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Tolerance to Morphine-Induced Antinociception Is Decreased by Chronic Sucrose or Polycose Intake

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D'ANCI, K. E. *Tolerance to morphine-induced antinociception is decreased by chronic sucrose or Polycose intake.* PHARMACOL BIOCHEM BEHAV **63**(1) 1–11, 1999.—Chronic intake of palatable fluids alters morphine-induced antinociception. Two experiments were conducted to evaluate how long-term access to palatable fluids alters the development of tolerance to morphine-induced antinociception. In Experiment 1, 40 adult male Long–Evans rats were used. In addition to ad lib chow and water, 10 rats were given a 0.15% saccharin solution, 10 were given a 32% sucrose solution, and 10 were given a 32% Polycose solution to drink for 3 weeks. Ten rats were given chow and water alone, and served as dietary controls. Morphine-induced antinociception was assessed using the radiant-heat tail-flick method (TF). Half of the animals in each dietary condition were given preexposure to 7.5 mg/kg morphine; the other half received saline. All rats were given a TF 30-min postinjection. To determine whether tolerance developed, a cumulative dose paradigm (0.625, 1.25, 2.5, 5.0, 10.0 mg/kg) was employed 1 week after initial morphine injections, and was repeated at weekly intervals for 3 weeks. Antinociception was significantly lower in rats preexposed to morphine relative to rats preexposed to saline. Although all rats displayed decreased antinociception relative to the first morphine injection, rats that drank saccharin showed greater reductions in morphine-induced antinociception relative to rats that drank sucrose or Polycose. Experiment 2 was conducted to determine whether initial pairing of the TF with morphine preexposure produced differences in the development of opioid tolerance. All conditions and procedures were identical to Experiment 1, except that the initial morphine and saline injections were not followed by TF. As in Experiment 1, rats that drank saccharin showed less antinociception than rats that drank sucrose or Polycose. The present results suggest that long-term intake of palatable nutritive solutions curbs tolerance to morphine-induced antinociception, whereas long-term intake of a nonnutritive, sweet saccharin solution does not. © 1999 Elsevier Science Inc.

Morphine Tolerance Pain Sucrose Saccharin Polysaccharide Rats Polycose Opiates Tail flick Sweet taste Antinociception Mu-receptor

TOLERANCE to the analgesic properties of morphine develops rapidly, potentially after a single injection (5,37). Recently, it has been suggested that the development of analgesic tolerance to morphine may be influenced by environmental factors such as diet, stress, and prior experience with painful stimuli (10,11,27,36). For example, it is commonly held that experience with chronic pain offsets the development of tolerance to the analgesic potency of morphine (36). In contrast, experience with acute pain stimuli (21) or experience of social defeat stress (27) can accelerate the development of tolerance to the analgesic properties of opioid drugs.

An interaction between opiate activity and feeding behaviors is widely recognized [e.g. (6,7)]. Opioid agonists and antagonists influence both amount of food intake and selection of dietary variables (6). Opioid agonists typically increase voluntary consumption of foods, whereas opioid antagonists typically decrease feeding behavior (7). Reciprocity of the relationship between opioid activity and ingestive behavior is indicated by data showing that anticipation of palatable foods can cause increased levels of endogenous beta-endorphin (14). Thus, administration of exogenous opioids can modulate feeding behavior, and food intake can mediate endogenous

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levels of opioid peptides. Interestingly, evaluation of the diet of opiate addicts suggests that they ingest a greater proportion of their daily nutrients from simple sugars relative to nonaddicts, empirically supporting reports of sweet cravings in opiate addicts (29).

It has been repeatedly demonstrated that rats chronically consuming palatable, nutritive sucrose solutions show enhanced levels of opioid-induced antinociception relative to rats drinking water (10,11,18,19,31). In contrast, rats that chronically consume minimally caloric sweet solutions (e.g., saccharin) typically do not show elevations in opioid-induced antinociception (2,11,15,16,18). Furthermore, Lieblich and colleagues (23) found that rats bred for elevated saccharin intake displayed greater analgesic tolerance to morphine following saccharin intake. Polycose is a nutritive palatable, nonsweet polysaccharide that can be dissolved in water and is avidly consumed by rats (34). Recent studies have shown that Polycose affects nociception in a similar manner as sucrose (11). In a recent study (11), rats drinking sucrose or Polycose solutions showed enhanced morphine-induced antinociception following repeated exposure to morphine, whereas rats drinking a palatable nonnutritive saccharin solution showed reduced morphine-induced antinociception. These observations suggest that opioid-induced antinociception is enhanced by palatable nutritive fare but not by nonnutritive palatable solutions.

