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# Chronic access to a sucrose solution enhances the development of conditioned place preferences for fentanyl and amphetamine in male Long–Evans rats

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**Abstract**

Consumption of palatable food and fluids alters the behavioral consequences of psychoactive drugs. To further investigate the effects of intake of palatable nutrients on the rewarding properties of these drugs, the effects of chronic intake of a sweet sucrose solution on the development of conditioned place preferences (CPP) to a mu-opioid agonist, fentanyl, and to a stimulant drug, amphetamine, were examined. Male Long–Evans rats consumed laboratory chow and water or chow, water, and a 32% sucrose solution. CPP testing was conducted in a three-chamber apparatus. In Experiment 1 (over four conditioning days), rats received saline, 0.004, or 0.016 mg/kg sc fentanyl citrate before being placed on the nonpreferred side of the apparatus and saline (subcutaneously) before being placed on the preferred side during a separate session on the same day. When given access to all three chambers, rats injected with 0.016 mg/kg fentanyl spent significantly more time on the drug-paired side than rats injected with saline. Furthermore, sucrose-fed rats displayed a significantly greater CPP than chow-fed rats. After conditioning, rats were tested for fentanyl-induced antinociception using the tail-flick test. Using a cumulative dose procedure, fentanyl (0.003, 0.010, 0.030, and 0.100 mg/kg sc) led to dose-dependent increases in tail-flick latencies. Rats fed with sucrose displayed significantly greater responses to fentanyl than those in the chow group. In Experiment 2, rats spent significantly more time on the drug-paired side of the CPP apparatus following injections of 0.33 or 1.0 mg/kg amphetamine than after saline injections. Additionally, following injection of 0.33 mg/kg amphetamine, sucrose-fed rats spent significantly more time on the drug-paired side of the chamber than chow-fed rats.


*Keywords:* Fentanyl; Amphetamine; Conditioned place preference; Sucrose; Antinociception; Reward; Dopamine; Mu-opioid agonists

## 1. Introduction

Consumption of palatable foods and fluids alters the behavioral consequences of a number of psychoactive drugs including morphine, amphetamine, cocaine, and nicotine (Kanarek and Marks-Kaufman, 1988a,b; Kanarek et al., 1991; Carroll and Lac, 1993; Yeomans, 1993; D'Anci et al., 1996, 1997; Mandillo and Kanarek, 2001). For example, the antinociceptive actions of morphine, other opioid agonists, and nicotine are more pronounced in rats and mice consuming a palatable sucrose solution in addition to a standard laboratory diet than in animals fed only the standard diet (Roane and Martin, 1990; Kanarek et al., 1991, 1997a, 2000; Kanarek and Homoleski, 2000; D'Anci et al., 1996, 1997; Mandillo and Kanarek, 2001). Additionally, rats consuming a palatable diet are more responsive to the anorectic effects of opioid antagonists than rats eating a less palatable diet (Yeomans, 1993; Rudski et al., 1997; Kanarek et al., 1997b).

Self-administration of a variety of drugs of abuse is also modified when animals are given access to palatable foods and fluids. Rodefer and Carroll (1997) reported that behaviors maintained by phencyclidine were reduced in rhesus monkeys when water was replaced by a saccharin solution. Along similar lines, Carroll and Lac (1993) found that rats consuming a sweet glucose and saccharin solution displayed delayed acquisition of operant responding for cocaine when compared to control animals. Furthermore, it has been demonstrated that rats drink less of an oral amphetamine solution or morphine solution when consuming granulated sucrose and laboratory chow than when eating only chow (Kanarek and Marks-Kaufman, 1988a,b).

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While self-administration studies are instructive for studying how a palatable diet can alter drug reinforced behavior, one confound is that the effects of the drug on motor behavior can alter the rate of responding for the drug, independent of the drug's reinforcing effect. Conditioned place preferences (CPP) procedures have been used as a complement to drug self-administration studies to assess the rewarding effects of drugs of abuse (Carr et al., 1989; Schechter and Calcagnetti, 1993; Bardo et al., 1995; Tzschentke, 1998; Bardo and Bevins, 2000). In a CPP procedure, two or more sets of distinct visual, spatial, tactile, and/or olfactory cues are differentially paired with a drug injection and a saline injection. These cues are confined to separate locations or compartments of the conditioning chamber, such that different areas of the chamber may have floors of varying textures, different wall colors and patterns, and/or different scents. The animal is initially given free access to all compartments, and the time spent in each compartment recorded. Conditioning involves an animal receiving pairings of injections of a rewarding drug (the unconditioned stimulus or US) in one compartment (the conditioned stimulus or CS), and pairings of saline injections in a different compartment. A choice test, in which animals receive free access to the compartments in the absence of the drug, follows several conditioning pairings. An increase in time spent in the drug-paired location after conditioning, relative to the amount of time spent in this location before drug injections, is considered evidence that a CPP has developed and that the drug has rewarding consequences.

