1979) reported nicotine had potent antinociceptive actions when administered directly into the brain, while Tripathi et al. (1982) observed a significant correlation between antinociceptive responses and brain levels of nicotine. Additionally, it has been shown that nicotine's antinociceptive actions are blocked by the centrally acting noncompetitive nicotine receptor antagonist, mecamylamine, but not by the peripherally acting quaternary nicotine receptor antagonist, hexamethonium (Molinero and Del Rio, 1987; Sahley and Berntson, 1979).

Taking together nicotine's effects on intake of palatable food with its antinociceptive actions, it was hypothesized that chronic intake of a sweet-tasting sucrose solution would alter the drug's pain relieving properties. Additionally, because previous data indicated that gender differences exist in nicotine's behavioral and physiological effects (Craft and Milholland, 1998; Donny et al., 2000; Grunberg et al., 1987, 1991; Perkins, 1999), the actions of sucrose on nicotine-induced analgesia were examined in male and female rats.

1. Methods

1.1. Animals

Sixteen male and 16 female adult Long–Evans rats (Charles River Laboratories, Portage, MI), weighing 200–300 g at the beginning of the experiment, were used. Animals were housed individually in standard hanging stainless-steel cages in a temperature (22 ± 20°C)- and humidity-controlled room maintained on a reverse 12 h light/12 h dark cycle (lights on at 20:00 hours).

1.2. Drugs

Nicotine hydrogen tartrate salt (Sigma, St Louis, MO) was dissolved in saline (0.9% NaCl), and was administered subcutaneously in the scruff of the neck at doses of 0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg of body weight using a cumulative dose regimen. Drug concentrations were adjusted to allow for injections of 1 ml/kg of body weight. All doses are expressed as the free base.

1.3. Experimental procedure

Upon arrival, the animals were randomly assigned to one of two experimental groups. Animals in the control group had continuous access to water and ground laboratory chow (no. 5001 Purina Laboratory Chow), while those in the sucrose group had continuous access to water, ground chow and a 32% (w/v) sucrose solution (1.28 kcal/g; pure sucrose, Dixie Crystals, Savannah, GA). Chow was given in Wahmann LC306A (Timonium, MD) stainless-steel food cups with lids. The food cups were clipped to the cage floors to prevent spillage. Both water and the sucrose solution were presented in glass bottles with rubber stoppers and drip-proof stainless-steel spouts. Food, sucrose and water intakes and body weights were measured every other day. The positions of the bottles were switched at the time of weighing to avoid the development of a side preference.

1.4. Antinociception test

Three weeks after exposure to the dietary conditions, the animals were tested using the radiant heat tail flick method (D'Amour and Smith, 1941). All tests were performed under red light during the dark phase of the 24-h dark/light cycle. All rats were held gently in a clean cloth by the same experimenter. The animals were placed on the tail flick apparatus with their tails smoothed into the tail groove. The light source was activated and remained focused on the tail until the rat moved its tail, thus switching off the light or until 9 s had elapsed. The cut-off time of 9 s was used to minimize damage to the rats' tails.

A baseline measure was determined by using the median of three tail flick tests, separated by approximately 10 s. Animals were then injected with the lowest dose of nicotine and returned to their cages. After 10 min, animals were again tested for antinociception using a single tail flick determination, and then injected with the next dose of nicotine. Because initial data suggested that males were less sensitive to the antinociceptive effects of nicotine than females, the maximal dose of the drug for males was 3.0 mg/kg and for females was 1.0 mg/kg. However, because

approximately 50% of the males displayed seizures following the 3.0 mg/kg dose of nicotine, these data are not presented. Additionally, to determine the duration of the antinociceptive actions of nicotine in the females, tail flick latencies were measured 20, 40, 60 and 90 min after the dose of 1.0 mg/kg nicotine.

To determined if prolonged access to sucrose would continue to affect nicotine-induced antinociception, females were retested after an additional 2 weeks. The procedure was similar to that described above with the exception that the maximal dose of nicotine was 3.0 mg/kg.