Although the effects of diet on morphine-induced antinociception have been widely examined, the effects of diet on the development of tolerance to morphine-induced antinociception are less well understood [e.g. (32)]. The present experiments were undertaken to further understand the role of dietary variables in the mediation of sensitivity to opioid drugs. The primary goal was to evaluate the ways in which palatable fluids act on the development of tolerance to the analgesic effects of morphine. It was proposed that pretreatment with morphine would result in tolerance to morphine-induced antinociception in rats drinking saccharin or water, but not in rats drinking sucrose or Polycose. Because tolerance to morphine antinociception may develop differently, depending on the presence or absence of a noxious stimulus (36), two experiments were conducted. In the first experiment, all rats were given a single nociceptive test following morphine or saline pretreatment. In the second experiment, there was no pairing of the nociceptive test with the priming injections.

GENERAL METHOD

Subjects

Forty adult male Long–Evans rats (Charles River, Portage, MI) weighing between 225–250 g were used in each experiment. Rats were housed individually in standard hanging cages in a climate controlled room (22 ± 2°C), which was kept on a 12:12 h reverse light:dark cycle (lights on at 2000 h). All experimental manipulations were conducted under red lights during the dark cycle.

Diets

All rats were maintained on ad lib ground Purina chow #5001 and water. In addition to chow and water, 10 rats were given ad lib access to a 0.15% w/v sodium saccharin solution, 10 were given a 32% w/v sucrose solution (1.28 kcal/ml), and 10 were given a 33.68% w/v Polycose® (Ross Laboratories, Colombus, OH) (1.28 kcal/ml) to drink. A final group of 10 rats received only chow and water. A 32% sucrose solution was used based on prior research demonstrating sucrose modulated sensitivity to opioid-induced analgesia [e.g., (18,19)]. The saccharin solution was chosen based on previous studies demonstrating that under similar conditions to the present experiments, rats consume equivalent amounts of a 0.15% saccharin solution or a 32% sucrose solution (26). Chow was presented in Wahman (Timonium, MD) LC-306A stainless steel food cups with lids, which were clipped to the floor to prevent spillage. Fluids were presented in glass bottles fitted with drip-proof stainless steel stoppers. Food and fluid intakes and body weights were measured every other day. Chow intakes were recorded to the nearest 0.1 g. Fluid intakes and body weights were recorded to the nearest 1.0 g. The positions of the bottles were switched at the time of weighing to prevent the development of a side preference. Rats in the water-alone condition were given only one bottle to drink from. Previous data show that the choice of two water bottles does not significantly alter nociceptive responses (7). Rats were given 3 weeks to acclimate to handling procedures and diets before the start of nociceptive testing. Feeding conditions were the same in Experiment 1 and Experiment 2.

Drugs

Morphine sulfate (generously provided by the National Institute on Drug Abuse) was dissolved in 0.9% saline. All injections were given sc in a volume of 1.0 ml/kg.

Nociceptive Testing

Pain thresholds were determined via the radiant-heat tail-flick assay (8). The tail-flick procedure has been described extensively elsewhere [e.g., (9–11)]. Briefly, all animals were placed on the tail-flick apparatus (Endie Instrument Co., Montpelier, VT) with their tails smoothed into the tail groove that contained a photocell. The light beam was activated and remained focused on the tail until the rat moved its tail, thus switching the light off. The intensity of the light was adjusted so that mean basal tail-flick latencies were 2–3 s. To prevent tissue damage, the light was set to turn off after 9 s if the rat failed to move its tail. Baseline tail-flick latencies were determined by using the median of three tail flick tests, separated by approximately 15 s. Tail-flick latencies following morphine administration were determined by the mean of two tail-flick tests, separated by approximately 15 s (3,4). Two tail-flick tests were used to reduce variability in responses while attempting to reduce unnecessary exposure to the noxious stimulus. All nociceptive test sessions were separated by 7 days.

Morphine Preexposure

In Experiment 1, baseline tail-flick latencies were determined for all rats. Half of the rats were given 7.5 mg/kg morphine and then returned to their cages. The other half received saline injections and were then returned to their cages. Antinociception was measured 30 min subsequent to the priming injections.

As described earlier, the development of analgesic tolerance can vary with the presence or absence of a noxious stimulus (36). In Experiment 1, it was possible that exposure to the tail-flick test could have produced differences in analgesic tolerance. To examine this possibility in Experiment 2 one-half of the rats were given 7.5 mg/kg morphine and the other half received saline injections. There were no tail-flick tests given before or after these injections.

Assessment of Tolerance

One week following priming injections, rats were injected with morphine according to a cumulative dosing procedure (0.625, 1.25, 2.5, 5.0, 10.0 mg/kg) (9–11). Tail-flick latencies were measured immediately prior to and 30 min subsequent to each injection. All doses were given in ascending order, and all rats received all doses. To determine the development of tolerance to the antinociceptive effects of morphine over time, nociceptive testing was repeated once a week for a total of 3 weeks.