The CPP paradigm provides a way to assess the motivational effects of drugs of abuse without the confound of drug effects on motor behavior associated with self-administration studies. In addition, the CPP paradigm is beneficial in that (1) it does not require surgery, (2) it is relatively inexpensive, (3) it requires minimal training of the animals (since a CPP can be attained with a single drug pairing) (Carr et al., 1989), and (4) it develops for a variety of abused drugs, including cocaine (Nomikos and Spyraki, 1988), amphetamine (Mackey and van der Kooy, 1985; Lett, 1988; Baker et al., 1998; Bardo et al., 1999), nicotine (Shoaib et al., 1994), morphine (Bardo and Neisewander, 1986; Miller and Nation, 1997), and fentanyl (Finlay et al., 1988; Shippenberg et al., 1988; Miller and Nation, 1997).

Environmental factors can moderate the development of a CPP. For example, rats raised in groups or in an enriched environment are more sensitive to amphetamine's rewarding properties as measured by a CPP than rats maintained in standard laboratory cages (Bowling and Bardo, 1994). With respect to opioids, rats that were food-deprived (Gaiardi et al., 1987) or exposed to a chronic stressor (Papp et al., 1992) are more sensitive to the rewarding effects of morphine than their nonstressed counterparts. On the other hand, rats exposed to environmental toxins display a decrease in a morphine-induced CPP relative to control animals (Miller and Nation, 1997). A study by Lett (1989) also suggested that intake of a sweet solution could enhance the rewarding effects of morphine as measured by a CPP procedure.

Based on previous studies demonstrating that intake of palatable foods and fluids can alter the behavioral consequences of psychoactive drugs, including the development of a CPP (Lett, 1989), it was hypothesized that consumption of a sweet-tasting solution would enhance the development of a CPP to opioid and stimulant drugs. To test this hypothesis, in Experiment 1, the effects of chronic intake of a sucrose solution on the formation of CPP to the mu-opioid receptor agonist, fentanyl, were examined. Fentanyl was chosen because it is a fast-acting opioid agonist, is more selective for the mu-opioid receptor than morphine, and is a frequently used analgesic in human adults and children (National Institute on Drug Abuse [NIDA], 2001). Previous studies have demonstrated the development of CPP for fentanyl at doses similar to those used in the present experiment (Mucha and Herz, 1985; Shippenberg et al., 1988). Experiment 2 examined whether chronic intake of a sucrose solution would enhance the development of a CPP for amphetamine. A number of investigators have reported that a reliable dose-related CPP results when amphetamine is used as the US (for reviews, see Bardo et al., 1995; Tzschentke, 1998). Additionally, environmental factors such as housing conditions, restraint stress, and chronic, unpredictable, mild stress have been found to influence the development of CPP for amphetamine (Papp et al., 1992; Bardo et al., 1995; Wongwidecha and Marsden, 1995).

## 2. Methods

### 2.1. Animals

Male Long–Evans rats (Charles River Laboratories, Portage, MI), weighing approximately 250 g at the beginning of the experiment, were housed individually in stainless steel cages in a temperature- ($22 \pm 2$ °C) and humidity-controlled room maintained on a 12-h light/12-h dark cycle (lights on at 08:00 h).

### 2.2. Diets

Upon arrival in the laboratory, rats were randomly divided into two diet groups. Rats in the chow group received ad libitum access to ground rodent chow (3.6 kcal/g, #5001 Purina Laboratory Chow) and tap water. Rats in the sucrose group received ad libitum access to rodent chow, water, and a 32% (w/v) sucrose solution (1.28 kcal/g; pure sucrose, Dixie Crystals, Savannah, GA). Chow was provided 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, water, and sucrose intakes and body weights were recorded daily

during the second week of the experiment. The position of the bottles was switched each day to avoid the development of a side preference.

### 2.3. Drugs

Fentanyl citrate (generously supplied by NIDA) and D-amphetamine sulfate (Sigma, St. Louis, MO) were dissolved in physiological saline to concentrations that allowed for subcutaneous injections of 1 ml/kg.

### 2.4. Conditioning procedures

Conditioning procedures began 3 weeks after the initiation of the dietary conditions. Place conditioning and testing were conducted in four square Plexiglas boxes ($60 \times 60 \times 35$ cm, $L \times H \times W$) containing three separate compartments approximately 120° apart (Fig. 1). The central starting compartment was painted gray and had a smooth Plexiglas floor and was separated from the conditioning chambers by guillotine doors. Both conditioning compartments were painted in black and white patterns, in an approximately 50:50 ratio of black to white; the left compartment had a striped black and white pattern, while the right compartment had a speckled black and white dot pattern. The floor of the striped compartment was fitted with a removable plastic grid floor that had $1 \times 0.5$ cm diamond-shaped perforations, while the floor of the dotted compartment was fitted with a removable solid latex floor that was covered with raised square $3 \times 3$-cm black tiles made of the same material.