The antinociceptive effect of nicotine was determined by calculating the Percent of Maximum Possible Effect (%MPE) and was calculated as follows:

$$\%\text{MPE} = \frac{(\text{response latency} - \text{baseline latency})}{(\text{cut} - \text{off latency} - \text{baseline latency})} \times 100$$

All procedures were approved by the Tufts University Institutional Animal Care and Use Committee (IACUC).

1.5. Statistical analysis

Food and sucrose intake data were analyzed with repeated-measures ANOVA with diet group (control vs. sucrose) and sex (male vs. female) as the between-subjects factors, and days of the experiment as the within-subjects factor. Antinociceptive responses were analyzed with repeated-measures ANOVA with diet and sex as the between-subjects factors and drug dose or time since the final injection as within-subjects factors. Antinociceptive responses then were calculated separately for each dietary condition and for males and females. Differences were considered statistically significant when $P<.05$. Independent sample t tests were conducted to determine differences between diet groups and sex at each time and dose.

Additionally, to determine if there were relationships between either total caloric intake, or body weight and antinociceptive responses, correlation analyses were performed between antinociceptive response at the highest dose of nicotine and both mean daily total caloric intake and body weight.

2. Results

2.1. Food and sucrose intakes and body weight

During the 3 weeks preceding the antinociception test, daily caloric intake from chow was, as expected, significantly lower in the animals fed the sucrose solution compared to controls [$F(1,20)=222.81$, $P<.001$], and in female rats compared to males [$F(1,20)=65.62$, $P<.001$] (Table 1). While there were no differences in absolute sucrose intake as a function of gender, females consumed a significantly larger portion of their calories from the sucrose solution than males [$F(1,8)=9.62$, $P<.02$]. Total caloric intakes of sucrose animals were greater than those of controls [$F(1,22)=9.22$, $P<.01$] and intakes of males greater than those of females [$F(1,22)=32.30$, $P<.001$]. Analyzing total caloric intakes separately for males and females, revealed that the difference in intakes as function of dietary condition were significant in females [$F(1,11)=11.20$, $P<.01$] but not in males (Table 1).

On the test day, both males and females given sucrose weighed more than the same sex controls, however, in neither sex were body weights found to be significantly different (Table 1).

2.2. Antinociceptive responses in males and females after 3 weeks of access to sucrose

One male and one female were excluded from the data analysis because their baseline tail flick values were two standard deviations away from the mean of their group.

Table 1
Mean daily food and sucrose intakes, and body weight in male and female rats

	Food (g)	Sucrose (g)	Food (kcal)	Sucrose (kcal)	Total (kcal)	Sucrose (% of tot kcal)	Sucrose (kcal/100 g BW)	Body weight (g)
Males								
Control	26.89		88.72		89.92			469.25
S.E.M.	0.42		1.39		2.98			6.41
Sucrose	13.21 *	39.39	43.59 *	50.42	95.37	53.52	10.60	477
S.E.M.	0.69	1.39	2.29	1.78	5.31	1.72	0.38	12.79
Females								
Control	19.36**		63.9**		71.37**			305**
S.E.M.	0.68		2.26		7.59			9.49
Sucrose	7.47 *,**	43.57	24.66 *,**	55.77	78.67 *,**	69.34**	16.94**	330.5**
S.E.M.	0.70	2.80	2.34	3.59	3.18	2.69	0.89	15.71

* $P<.01$ compared to control group.
** $P<.01$ compared to males.

Table 2
Mean baseline tail flick latency

	Baseline latency (s)
Males	
Control	3.39
S.E.M.	0.12
n	7
Sucrose	3.83
S.E.M.	0.35
n	8
Females	
After 3 weeks of sucrose	
Control	3.60
S.E.M.	0.26
n	8
Sucrose	3.16
S.E.M.	0.32
n	7
After 5 weeks of sucrose	
Control	3.26
S.E.M.	0.49
n	8
Sucrose	3.44
S.E.M.	0.35
n	8

Baseline tail flick latencies did not differ as a function of diet for either males or females (Table 2).