Statistical Analysis

Food intake and body weight data were analyzed using one-way ANOVA (diet). Nociceptive data were converted into percent maximal possible effect (%MPE) (13), which was calculated as follows:

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

where the maximal latency is 9 s. The %MPE is reflective of the level of antinociception relative to both the baseline and the maximum latency. Rats with baseline TF latencies greater than 4.0 s were eliminated from analysis, as indicated by post hoc analysis for outliers (SPSS 7.0 for Windows 95). Individual ED_{50} (IED_{50}) values were calculated from each rat's %MPEs using linear regression to determine at what dose each rat showed 50% MPE (GraphPad Prism 2.01). The IED_{50} data were analyzed using two-way ANOVAs (diet × dose) and three-way ANOVAs (diet × dose × week), with dose and week as repeated measures. Where necessary, a conservative *F*-test (F_C) was employed to offset violations of sphericity in the data (22). Post hoc comparisons were done with Bonferroni-Dunn's *t*-tests, and least-significant differences (LSD) tests. Significance was defined as a *p*-value of < 0.05.

RESULTS

Experiment 1

Food intake and body weights. Intake of Purina chow differed significantly as a function of diet, $F(3, 36) = 99.4$, $p < 0.001$. Post hoc analysis indicated that across the experiment, rats drinking either water or saccharin consumed significantly ($p < 0.05$) more chow than rats drinking sucrose or Polycose, and that rats drinking sucrose consumed significantly more chow than rats drinking Polycose (Table 1). Total mean daily caloric intakes differed as a function of diet, $F(3, 36) = 10.23$, $p < 0.001$. Post hoc analysis showed that rats drinking sucrose consumed significantly ($p < 0.05$) more calories than rats drinking either water or saccharin.

At the end of the experiment, body weights differed significantly as a function of diet, $F(3, 36) = 5.33$, $p < 0.005$. Post hoc analysis showed that rats which drank sucrose weighed significantly more than rats drinking water.

Nociceptive responses. There were no differences in baseline tail-flick latencies as a function of diet (water: 3.01 ± 0.77 s; saccharin: 2.89 ± 0.55 s; sucrose: 2.34 ± 0.38 s; Polycose: 2.81 ± 0.59 s). Following initial morphine exposure, %MPEs were significantly greater for rats given 7.5 mg/kg morphine relative to rats given saline, $F(1, 31) = 369.53$, $p < 0.0001$. Tail-flick latencies for rats given saline did not differ significantly from baseline.

One week after morphine preexposure, baseline tail-flick latencies differed significantly as a function of diet, $F(3, 36) = 4.89$, $p < 0.01$ (water: 2.58 ± 0.38 s; saccharin: 2.42 ± 0.38 s; sucrose: 2.15 ± 0.32 s; Polycose: 2.05 ± 0.30 s). Post hoc comparisons indicated that rats drinking Polycose had significantly lower baseline tail-flick latencies than rats drinking water. No differences in baseline tail-flick latencies were seen at the second and third weeks of nociceptive testing.

IED_{50} values varied as a function of both diet and priming conditions 1 week following priming injections. Rats given preexposure to morphine had significantly higher IED_{50} values than rats given saline, $F(1, 32) = 12.76$, $p < 0.005$. Post hoc analysis indicated that within the morphine preexposed condition, IED_{50}s were significantly greater for rats drinking either saccharin or water. IED_{50}s also varied as a function of diet, $F(3, 32) = 5.69$, $p < 0.005$. Rats that drank water or saccharin had significantly greater IED_{50}s than rats drinking sucrose or Polycose. At the second week of nociceptive testing, rats that drank water had significantly ($p < 0.05$) greater IED_{50} values than rats that drank Polycose. During the third week of nociceptive testing, rats drinking saccharin had significantly greater IED_{50} values than rats drinking Polycose (Table 2).

Across all 3 weeks, IED_{50}s varied significantly as a function of diet, $F(3,3\ 2) = 3.68$, $p < 0.05$. IED_{50}s also increased significantly over time, $F_c(2, 40) = 23.60$, $p < 0.005$. Analysis of each diet across all 3 weeks showed that while IED_{50}s increased significantly for rats that drank water, $F(2, 16) = 12.6$, $p < 0.005$, or saccharin, $F_c\ (2, 9) = 8.18$, $p < 0.01$, IED_{50}s did

TABLE 1

MEAN (±SD) BODY WEIGHT AND FOOD INTAKE DATA

	Body Weight*	Total kcals	Chow (g)	Palatable Fluid (ml)
Water	394.9 (15.34)	92.8 (6.78)	25.8§¶ (1.88)	
Saccharin	408.6 (23.27)	97.3 (6.71)	27.0§¶ (1.86)	48.0 (14.69)
Sucrose	437.4† (39.52)	118.2‡ (17.89)	14.8§ (3.52)	50.8 (43% of kcals) (9.30)
Polycose	425.1 (27.95)	106.4 (9.05)	11.2 (2.38)	51.6 (49% of kcals) (5.08)

*Body weight determinations are from the final nociceptive test.

†Indicates that rats drinking sucrose weighed significantly ($p < 0.05$) more than rats drinking water.

‡Indicates that rats drinking sucrose consumed significantly ($p < 0.05$) more kcals than rats drinking either water or saccharin.

§Indicates that rats consumed significantly ($p < 0.05$) more Purina chow than rats drinking Polycose.

¶Indicates that rats consumed significantly ($p < 0.05$) more Purina chow than rats drinking sucrose.