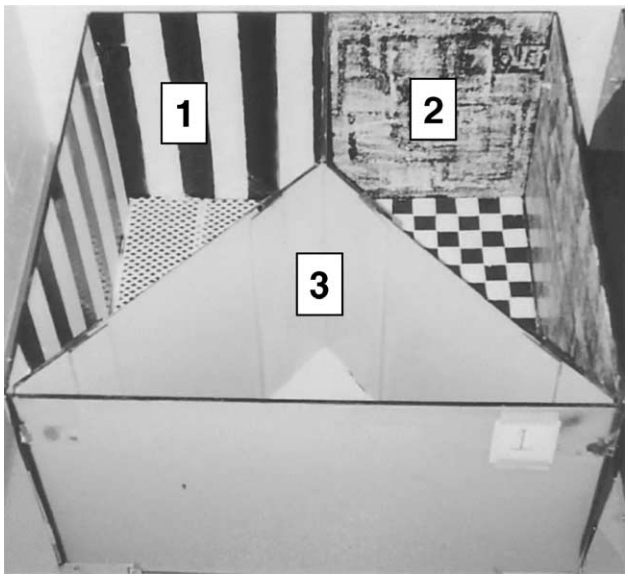


Fig. 1. A photograph of the conditioning apparatus with the guillotine doors lowered. The apparatus consisted of the following distinct compartments: (1) the striped conditioning compartment, (2) the dotted conditioning compartment, and (3) the gray starting compartment.

The central gray section of the conditioning apparatus was the starting compartment in which rats were placed. When the two guillotine doors of the chamber were raised, both conditioning compartments were visible and accessible. To familiarize the rats with the apparatus, on the first day of the study, rats were given free access to all three chambers of the CPP apparatus for 15 min without data being collected. On the second day of the study, this procedure was repeated, and the time spent in each compartment recorded using a Sony Handycam 200x video camera.

Drug conditioning took place on four consecutive days. Each day, there was a morning session and an afternoon session that were separated by 6 h, for a total of eight injection pairings. In the morning session, rats were injected with either drug or saline and immediately placed in one compartment of the CPP chamber. In the afternoon, rats were given the opposite injection treatment (drug or saline) and immediately placed in the other compartment of the CPP chamber. On the first conditioning day, half of the rats in each dietary group received drug and half saline in the morning session. On the following day, rats that had received drug in the morning received saline in the morning, and vice versa. This procedure was repeated on the two subsequent conditioning days. The drug-paired compartment for each rat was the compartment in which the rat spent the least amount of time during the preconditioning trial. The doors between the chambers were shut during conditioning trials.

In Experiment 1, on drug trials, six rats in the chow group and seven rats in the sucrose group were injected with saline, eight rats in the chow group and nine rats in the sucrose group with 0.004 mg/kg fentanyl, and eight rats in the chow group and nine rats in the sucrose group with 0.016 mg/kg fentanyl and placed in the previously nonpreferred side of the apparatus for 20 min. On nondrug trials, rats were injected with saline and placed in the previously preferred side of the conditioning apparatus for 20 min. If the drug (saline) was injected in the morning, then saline (the drug) was injected 6 h later in the afternoon. The order of drug and saline administration was alternated daily for each animal.

The conditioning procedure was identical in Experiment 2 with the exception that six rats in the chow group and six in the sucrose group were injected subcutaneously with saline, eight rats in the chow group and eight rats in the sucrose group with 0.33 mg/kg amphetamine, and eight rats in the chow group and eight rats in the sucrose group with 1.0 mg/kg amphetamine before being placed on the previously nonpreferred side of the CPP apparatus for 20 min.

The day after the four conditioning days, each rat was again placed in the central starting compartment with free access to all three compartments for 15 min, exactly as in the preconditioning phase. The animal's location in the apparatus was video taped. The establishment of a CPP was determined by subtracting the time spent in the drug-

paired compartment during the preconditioning session from the time spent in the drug-paired compartment in the postconditioning session. For control rats, in which both chambers were paired with saline injections, the initially nonpreferred chamber was defined as the drug-paired chamber.

For all preconditioning, conditioning, and postconditioning trials, the same conditioning box was used for each animal. Additionally, the time of day of postconditioning testing was always within 2 h of the time of the preconditioning session for each animal.

After all preconditioning, conditioning, and postconditioning trials, the apparatus floors and walls were thoroughly cleaned with a diluted Pine Sol solution to minimize the possibility that odor cues influenced approach behaviors.

### 2.5. Scoring of video tapes

Video tapes were scored by two independent individuals. The scores recorded by the two individuals were significantly correlated ($r$=.999, $P<.001$). A rat was scored as in a compartment when all four of its paws were in that compartment and was considered to still be in that compartment until all four of its paws left it.

### 2.6. Nociceptive tests

One week after the conditioning with fentanyl was completed, fentanyl-induced antinociception was measured in a subset of 14 rats consuming sucrose and chow, and 14 rats, consuming only chow. Within each dietary condition, six of the rats had received only saline, four rats, 0.004 mg/kg fentanyl, and four rats, 0.016 mg/kg fentanyl during the conditioning sessions. The animals in each drug group were chosen randomly by pulling numbers from a container. Antinociceptive responses were determined using the radiant heat tail-flick test (D'Amour and Smith, 1941). Each rat was held gently in a clean cloth by the same experimenter. The rat was placed on the tail-flick apparatus with its tail smoothed into the tail groove. A 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 20 s. Fentanyl then was administered using a cumulative dosing procedure in which each animal was injected subcutaneously every 10 min with increasing doses of the drug. The resulting cumulative doses for fentanyl were 0.003, 0.010, 0.030, and 0.100 mg/kg. The cumulative dose procedure was stopped at 0.100 mg/kg, or once a rat showed a maximal antinociceptive response.

All of the procedures were approved by the Tufts University Institutional Animal Care and Use Committee.