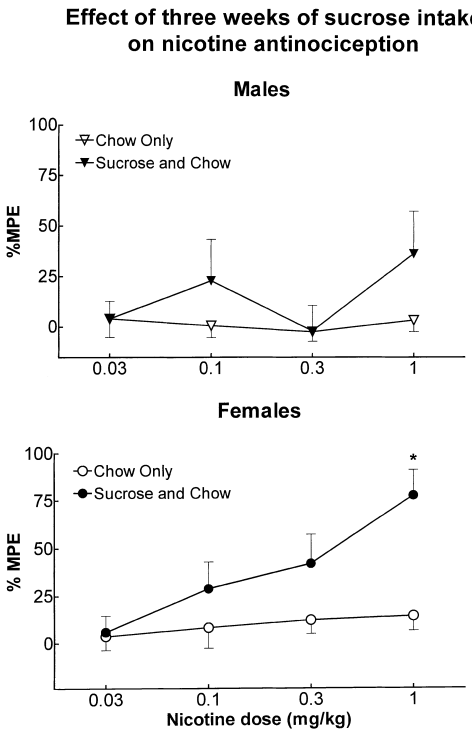

Fig. 1. Antinociceptive responses following cumulative administration of nicotine in male (top) and female rats (bottom) fed either chow and a 32% sucrose solution (solid symbols) or chow alone (open symbols) for 3 weeks. Data are expressed as mean (±S.E.M.) %MPE. $*P<.05$.

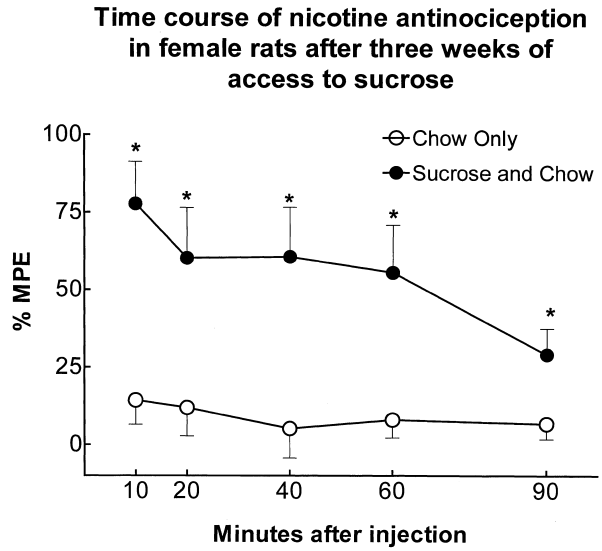

Fig. 2. Antinociceptive responses 10, 20, 40, 60 and 90 min following a final injection of nicotine in female rats fed either chow and a 32% sucrose solution (solid symbols) or chow alone (open symbols) for 3 weeks. Data are expressed as mean (±S.E.M.) %MPE. $*P<.05$.

When analyzed across gender, %MPEs increased significantly as a function of the dose of nicotine [$F(3,78)=9.33$, $P<.001$]. Additionally, it was found that %MPEs for rats drinking the sucrose solution were significantly greater than those of the controls [$F(1,26)=4.60$, $P<.05$] (Fig. 1A and B) and that the interaction of dose by diet was significant [$F(3,78)=6.29$, $P<.001$]. Although there was no main effect of gender on the antinociceptive actions of nicotine, there was a significant dose by gender interaction [$F(3,78)=3.22$, $P<.05$].

When data were analyzed separately for each dietary condition, %MPEs increased significantly as a function of drug dose for animals fed sucrose [$F(3,39)=10.44$, $P<.001$], but did not increase as a function of dose for animals fed only chow. Moreover, in the sucrose group, %MPEs of females were significantly greater than those of males [$F(1,13)=8.82$, $P<.01$]. No differences in %MPEs were observed as a function of gender for rats fed only chow.