TABLE 2
MEAN (± SD) IED_{50} VALUES (mg/kg)
ACROSS ALL THREE WEEKS OF NOCICEPTIVE TESTING

	Water*	Saccharin*	Sucrose	Polycose
Week 1	6.61†‡ (3.41)	6.63†‡ (2.32)	4.29 (0.91)	4.58 (1.17)
Week 2	7.02† (2.92)	6.28 (1.42)	5.47 (1.08)	5.42 (0.61)
Week 3	11.12 (4.08)	12.80† (5.95)	8.58 (5.72)	8.08 (3.87)

Data are collapsed across priming condition.

*Indicates that IED_{50} values increased significantly over 3-week test period for rats drinking water or saccharin.

†Indicates that IED_{50} values were significantly (LSD: $p < 0.05$) greater for rats that drank water or saccharin than rats that drank Polycose.

‡Indicates that IED_{50} values were significantly (LSD: $p < 0.05$) greater for rats that drank water or saccharin than rats that drank sucrose.

not significantly vary over time for rats drinking either sucrose or Polycose. For rats drinking saccharin, there was a significant difference in IED_{50}s as a function of priming condition, $F(1, 8) = 5.88$, $p < 0.05$ (Figs. 1 and 2).

Experiment 2

Food intake and body weights. Intake of Purina chow differed significantly as a function of diet, $F(3, 36) = 101.27$, $p < 0.001$. Post hoc analysis indicated that across the experiment, rats drinking either water or saccharin consumed significantly ($p < 0.05$) more chow than rats drinking sucrose or Polycose, and that rats drinking sucrose consumed significantly more chow than rats drinking Polycose (Table 3). Total mean daily caloric intakes differed as a function of diet, $F(3, 36) = 15.71$, $p < 0.05$. Post hoc analysis showed that rats drinking sucrose consumed significantly ($p < 0.05$) more calories than rats drinking either water or saccharin.

Body weights differed significantly as a function of diet, $F(3, 36) = 4.91$, $p < 0.01$. Post hoc analysis showed that rats drinking sucrose gained significantly more weight than rats drinking either saccharin or water.

Nociceptive responses. One week following priming injections, baseline tail-flick latencies differed significantly as a function of diet, $F(3, 36) = 3.68$, $p < 0.05$ (water: 2.17 ± 0.48 s; saccharin: 2.89 ± 1.00 s; sucrose: 2.03 ± 0.25 s; Polycose: 2.32 ± 0.50 s). Post hoc comparisons indicated that rats drinking sucrose had significantly lower baseline tail-flick latencies than rats drinking saccharin. No differences in baseline tail-flick latencies were seen at the second and third weeks of nociceptive testing.

As in Experiment 1, IED_{50} values varied as a function of both diet and priming conditions during the first week following priming injections. Rats given preexposure to morphine had significantly higher IED_{50} values than rats given saline, $F(1, 32) = 29.88$, $p < 0.001$. IED_{50}s varied as a function of diet, $F(3, 32) = 3.70$, $p < 0.05$, rats that drank saccharin and that had morphine preexposure had significantly ($p < 0.05$) higher IED_{50}s than rats that drank sucrose. Rats that drank saccharin and that had morphine preexposure also had significantly higher IED_{50}s than rats that drank saccharin and that had saline.

The differences in IED_{50} values continued through the second week of nociceptive testing. IED_{50} values were significantly higher for morphine preexposed rats, $F(1, 32) = 12.29$, $p = 0.001$, and for rats that drank saccharin, $F(3, 32) = 4.60$, $p < 0.01$ (see Table 4). There was a priming by diet interaction, $F(3, 32) = 3.52$, $p < 0.05$; post hoc *t*-tests indicated that rats drinking saccharin and that were morphine preexposed had significantly higher ($p < 0.05$) IED_{50} values than rats that drank saccharin and had saline at the time of preexposure. The same rats also had significantly higher ($p < 0.05$) IED_{50} values than rats that drank sucrose and were morphine preexposed.

Across the 3-week test period, IED_{50}s varied significantly as a function of diet, $F(3, 32) = 4.44$, $p = 0.01$, and morphine preexposure, $F(1, 32) = 9.36$, $p < 0.005$. IED_{50}s also increased significantly over time, $F(2, 64) = 10.34$, $p < 0.001$. Analysis of each diet across all 3 weeks showed that IED_{50}s increased significantly for rats that drank saccharin, $F(2, 16) = 4.35$, $p < 0.05$, IED_{50}s did not significantly vary over time for rats drinking water, sucrose, or Polycose. However, for rats drinking water, there was a significant difference in IED_{50}s as a function of priming condition, $F(1, 8) = 5.40$, $p < 0.05$. Rats that drank water and had morphine preexposure showed greater tolerance to morphine-induced antinociception than rats that had saline (Figs. 3 and 4).