### 2.7. Statistical analysis

Statistical analyses were performed using SPSS 98 for Microsoft Windows. Food, sucrose, and caloric intake data were analyzed using a one-way ANOVA with diet as the between-subjects factor. Conditioning scores were analyzed using a two-way ANOVA with diet group and conditioning drug dose as the between-subjects factors.

The antinociceptive effect of fentanyl was expressed as the percent maximal possible effect (%MPE), which was calculated as follows:

$$\%\text{MPE} = [(\text{test latency} - \text{baseline latency}) / (\text{maximal latency} - \text{baseline latency})] \times 100$$

where maximal latency was the cut off time of 9 s (Dewey and Harris, 1975). Resulting data were analyzed using a repeated measures ANOVA with diet as the between-subjects factor and dose of fentanyl as the within-subjects factor. Additionally, the log dose at which 50% maximal effect of the drug was obtained ($IED_{50}$) was calculated for each subject using linear interpolation of the log dose–response curves. Comparison of the $IED_{50}$ between the dietary groups was made using a one-way ANOVA.

Pearson's $r$ analyses was conducted to investigate if there was a correlation between fentanyl antinociceptive $IED_{50}$ and CPP scores in animals in the sucrose group. Lastly, Pearson's $r$ analyses was conducted to determine if there was a correlation between body weight, sucrose intake, or caloric intake and the behavioral responses for the CPP and antinociception.

Differences were considered statistically significant when $P<.05$. For both conditioning and antinociception data, post hoc comparisons were conducted using the LSD test to determine differences between diet groups at each dose.

## 3. Results

### 3.1. Nutrient intakes and body weight

In Experiment 1, the mean total daily caloric intake of rats given sucrose was significantly greater (105.4 ± 2.1 kcal/day) than intake of rats not fed the sugar (94.9 ± 2.3 kcal/day) [$F(1,45)=11.98$, $P<.01$]. Although rats in the sucrose group consumed more calories, body weights of the two groups on the first day of conditioning did not differ (chow-fed rats = 349.1 ± 6.10 g; sucrose-fed rats = 346.0 ± 4.32 g).

Similarly in Experiment 2, the mean daily caloric intake of rats fed the sucrose solution in addition to laboratory chow (113.5 ± 4.3 kcal/day) was significantly greater than the intake of rats fed only chow (99.1 ± 5.7 kcal/day). On the first day of conditioning in Experiment 2, rats consuming

sucrose weighed significantly ($P<.05$) more (333.0 ± 6.88 g) than rats given only chow (314.8 ± 6.68 g).

### 3.2. CPP for fentanyl

Although individual rats displayed a preference for one of the chambers during the preconditioning trials, when averaged across animals there was no difference between the time spent in the striped compartment and in the dotted compartment (mean time in striped compartment = 304 ± 11.8 s; mean time in dotted compartment = 322 ± 14.9 s).

There was a nonsignificant trend for animals injected with increasing doses of drug to spend more time in the drug-paired compartment [$F(2,41)=2.867$, $P=.068$]. An LSD post hoc analysis revealed that rats conditioned with 0.016 mg/kg fentanyl spent significantly more time in the drug-paired compartment than those injected with saline alone ($P<.05$) (Fig. 2, top).

When data were analyzed separately for each dietary group, conditioning scores following 0.016 mg/kg fentanyl were significantly greater than scores after saline for rats in the sucrose group ($P<.05$), but not for rats in the chow group. Additionally, following injections of 0.016 mg/kg fentanyl, rats in the sucrose group spent significantly more time in the previously drug-paired side of the apparatus than rats in the chow group [$t(14)=-1.758$, $P=.05$] (Fig. 2, bottom).

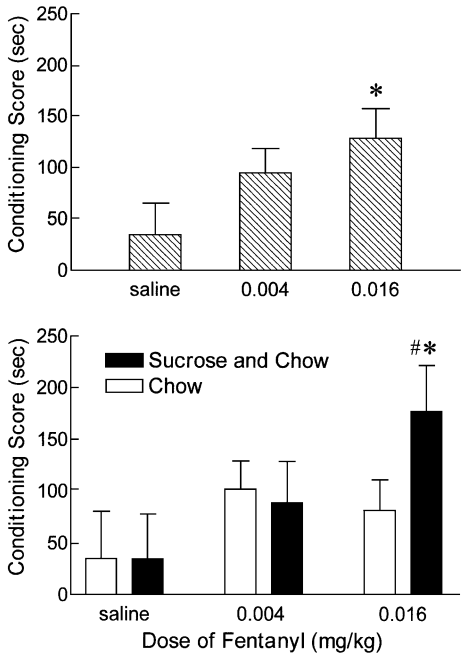


Fig. 2. Mean (±S.E.M.) conditioning scores following injections of saline, 0.004, or 0.016 mg/kg fentanyl combined for rats in both diet groups (top), and as a function of dietary condition (bottom). Conditioning scores for rats receiving fentanyl significantly (*$P<.05$) different from the scores of the corresponding group receiving saline. Conditioning scores to 0.016 mg/kg fentanyl significantly ($^{\#}P<.05$) greater for sucrose-fed rats than for chow-fed rats.