Table 3
Pearson product moment correlations (r's) and significance levels (P's) between %MPEs following administration of the highest dose of nicotine (1 mg/kg) and mean total daily caloric intake and body weight at the time of nociceptive tests for all animals and separately for males and females

	%MPEs (males and females, $n=30$)	%MPEs (males, $n=15$)	%MPEs (females, $n=15$)
Mean total daily caloric intake	$r=-.094$	$r=-.096$	$r=-.179$
	$P=.620$	$P=.734$	$P=.385$
Body weight	$r=-.017$	$r=-.056$	$r=-.385$
	$P=.370$	$P=.843$	$P=.156$

Next, data were analyzed separately for males and females. In males, while there was a trend for %MPEs to increase as a function of drug dose [$F(3,39)=2.57$, $P<.068$], %MPEs did not vary as a function of diet. In comparison, in females, %MPEs increased directly as a function of drug dose [$F(3,39)=11.26$, $P<.001$], and were significantly greater in rats fed sucrose and chow than in those fed only chow [$F(1,13)=5.51$, $P<.01$]. Additionally, it was found that %MPEs of female rats fed sucrose remained greater than those of females fed only chow for up to 90 min after nicotine injections (Fig. 2).

Correlational analyses revealed that there were no significant relations between antinociceptive responses following the highest dose of nicotine (1 mg/kg) and either total caloric intake or body weight (Table 3).

2.3. Antinociceptive responses in females after 5 weeks of access to sucrose

Baseline tail flick latencies did not vary as a function of diet (Control group = 3.43 ± 0.35 s; Sucrose group = 3.26 ± 0.49 s), and were not different from the first time animals were tested (Table 3).

As observed in the first portion of the experiment, %MPEs increased significantly as a function of the dose of nicotine [$F(3,42)=7.97$, $P<.001$]. Moreover, female rats that had consumed the sucrose solution for 5 weeks displayed significantly greater %MPEs than controls [$F(1,14)=9.90$, $P<.01$] (Fig. 3). When data were analyzed separately for each dietary condition, it was revealed that %MPEs increased significantly as a function of drug dose for rats in both the sucrose [$F(3,21)=3.36$, $P<.05$] and chow groups [$F(3,21)=5.27$, $P<.01$]. As after 3 weeks, nicotine's duration of action was prolonged in animals in the sucrose group relative to its duration in the control group [$F(1,14)=4.25$, $P<.058$] (Fig. 4).

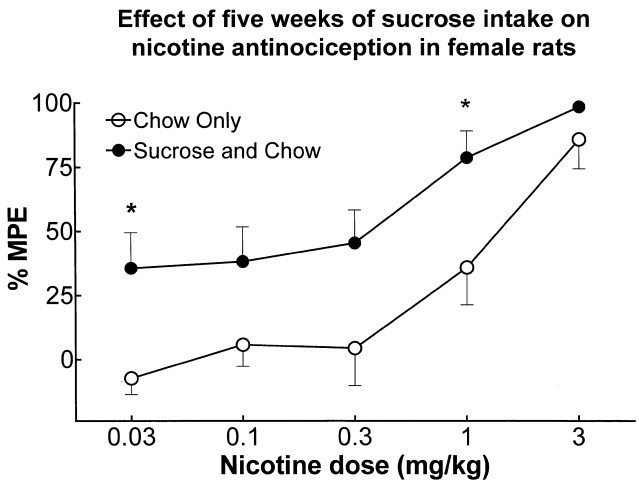

Fig. 3. Antinociceptive responses following cumulative administration of nicotine in female rats either chow and a 32% sucrose solution (solid symbols) or chow alone (open symbols) fed for 5 weeks. Data are expressed as mean (±S.E.M.) %MPE. *$P<.05$.

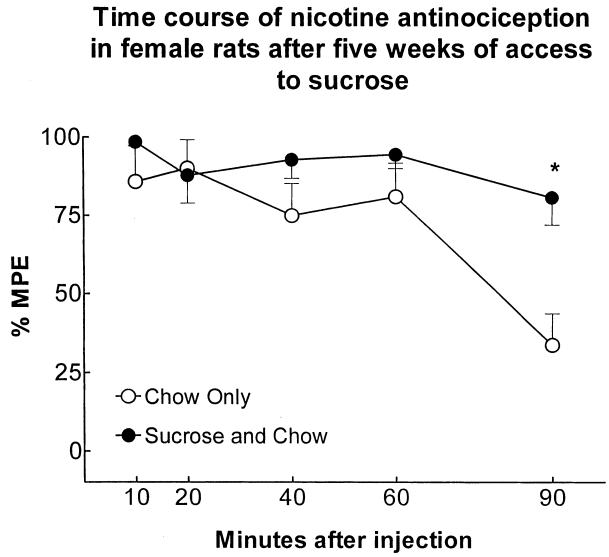

Fig. 4. Antinociceptive responses 10, 20, 40, 60 and 90 min following a final injection of 3 mg/kg nicotine in female rats fed either chow and a 32% sucrose solution (solid symbols) or chow alone (open symbols) fed for 5 weeks. Data are expressed as mean (±S.E.M.) %MPE. *$P<.05$.