DISCUSSION

The present experiments demonstrate that long-term intake of a palatable, nonnutritive saccharin solution or water resulted in increased IED_{50}s following repeated administration of morphine. In contrast, following chronic intake of palatable, nutritive fluids IED_{50}s did not significantly increase over time. These data indicate that rats given saccharin or water required more morphine to achieve the point of 50% maximal possible effect over time than did rats drinking sucrose or Polycose. In both experiments, the increases in IED_{50}s were most robust for the rats that drank saccharin, independent of initial morphine pretreatment. For rats that drank water, increases in IED_{50}s across time were strongest in the morphine pretreated group.

Chronic intake of palatable fluids significantly altered the development of tolerance to morphine-induced antinociception. Tolerance was defined as decreases in %MPEs for a given dose of morphine and, therefore, as increases in individual ED_{50} values. Rats that drank saccharin consistently showed greater tolerance to the analgesic potency of morphine than rats that drank sucrose or Polycose. In Experiment 1, when morphine preexposure was paired with a noxious stimulus (tail flick), rats that drank water or saccharin showed greater tolerance to morphine-induced antinociception than rats that drank sucrose or Polycose. Although rats that drank Polycose or sucrose also showed some degree of tolerance to morphine-induced antinociception, these data did not reach

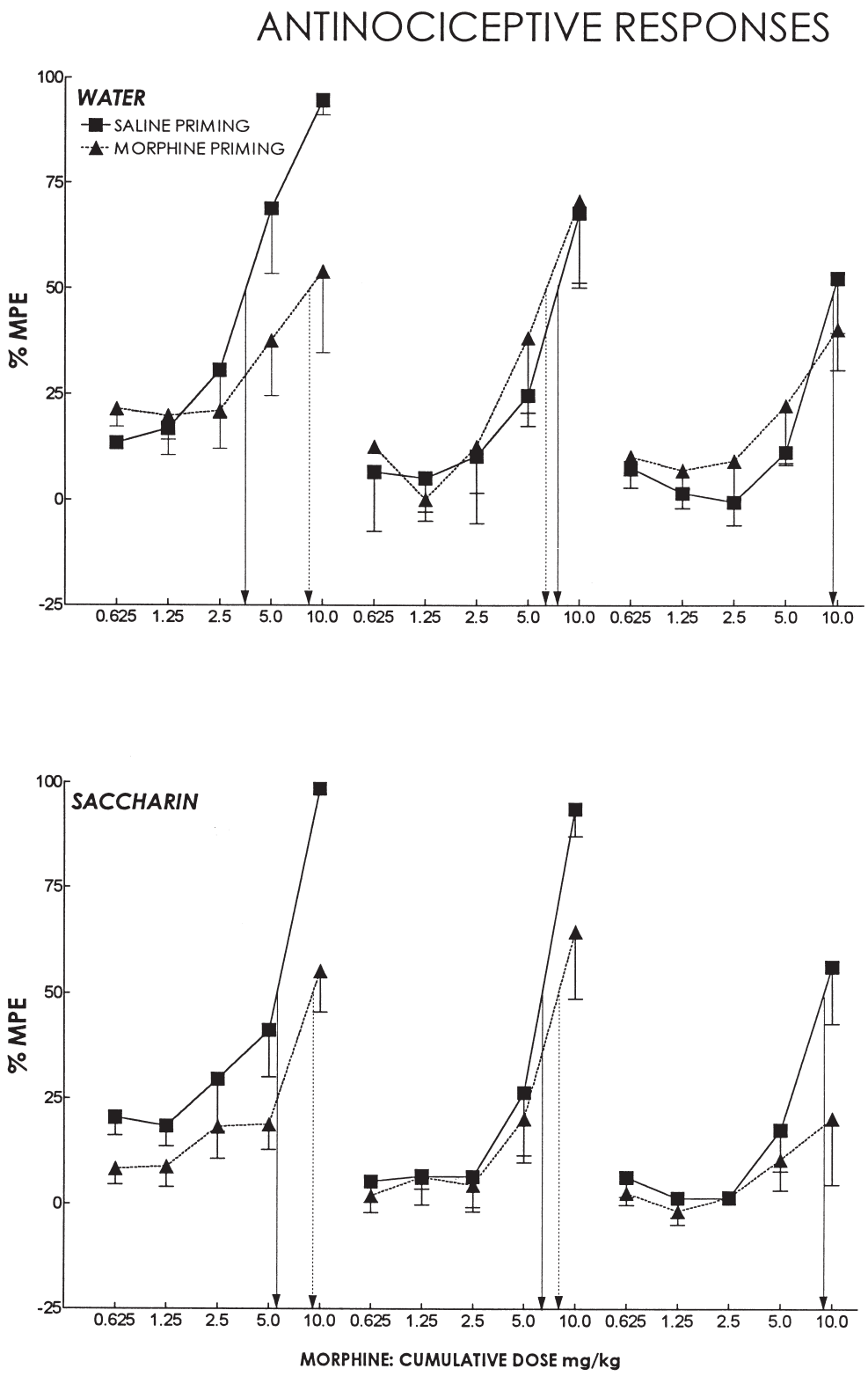

FIG. 1. Antinociception data for rats given water or saccharin are expressed as mean (SEM) %MPEs. Downward arrows indicate mean IED_{50}s for each priming group. Data are presented across 3 weeks of nociceptive testing. The previous week all rats were given a pretest on a tail-flick apparatus. Over the 3 weeks, %MPEs significantly decreased, indicating that tolerance developed to morphine's analgesic properties.