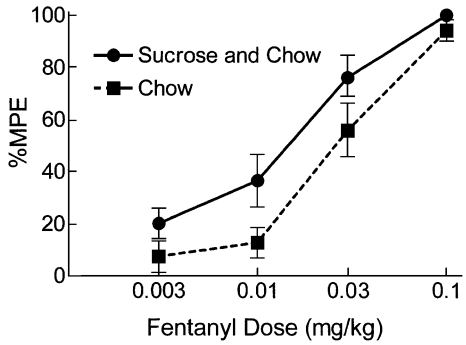


Fig. 3. Mean (±S.E.M.) %MPE following cumulative administration of fentanyl. Antinociceptive responses increased as a function of drug dose in both diet groups. %MPEs of rats consuming sucrose were significantly greater than those of rats fed only chow, [$F(1,24)=5.72$, $P<.05$].

### 3.3. Antinociceptive responses to fentanyl

Two animals were excluded from the data analysis because their baseline tail-flick latencies were two standard deviations away from the mean. With the exclusion of these two outliers, the mean baseline tail-flick latencies for rats in the two dietary conditions did not differ (baseline latency sucrose-fed group = 2.64 ± 0.20 s; baseline latency chow-fed group = 2.98 ± 0.18 s). %MPEs varied directly as a function of the dose of fentanyl [$F(3,72)=80.50$, $P<.001$]. Across fentanyl doses, %MPEs were higher for rats in the sucrose-fed group than rats in the chow-fed group [$F(1,24)=5.72$, $P<.05$] (Fig. 3). Furthermore, animals consuming sucrose had significantly lower $IED_{50}$ than animals drinking water alone (sucrose-fed group = 0.014 ± 0.028 mg/kg; chow = 0.033 ± 0.009 mg/kg) [$t(24)=2.38$, $P<.05$]. Antinociceptive responses did not differ as a function of what treatment rats had received during the CPP test.

The CPP scores were not correlated with the $IED_{50}$ for antinociceptive responses. Additionally, no significant correlation was observed between body weight, total caloric intake, or sucrose intake and either CPP scores or the $IED_{50}$ for antinociceptive responses.

### 3.4. CPP for amphetamine

Across dietary conditions, administration of amphetamine led to the development of a CPP as measured by a significant increase in the time drug-treated rats spent in the previously nonpreferred side of the conditioning apparatus [$F(2,38)=5.34$, $P<.01$] (Fig. 4, top). Post hoc tests showed that the conditioning scores of rats injected with 0.33 and 1.0 mg/kg amphetamine were significantly ($P$'s $<0.05$) greater than those of rats injected only with saline.

There also was a significant Diet × Dose interaction [$F(2,38)=3.29$, $P<.05$]. Subsequent analyses for each dietary condition revealed that although rats fed only chow did increase time spent in the previously nonpreferred side of the apparatus as a function of amphetamine administration, this increase failed to reach statistical significance. In

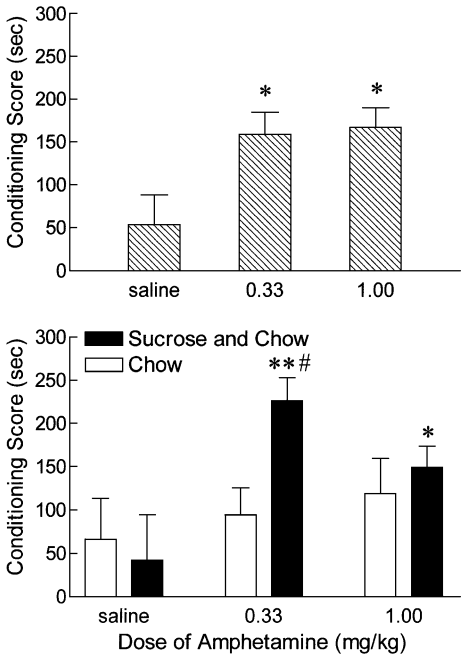


Fig. 4. Mean (±S.E.M.) conditioning scores following injections of saline, 0.33, or 1.0 mg/kg amphetamine combined for rats in both diet groups (top), and as a function of dietary condition (bottom). Conditioning scores of rats receiving amphetamine significantly (* $P<.05$, ** $P<.01$) different from the scores of the corresponding group given saline. Conditioning scores to 0.33 mg/kg amphetamine significantly ($^{\#}P<.05$) greater for sucrose-fed rats than for chow-fed rats.

contrast, conditioning scores of rats fed sucrose in addition to chow varied significantly as a function of amphetamine administration [$F(2,19)=6.75$, $P<.01$] (Fig. 4). LSD post hoc analyses demonstrated that following injections of 0.33 and 1.0 mg/kg amphetamine, conditioning scores of sucrose-fed rats were significantly greater ($P$'s $<.05$) than scores following saline injections.

Comparisons of conditioning scores of rats in the two dietary conditions revealed that following administration of 0.33 mg/kg amphetamine, scores of sucrose-fed rats were significantly ($P<.01$) greater than those of rats fed only chow.

There was no significant correlation between body weight, caloric intake, or sucrose intake and conditioning scores. However, when data were divided by dose and sucrose intake subjected to a median split, following the administration of 1.0 mg/kg amphetamine, conditioning scores of rats consuming greater than the median amount of sucrose were significantly greater than scores of rats consuming less than the median [$t(6)=3.06$, $P<.05$].