3. Discussion

As previously reported, in the present experiment, nicotine administration led to dose-related increases in antinociceptive responses. However, in comparison to previous studies in which near maximal levels of antinociception on the tail flick test typically occurred with doses between 0.5 and 1.0 mg/kg nicotine (e.g. Block et al., 1993; Cepeda-Benito et al., 1998; Cooley et al., 1990; Mousa et al., 1988; Sahley and Berntson, 1979; Tripathi et al., 1982), in the present experiment, a dose of 1 mg/kg nicotine failed to produce significant antinociception in control male and female rats after the first drug administration. However, when the chow-fed females were tested a second time, nicotine did lead to dose-related increases in antinociceptive responses.

Several factors may have contributed to the differences in nicotine's antinociceptive effects observed between this and previous studies. First, the majority of earlier experiments assessing nicotine's pain relieving actions used Sprague–Dawley rats (e.g. Block et al., 1993; Caggiula et al., 1995; Cepeda-Benito et al., 1998; Chin et al., 1993; Cooley et al., 1990; Mousa et al., 1988; Sahley and Berntson, 1979; Tripathi et al., 1982), while Long–Evans rats were used in the present study. Recent work has shown that these two strains of rats differ significantly in their responses to nicotine (Faraday et al., 1999). While nicotine enhanced the startle response in Sprague–Dawley rats, the drug

reduced the response in Long–Evans rats (Faraday et al., 1999). In the same experiment, Long–Evans rats developed tolerance more rapidly to nicotine's effect on the startle response than did Sprague–Dawley rats (Faraday et al., 1999). Additionally, it has been reported that nicotine-metabolizing activity in hepatic homogenates is greater in Long–Evans than in Sprague–Dawley rats (Kyerematen et al., 1998). More rapid metabolism of nicotine may have contributed to the lack of a more pronounced antinociceptive response in Long–Evans rats. Another factor to consider is the time at which antinociceptive responses were measured. Nicotine rapidly leads to antinociception with maximal responses commonly reported between 2 and 8 min following peripheral injections (e.g. Block et al., 1993; Cepeda-Benito et al., 1998; Mousa et al., 1988; Tripathi et al., 1982; Wewers et al., 1999). In the present study, the first determination of tail flick latency was conducted 10 min after drug injections, a time when some investigators have already noted a decrease in the antinociceptive actions of nicotine (Cepeda-Benito et al., 1998; Mousa et al., 1988; Tripathi et al., 1982). Indeed, in ongoing studies, we have observed more significant antinociceptive effects on nicotine in Long–Evans rats when they were tested 5 min following drug injections. Finally, our use of a cumulative dosing regime may have led to a reduction in the antinociceptive potency of nicotine. Tolerance to nicotine's antinociceptive actions develops rapidly (Caggiula et al., 1993; Mousa et al., 1988; Tripathi et al., 1982; Wewers et al., 1999). For example, Tripathi et al. (1982) found that pretreatment with nicotine decreased the antinociceptive actions of a second injection given 10 min later. It is thus possible that acute tolerance to the higher doses of nicotine used in the present experiment occurred as a result of the prior injections of lower drug doses. In fact, in subsequent experiments, when Long–Evans rats were given a single dose of 1.0 mg/kg nicotine, they displayed near maximal antinociceptive responses (Mandillo and Kanarek, unpublished results).