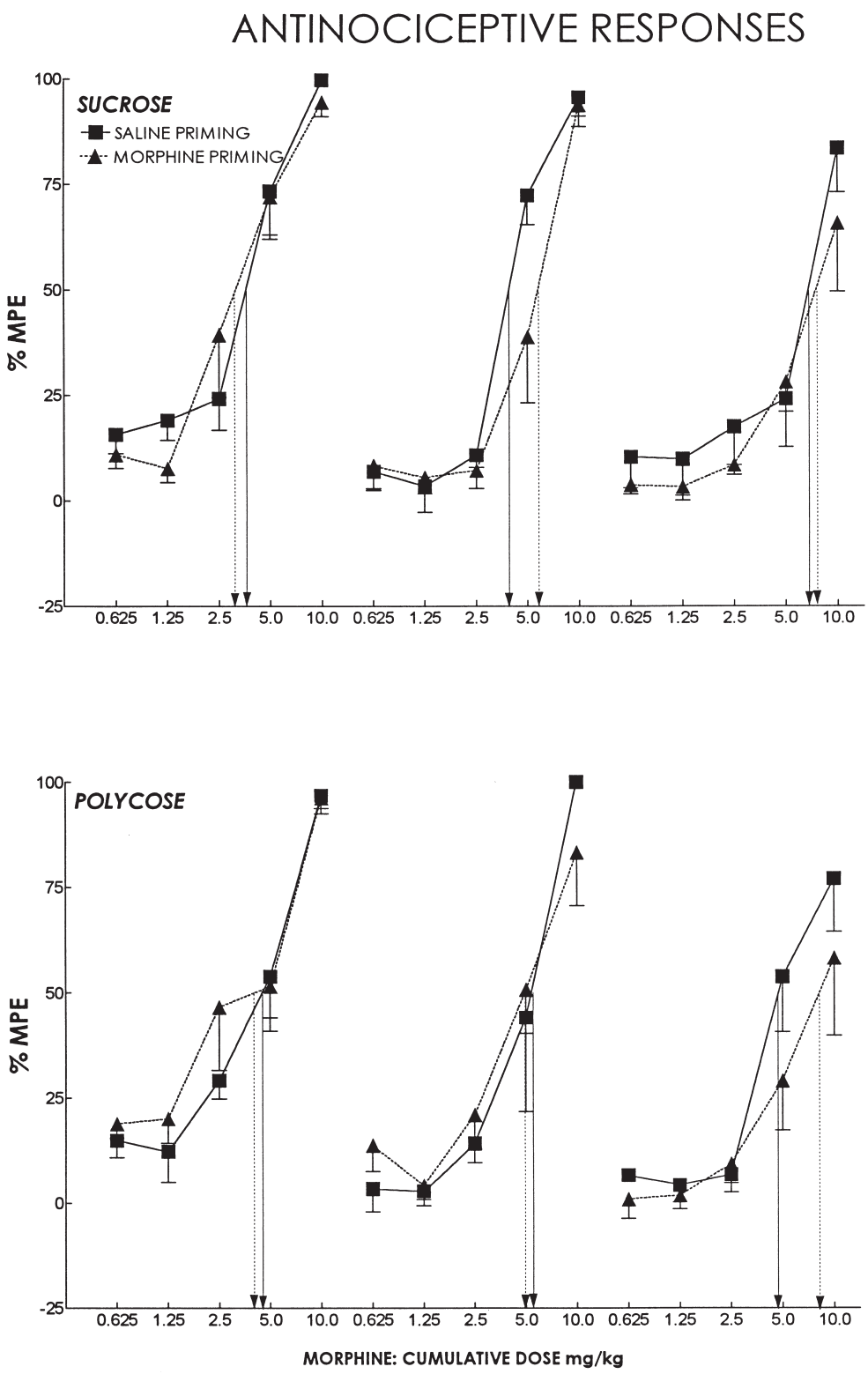

FIG. 2. Antinociception data for rats given sucrose or Polycose are expressed as mean (SEM) %MPEs. Downward arrows indicate mean IED_{50}s for each priming group. Data are presented across 3 weeks of nociceptive testing. The previous week all rats were given a pretest on a tail-flick apparatus. %MPEs did not vary significantly over the 3-week test period, indicating that tolerance did not develop to morphine's analgesic properties.