## 4. Discussion

Administration of both fentanyl and amphetamine resulted in the development of CPPs. With fentanyl, when data from the two dietary conditions were combined, the amount of time spent on the drug-paired side of the apparatus increased directly as a function drug dose. Post hoc tests revealed that rats conditioned with 0.016 mg/kg of fentanyl spent significantly more time in the drug-paired compartment than rats injected with saline. Across dietary conditions, amphetamine administration also resulted in an increase in the time spent on the drug-paired side of the conditioning chamber. The time spent on the drug-paired side was significantly greater for rats that received either 0.33 or 1.0 mg/kg amphetamine than for rats that received saline. However, there were no differences in conditioning scores between rats in the two drug groups. These results are similar to those of previous studies that found that conditioning scores typically reach asymptotic values at doses of 0.33 mg/kg, and may decline at doses higher than 1.0 mg/kg amphetamine (Bardo et al., 1995, 1999). These results are in accordance with those of a large number of other studies employing the CPP procedure for assessing the rewarding effects of psychoactive drugs (for reviews, see Tzschentke, 1998; Bardo and Bevins, 2000). What is novel about the results of the present studies is that chronic intake of sucrose enhanced the rewarding aspects of both drugs.

Intake of the sucrose solution significantly enhanced the development of a CPP when injection of fentanyl was the US. More specifically, when the data were analyzed separately for each dietary group, conditioning scores did not increase as a function of the dose of fentanyl for rats in the chow group, but did increase significantly for rats in the sucrose group. The failure to find increases in conditioning scores as a function of fentanyl injections in chow-fed rats was somewhat unexpected as prior studies using rats fed a chow diet did show the development of CPP with 0.016 mg/kg fentanyl (Mucha and Herz, 1985; Shippenberg et al., 1988). It should be noted however, that in most studies, doses higher than 0.016 mg/kg fentanyl were needed to produce a robust CPP (Mucha and Herz, 1985; Finlay et al., 1988; Shippenberg et al., 1988; Miller and Nation, 1997). Thus, if higher doses of the drug had been used in this study, a CPP for fentanyl may have developed in chow-fed rats. Fentanyl was used in the present study because it is a short acting opiate with a half-life of 2.5–4 h. However, because there were two conditioning sessions a day, it is possible that on the two of the four conditioning days when the drug was injected in the morning, residual effects of the drug were present in the afternoon session, and thus, reduced the development of a CPP.

Following the condition with 0.016 mg/kg fentanyl, sucrose-fed rats spent approximately twice as much time in the drug-paired side of the CPP chamber than chow-fed rats. This increase in time was greater than that observed between chow-fed rats in the saline group and either of the fentanyl groups. This finding is similar to that of a previous study demonstrating enhancement of a morphine CPP in rats consuming a sweet solution (Lett, 1989).

Consistent with previous studies examining fentanyl-induced antinociception (Thornton et al., 1998; Thornton

and Smith, 1998), fentanyl administration led to dose-related increases in tail-flick latencies. Rats drinking a sucrose solution exhibited enhanced antinociceptive responses to fentanyl, as measured both by elevated %MPEs and decreased $IED_{50}$ in sucrose-consuming rats relative to controls. As with the CPP scores, this enhancement of antinociception was not related to body weights or caloric intakes of the animals, but varied only as a function of diet group. While other studies have demonstrated that access to a palatable solution increases the antinociceptive potency of opioid agonists, such as morphine and spiradoline (e.g., Roane and Martin, 1990; Kanarek et al., 1991, 1997a; D'Anci et al., 1996, 1997), these are the first results demonstrating a sucrose-mediated enhancement of fentanyl-induced antinociception. Therefore, chronic access to a sweet-tasting sucrose solution enhanced both the rewarding and the antinociceptive properties of the selective mu-opioid agonist, fentanyl.

Chronic sucrose intake also augmented the development of a CPP for amphetamine. When data were analyzed separately for rats in each dietary condition, it was found that although chow-fed rats spent more time in the drug paired side of the conditioning apparatus following amphetamine injections than after saline injections, this increase was not significant. Several factors may have contributed to the lack of an amphetamine-induced CPP in chow-fed rats. First, when data were analyzed separately for each dietary condition, the number of rats in each drug condition was small (six or eight animals), and the variability in time spent on the drug-paired side among rats relatively high. Second, a meta-analysis by Bardo et al. (1995) indicated that the genetic background of the animals plays a role in determining the strength of an amphetamine-induced CPP. Long–Evans rats, which were used in this experiment, were reported to be less sensitive to amphetamine's rewarding properties than Sprague–Dawley or Wistar rats, which have been the subjects in the majority of studies investigating amphetamine-induced CPP (Bardo et al., 1995). Third, although the half-life of amphetamine in rats is relatively short (approximately 60–90 min) (Clausing and Bowyer, 1999; Cho et al., 2001), because there were morning and afternoon conditioning sessions, it is possible that on the two conditioning days when amphetamine was administered in the morning, residual effects of the drug were present in the afternoon session. Other variables including the use of a preconditioning trial, short conditioning sessions (less than 30 min), and administration of the drug subcutaneously rather than intraperitoneally may also retard the development of an amphetamine-induced CPP (Bardo et al., 1995).