Chronic intake of a sucrose solution enhanced the pain relieving actions of nicotine. This finding is reminiscent of that of previous studies demonstrating that sucrose intake augments the antinociceptive potency of opioid drugs (e.g. D'Anci et al., 1996, 1997; Kanarek et al., 1991, 2000; Roane and Martin, 1990). When assessing the effects of chronic sucrose intake on the behavioral consequences of morphine and nicotine there are obvious differences in nutrient intake and body weight between rats consuming only chow and those consuming chow and sucrose. When rats are given water, chow and a sucrose solution, they typically consume 50–60% of their calories as sucrose, and the remainder as chow. Because chow provides protein, vitamin and minerals, this means that intake of these nutrients is reduced to approximately 50% of that consumed by rats fed only chow. Additionally, rats consuming sucrose generally have greater daily caloric intakes and weigh more than rats fed only chow. Thus, it is possible that enhancement of nicotine and/or morphine-induced antinociception in sucrose-fed rats results from reductions in intakes of essential nutrients and/or increased caloric intake and body weight, rather than from sucrose intake, per se. While this is a possibility, results of previous studies have demonstrated that morphine-induced antinociception does not vary as a function of either reductions in protein or micronutrient intake (Kanarek et al., 1999). Although further research is needed to assess the effect of nutrient intake on nicotine-induced antinociception in sucrose-fed animals, we propose that results similar to those observed with morphine will be found. Moreover, the failure to obtain significant correlations between %MPEs and either total caloric intake or body weight in this study and others using morphine (D'Anci and Kanarek, unpublished results), suggest that the enhancement in antinociceptive responses in sucrose-fed rats is not related to either caloric intake or body weight.

One possibility for the similarity in the actions on sucrose on the pain relieving qualities of opioid drugs and nicotine is that both types of drugs produce their antinociceptive actions by acting on the endogenous opioid system. Indeed, there is substantial evidence of interactions between nicotine and the opioid system (e.g. Brauer et al., 1999; Covey et al., 1999; Davenport et al., 1990; Houdi et al., 1991, 1998; Ismail and el-Guebaly, 1998; Karras and Kane, 1980; Malin et al., 1996; Wewers et al., 1998, 1999). As examples of these interactions, administration of opioid agonists, such as methadone and heroin, increases cigarette smoking in human subjects, while administration of opioid antagonists reduces cigarette smoking and self-reported satisfaction with smoking (Brauer et al., 1999; Covey et al., 1999; Gorelick et al., 1989; Karras and Kane, 1980; Wewers et al., 1998). Additionally, cross tolerance can develop between the antinociceptive effects of morphine and nicotine (Zarrindast et al., 1999), and low doses of nicotine potentiate morphine's antinociceptive actions in mice (Zarrindast et al., 1996). Further indications of interactions between nicotine and opioid peptides comes from studies demonstrating that acute nicotine administration enhances plasma levels of endogenous opioid peptides, stimulates the release of these peptides in a variety of brain regions, and increases levels of preproenkephalin A mRNA in striatum and hippocampus (Houdi et al., 1991, 1998). Nicotine injections also can attenuate the inhibitory effect of the irreversible mu-opioid antagonist, *b*-funaltrexamine, on subsequent morphine-induced analgesia (Davenport et al., 1990). Taken together, the results of the preceding studies suggest that at least some of nicotine's behavioral actions are mediated through the activation of the endogenous opioid peptide system.

Although data support the existence of interactions between nicotine and the endogenous opioid system, the involvement of the opioid system in nicotine-induced analgesia is not clear cut. In rats, nicotine-induced analgesia is not blocked by administration of the opioid antagonist, naloxone (Iwamoto and Marion, 1993; Tripathi et al., 1982). Additionally, while naltrexone reduces self-administration

of cocaine, as well as that of opioid drugs, the opioid antagonist fails to alter nicotine self-administration in rats (Corrigall and Coen, 1991).