TABLE 3
MEAN (±SD) BODY WEIGHT AND FOOD INTAKE DATA

	Body Weight*	Total kcals	Chow (g)	Palatable Fluid (ml)
Water	424.6 (35.82)	93.9 (8.58)	26.1§¶ (2.38)	
Saccharin	422.5 (38.22)	92.7 (8.94)	25.8§¶ (2.48)	61.5 (11.7)
Sucrose	478.7† (38.86)	116.8‡ (13.02)	15.6§ (2.40)	47.4 (52% of kcals) (6.8)
Polycose	466.4 (44.22)	119.3‡ (14.17)	11.6 (1.90)	60.5 (65% of kcals) (11.3)

*Body weight determinations are from the final nociceptive test.

†Rats drinking sucrose weighed significantly ($p < 0.05$) more than rats drinking either water or saccharin.

‡Rats drinking sucrose or Polycose consumed significantly ($p < 0.05$) more kcals than rats drinking either water or saccharin.

§Rats consumed significantly ($p < 0.05$) more Purina chow than rats drinking Polycose.

¶Rats consumed significantly ($p < 0.05$) more Purina chow than rats drinking sucrose.

significance. In Experiment 2, when there was no initial pairing of drug and the noxious stimulus, the differences in the development of tolerance to morphine-induced antinociception were similar to Experiment 1, but were more clearly delineated. Rats that drank sucrose or Polycose showed an attenuation of analgesic tolerance relative to rats that drank saccharin or water. This suggests that although differences in the development of tolerance to morphine-induced antinociception are seen following chronic intake of different diets, the presence of acute pain stimuli during the initial experience with morphine also influences the development of tolerance (21,36). However, without a specific experiment comparing the two conditions, the possibility of sampling bias cannot be entirely excluded.

In both experiments, during the first nociceptive test, there were minimal differences in morphine-induced antinociception as a function of diet in the nonmorphine preexposed groups. This is in contrast to the results of the majority of previous studies in that chronic consumption of nutritive palatable fluids produced dietary-mediated enhancement of morphine-induced antinociception (10,11,18,19,31). However, dietary enhancement of morphine-induced antinociception is not always found (32). Although dietary-induced differences in morphine-induced antinociception are usually seen with moderate doses of morphine (5.0–7.5 mg/kg), analgesic responses to morphine can differ, depending on the testing environment, stress, age, and prior exposure to morphine (1,27,38,41). In Experiment 1, there were no differences as a function of diet in analgesic responses 1 week subsequent to a pairing of saline injections and a tail-flick test. In Experiment 2, however, rats that drank saccharin had reduced morphine-induced antinociception at a single, low dose (2.5 mg/kg) relative to rats that drank sucrose. In other experiments where chronic intake of palatable fluids altered morphine-induced antinociception, there were no experimental manipulations that might be defined as noxious (e.g., injections or tail-flick tests) prior to the first day of nociceptive testing (19). It is possible that the absence of differences in morphine-induced antinociception may be an artifact of the saline-priming procedure.

Long-term intake of sucrose is frequently associated with a concurrent elevation in sensitivity to the analgesic properties of morphine (10,11,19,31) and other opioid agonists (18). Discontinuation of sucrose feeding is associated with a return to normal opioid sensitivity (10) as well as increased withdrawal symptoms in morphine-addicted rats (33). The present experiments demonstrate that long-term intake of sucrose also slows the development of tolerance to morphine-induced antinociception. Chronic intake of Polycose, a palatable nonsweet carbohydrate, is associated with increased sensitivity to morphine-induced antinociception [(11); D'Anci, unpublished data] and increased sensitivity to the anorectic effects of naltrexone (20). The present experiments indicate that long-term Polycose intake alters the development of tolerance to morphine-induced antinociception, but these effects are more variable than those of sucrose intake. These data are suggestive of an inhibiting effect of Polycose on the development of tolerance to morphine-induced antinociception, and support previous data that show that highly palatable, nutritive foods alter sensitivity to the analgesic potency of morphine independently of sweet orosensory characteristics (11).

As demonstrated previously (11), long-term saccharin intake results in differing sensitivity to morphine than intake of sucrose or Polycose. Many studies that employ saccharin solutions to examine dietary-mediated morphine-induced antinociception report a suppression in the analgesic potency of morphine (2,11,15,16). The present experiments indicate that long-term saccharin intake may lead to a more rapid onset of tolerance to morphine-induced antinociception than long-term intake of sweet and nonsweet nutritive fluids. Following chronic saccharin consumption, rats showed greater tolerance

TABLE 4
MEAN (± SD) IED_{50} VALUES (mg/kg)
ACROSS ALL THREE WEEKS OF NOCICEPTIVE TESTING

	Water	Saccharin*	Sucrose	Polycose
Week 1	6.24 (1.91)	6.64* (2.12)	5.05 (0.72)	6.46 (1.37)
Week 2	9.31 (5.00)	10.10†‡ (1.42)	6.15 (1.44)	6.68 (1.65)
Week 3	7.41 (1.43)	8.66 (3.98)	7.24 (1.72)	7.88 (1.80)

Data are collapsed across priming condition.

*Indicates that IED_{50} values increased significantly from week 1 to week 2 for rats drinking saccharin.

†Indicates that IED_{50} values were significantly (LSD: $p < 0.05$) greater for rats that drank saccharin than rats that drank Polycose.