In contrast to rats fed only chow, rats drinking the sucrose solution displayed a significant amphetamine-induced CPP. Rats consuming the sugar spent significantly more time on the drug-paired side of the chamber after conditioning with either 0.33 or 1.0 mg/kg amphetamine than after conditioning with saline. Moreover, following conditioning with 0.33 mg/kg amphetamine, the time spent on the drug-paired side of the chamber was significantly greater in sucrose-fed rats than in those fed only chow.

Based on the preceding data, it is hypothesized that sucrose intake augmented the conditioning properties of the low dose (0.33 mg/kg) of amphetamine by increasing the activity at dopaminergic neurons relative to that which occurred when only the drug was given. This increase would enhance the rewarding properties of the drug. When a higher dose of amphetamine (1.0 mg/kg) was used, there was a slight decrease in the conditioning scores of sucrose-fed rats relative to their scores after injections of the lower dose, and there was no difference in conditioning scores as a function of diet. These results raise the possibility that higher doses of amphetamine may have an aversive component. In support of this idea, studies have shown that after administration of doses greater than 1.0 mg/kg, there is a downward deflection in the dose–response curve for amphetamine-induced CPP (Bardo et al., 1995).

Several mechanisms can be proposed for sucrose-induced enhancement of CPPs for fentanyl and amphetamine. First, as mentioned above, it is possible that sucrose augmented the development of drug-induced CPPs by increasing activity in the dopaminergic system. There is growing evidence that indicates that both drug and food rewards are mediated by the mesolimbic dopamine system. For example, with respect to the rewarding properties of amphetamine, studies have shown that (1) an amphetamine-induced CPP is blocked by the administration of dopamine antagonists (e.g., Mackey and var der Kooy, 1985; Bardo et al., 1999), (2) injections of amphetamine into the nucleus accumbens produce a robust CPP (e.g., Carr and White, 1986; Baker et al., 1998; Schildein et al., 1998), and (3) destruction of the nucleus accumbens and related areas within the ventral striatum blocks the formation of CPP for amphetamine (e.g., Olmstead and Franklin, 1996).

Opioid drugs, such as fentanyl, also alters activity within the dopaminergic system. Extracellular dopamine concentrations in the nucleus accumbens increase as a function of opioid administration (for a review, see Boja and Meil, 1998). Additionally, electrophysiological studies have demonstrated that morphine stimulates the firing of dopamine neurons in the ventral tegmental area (Matthews and German, 1984). Furthermore, lesions of dopamine neurons or dopamine receptor antagonism attenuate opiate reward as measured by intracranial self-stimulation, drug self-administration, and CPP (Spyraki et al., 1983). In contrast to the ability of stimulant drugs to directly augment dopamine concentrations, opiates appear to enhance the concentrations of the neurotransmitter primarily by indirectly stimulating dopamine neurons (Ritz, 1999). Recent evidence also suggests that opiates act at the dopamine transporter. For example, repeated administration of morphine to rats was found to attenuate $B_{max}$ of [$^3$H]GBR12935 binding in the anterior

basal forebrain, including the nucleus accumbens (Simantov, 1993).

Ingestion of foods and fluids, particularly palatable items, also elicits activity in the mesolimbic dopamine system (for a review, see Smith, 1995). Dopamine metabolism, as determined by the ratio of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) to dopamine, is increased in the hypothalamus of rats sham-feeding sucrose. Moreover, the increase in the ratio of DOPAC to dopamine varies directly as a function of the concentration of sucrose being sham-fed (Smith et al., 1987). Microdialysis studies have shown that scheduled food intake elicits dopamine release in the striatum (Church et al., 1987; Salamone et al., 1989), and that dopamine release in the nucleus accumbens is significantly greater in rats eating a highly palatable diet than in rats consuming regular chow (Martel and Fantino, 1996).

Prior intake of sucrose can also predict the behavioral and neurochemical actions of psychoactive drugs. Rats display substantial variations in the amount of sucrose they ingest. Some animals avidly consume sucrose (high sucrose feeders), while others animals are less prone to take in the sugar (low sucrose feeders). Sills and Vaccarino (1994), Sill and Crawley (1996), and DeSousa et al. (2000) have reported that high sucrose feeders are more sensitive to the locomotor effects of amphetamine and more quickly initiate amphetamine self-administration than low sucrose feeders. Additionally, following amphetamine administration, high sucrose feeders have enhanced levels of dopamine in the nucleus accumbens relative to low sucrose feeders (Sill and Crawley, 1996). In conjunction with the previous results, in the present experiment, high sucrose feeders spent significantly more time on the side of the apparatus paired with the drug than low sucrose feeders following conditioning with 1.0 mg/kg amphetamine. These data suggest that sucrose intake may also serve as a predictor of amphetamine's rewarding properties, and provide evidence that palatable foods and drugs of abuse may be acting on the same neurochemical systems within the brain.