It has been hypothesized that nicotine leads to antinociception, at least in part, by acting on nicotinic acetylcholine receptors in the brain (Caggiula et al., 1995; Costa and Murphy, 1983; Hamann and Martin, 1992; Marubio et al., 1999; McCallum et al., 1999; Molinero and Del Rio, 1987; Sahley and Berntson, 1979; Tripathi et al., 1982). Evidence for central cholinergic mediation of nicotine's actions comes from studies demonstrating that nicotine's antinociceptive effects are blocked by centrally active nicotinic receptor antagonists, but are not blocked by antagonists, which do not readily cross the blood–brain barrier (Caggiula et al., 1995; Iwamoto, 1991; McCallum et al., 1999; Molinero and Del Rio, 1987; Sahley and Berntson, 1979; Tripathi et al., 1982). Moreover, administration of a disulfoton, a acetylcholinase inhibitor which leads to a reduction in the number of nicotinic binding sites in rat brain, reduces the antinociceptive effect of nicotine (Costa and Murphy, 1983). Finally, it has been reported that the antinociceptive properties of nicotine are significantly reduced in mice lacking a subunit of one of the nicotinic acetylcholine receptors (Marubio et al., 1999).

Although the effects of sucrose on central cholinergic activity have not been directly investigated, recent studies have suggested that intake of glucose, one of the monosaccharide components of sucrose, enhances memory in experimental animals and humans by increasing acetylcholine release within the central nervous system (Korol and Gold, 1998). Of particular relevance to the present work are the findings that glucose attenuates memory deficits, which result from the administration of the nicotinic cholinergic antagonist, mecamylamine (Ragozzino and Gold, 1991; Ragozzino et al., 1994) or from the administration of morphine (Stone et al., 1991; Talley et al., 1999) Thus, it is possible that sucrose intake enhanced nicotine-induced antinociception by acting directly on the cholinergic system.

The finding that sucrose intake can enhance the pain relieving properties of nicotine in animals also is interesting with respect to results of human studies demonstrating that intake of glucose or sucrose is associated with a reduction in the desire to smoke during periods of abstinence (Helmers and Young, 1998; West et al., 1990, 1999). These latter studies have led to the hypothesis that nutritive sugars may relieve nicotine craving by increasing blood glucose levels which could in turn alter nicotine's metabolic and neurological actions (West et al., 1990, 1999). Studies employing animal models of nicotine dependence could prove useful tools to assess this hypothesis. For example, this hypothesis could be investigated by examining the effect of sucrose intake in mediating the severity of nicotine withdrawal. Results of these types of studies could lead to dietary strategies to help individuals stop smoking.

Finally, the current experiments indicate a differential effect of sucrose on nicotine's actions in male and female rats. Previous studies also have demonstrated gender differences in the behavioral actions of nicotine (Craft and Milholland, 1998; Donny et al., 2000; Faraday et al., 1999; Grunberg et al., 1987, 1991; Perkins, 1999). For example, Craft and Milholland (1998) reported that the pain relieving actions of centrally administered nicotine were greater in female than male rats. Moreover, nicotine has more pronounced effects on food intake and body weight in females than in males in experimental animals (Grunberg et al., 1987) and human subjects (Hall et al., 1989). Recent work also has shown that female rats were more motivated to self-administered nicotine than male animals (Donny et al., 2000). Although it should be noted that human studies suggest that nicotine is less reinforcing in women than in men (Perkins, 1999).

Differences between males and female rats in the behavioral actions of nicotine may reflect gender differences in drug metabolism. Both in vivo and in vitro studies have demonstrated that male rats metabolize nicotine faster than females (Kyerematen et al., 1998). In the present experiment, gender differences in nicotine-induced antinociception were not observed in rats eating only chow, but were found in rats consuming the sucrose solution. This finding may be explained in part by differences in the amount of sucrose consumed between males and females. While males and females consumed similar amounts of sucrose on an absolute basis, sucrose intake calculated on the basis of body weight and the percent of daily calories obtained from sucrose were greater in females than in males. Thus, females consumed relatively more sucrose than males, which could explain the greater sucrose-induced enhancement of nicotine-induced analgesia in females than in males.

In conclusion, the results of this study demonstrate that chronic sucrose intake augments at least one of the behavioral consequences of nicotine, its pain relieving actions. This finding in conjunction with previous work demonstrating that sucrose potentiates the actions of opioid drugs (e.g. D'Anci et al., 1996, 1997; Kanarek et al., 1991, 2000; Roane and Martin, 1990; Rudski et al., 1997; Yeomans, 1993; Yeomans and Clifton, 1997), suggests that diet plays an important role in determining the behavioral properties of psychoactive drugs.

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