Further support for the idea that sucrose and drugs of abuse may have similar neurochemical actions comes from findings that CPP can be established when sucrose, rather than a drug, is used as the US (e.g., Spyraki et al., 1982; White and Carr, 1985; Agmo et al., 1995; Delamater et al., 2000). Moreover, the development of a CPP for sucrose can be blocked by the administration of a dopamine antagonist suggesting that the neurotransmitter is important in mediating the rewarding properties of sucrose intake (Agmo et al., 1995; Figlewicz et al., 2001).

Taking the preceding data together, it could be proposed that chronic sucrose consumption increases activity at dopamine neurons that, in turn, augments the rewarding effects of fentanyl and amphetamine. Based on this proposal, it would be predicted that sucrose intake should increase the development of CPP to other drugs (e.g., cocaine) that produce their rewarding effects by stimulating the mesolimbic dopaminergic system.

The endogenous opioid system represents another pathway by which sucrose could alter the behavioral actions of fentanyl and amphetamine. The rewarding effects of opioid agonists appear to be mediated in part by the endogenous opioid system, most clearly that part of the system associated with mu receptors. A number of studies using the CPP paradigm have shown that activation of the mu-opioid receptor reliably produces CPP, while antagonism of the mu receptor causes a conditioned place aversion (for a review, see Tzschentke, 1998). The endogenous opioid system also may play a role in determining the rewarding effects of amphetamine and palatable foods. In support of this idea, a number of investigators have reported that opioid antagonists block the formation of CPP not only to opioid drugs, but also to amphetamines (Trujillo et al., 1991; Tzschentke, 1998) and palatable foods (Agmo et al., 1995; Delamater et al., 2000; Imaizumi et al., 2001). Conversely, dopamine antagonists reverse the development of opioid and food-induced CPPs (Tzschentke, 1998; Figlewicz et al., 2001).

Further evidence that the endogenous opioid system is a viable pathway for the observed sucrose-induced alterations in drug-induced reward comes from studies assessing the behavioral and neurochemical consequences of palatable food intake. With respect to behavior, animals chronically consuming a sucrose solution are more sensitive to the antinociceptive actions of opioid agonists (e.g., Roane and Martin, 1990; Kanarek et al., 1991, 2000; Kanarek and Homoleski, 2000; D'Anci et al., 1996, 1997) and the anorectic actions of opioid antagonists (Yeomans, 1993; Kanarek et al., 1997a,b; Rudski et al., 1997). On the neurochemical side, relative to intake of a standard laboratory diet, consumption of a palatable diet by rats (1) increases whole brain opioid receptor binding (Marks-Kaufman et al., 1989), (2) leads to the release and breakdown of hypothalamic beta-endorphin (Dum et al., 1983), (3) augments hypothalamic levels of prodynorphin mRNA and dynorphin (Welch et al., 1996), and (4) elevates c-*fos* activity in the brainstem, an area rich in opioid receptors (Streefland et al., 1996). Additionally, recent work has shown that chronic intake of a sucrose solution decreases the ability of the irreversible mu-opioid antagonist, B-FNA, to block subsequent morphine-induced antinociception (Coy and Kanarek, unpublished results). Taking these results together, there is reason to believe that exposure to sweet substances may elevate endogenous opioid levels leading to increased occupation of opioid receptors that then could potentiate the behavioral consequences of exogenously administered opioid agonists.

In addition to promoting the formation of drug-induced CPPs, intake of sweet-tasting substances can result in a reduction in drug self-administration (Kanarek and Marks-Kaufman, 1988a,b; Carroll et al., 1989; Carroll and Lac, 1993; Gahtan et al., 1996; Rodefer and

Carroll, 1997). If, as hypothesized, sucrose intake stimulates rewarding neurochemical events, these two findings can be related. In the conditioning paradigm, the sucrose-induced increase in these rewarding events adds to the drug-induced increases, thereby leading to a more robust CPP than if only the drug was given. In self-administration studies, the reinforcing outcome of intake of palatable foods would mean that less drug is needed to produce optimal levels of relevant neurotransmitters when animals are consuming palatable fare then when they are prohibited from consuming favored items.

The present results generate a number of research questions. For example, it would be interesting to determine the role of palatable solutions in moderating the symptoms of withdrawal to opioids. While the highly rewarding consequences of opioid agonists is one factor contributing to the abuse of these drugs, another factor that contributes to opioid abuse is the severe withdrawal symptoms that result when drug administration is prohibited in dependent subjects or opioid antagonists are administered. If intake of palatable foods in some ways stimulates the same neurochemical systems as drugs of abuse, it is predicted that animals given access to a sucrose solution would display milder withdrawal symptoms than those not allowed to consume the sugar.

Another question is what is the relevance of the present findings to problems of human drug abuse. Intake of sweet-tasting foods and fluids has been reported to suppress alcohol intake in human subjects (Kampov-Polevoy et al., 1999) and to reduce the desire to smoke during periods of abstinence (West et al., 1990, 1999; Helmers and Young, 1998). Additionally, anecdotal reports and the results of a few studies suggest that withdrawal from a number of drugs of abuse, including heroin, nicotine, and alcohol, is associated with an increase in consumption of palatable, particularly sweet-tasting foods (e.g., Grunberg, 1982). Taking these findings together with the results of studies using experimental animals suggests that diet plays an important role in determining the behavioral properties of psychoactive drugs and that dietary strategies could be used as adjuncts to treatments for human drug addiction.

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