‡Indicates that IED_{50} values were significantly (LSD: $p < 0.05$) greater for rats that drank saccharin than rats that drank sucrose.

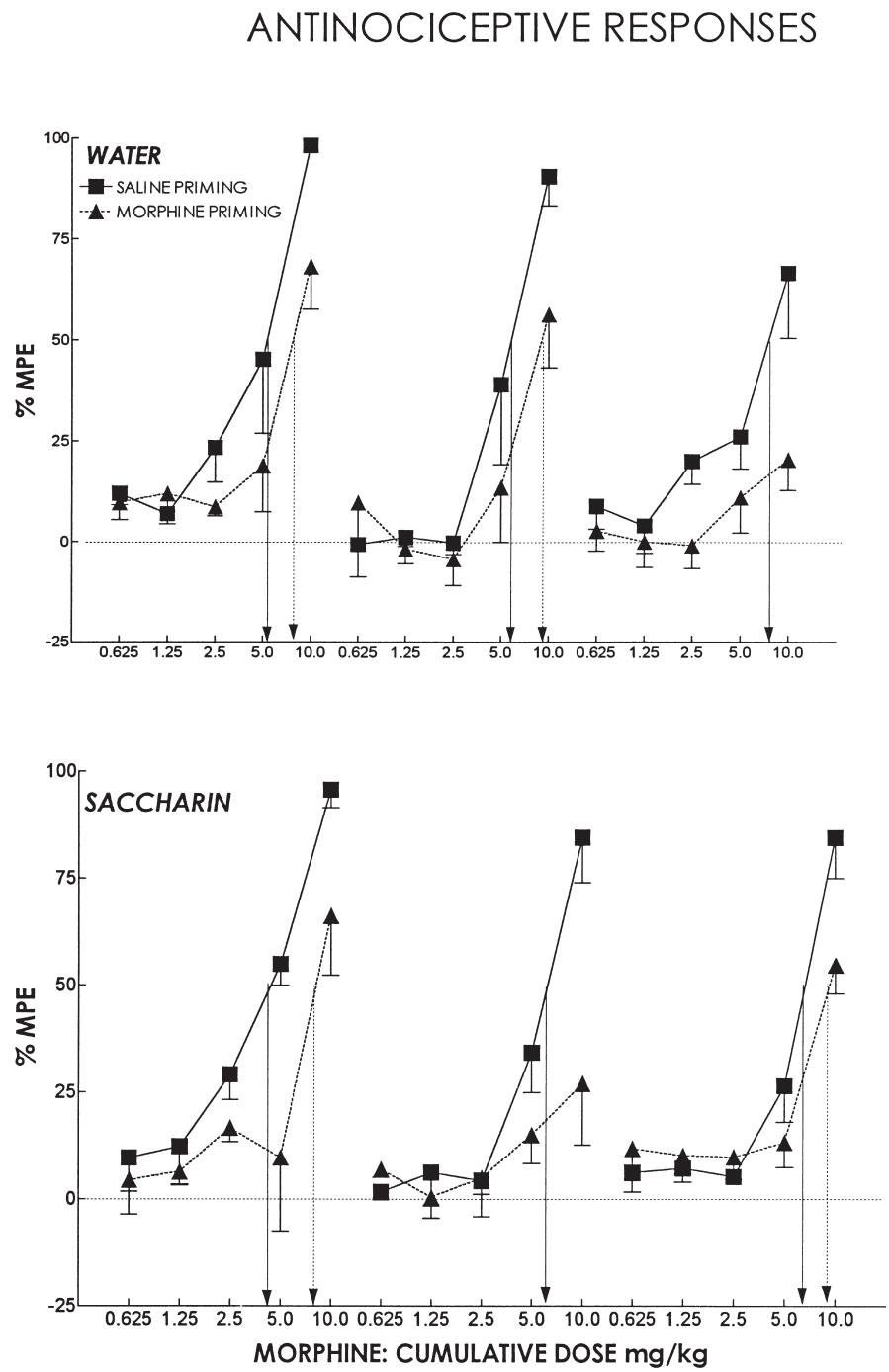

FIG. 3. Antinociception data for rats given water or saccharin are expressed as mean (SEM) %MPEs. Downward arrows indicate mean IED_{50}s for each priming group. Data are presented across 3 weeks of nociceptive testing. Over the 3 weeks, %MPEs significantly decreased, indicating that tolerance developed to morphine's analgesic properties.

to the analgesic effects of morphine than did rats that drank sucrose or Polycose.

Long-term intake of saccharin does not alter micro- and macronutrient intakes in rats. In contrast, long-term consumption of Polycose or sucrose can result in a proportional decrease in chow intake. Rats that drink palatable, nutritive fluids can typically consume 50% or more of their total caloric intake from these solutions. Rats will consume more calories overall, but may not eat comparable amounts of protein, fat, vitamins, and minerals as do rats drinking saccharin or water. It may be argued, therefore, that increased caloric intake or differences in body weight may be sufficient to alter sensitiv-

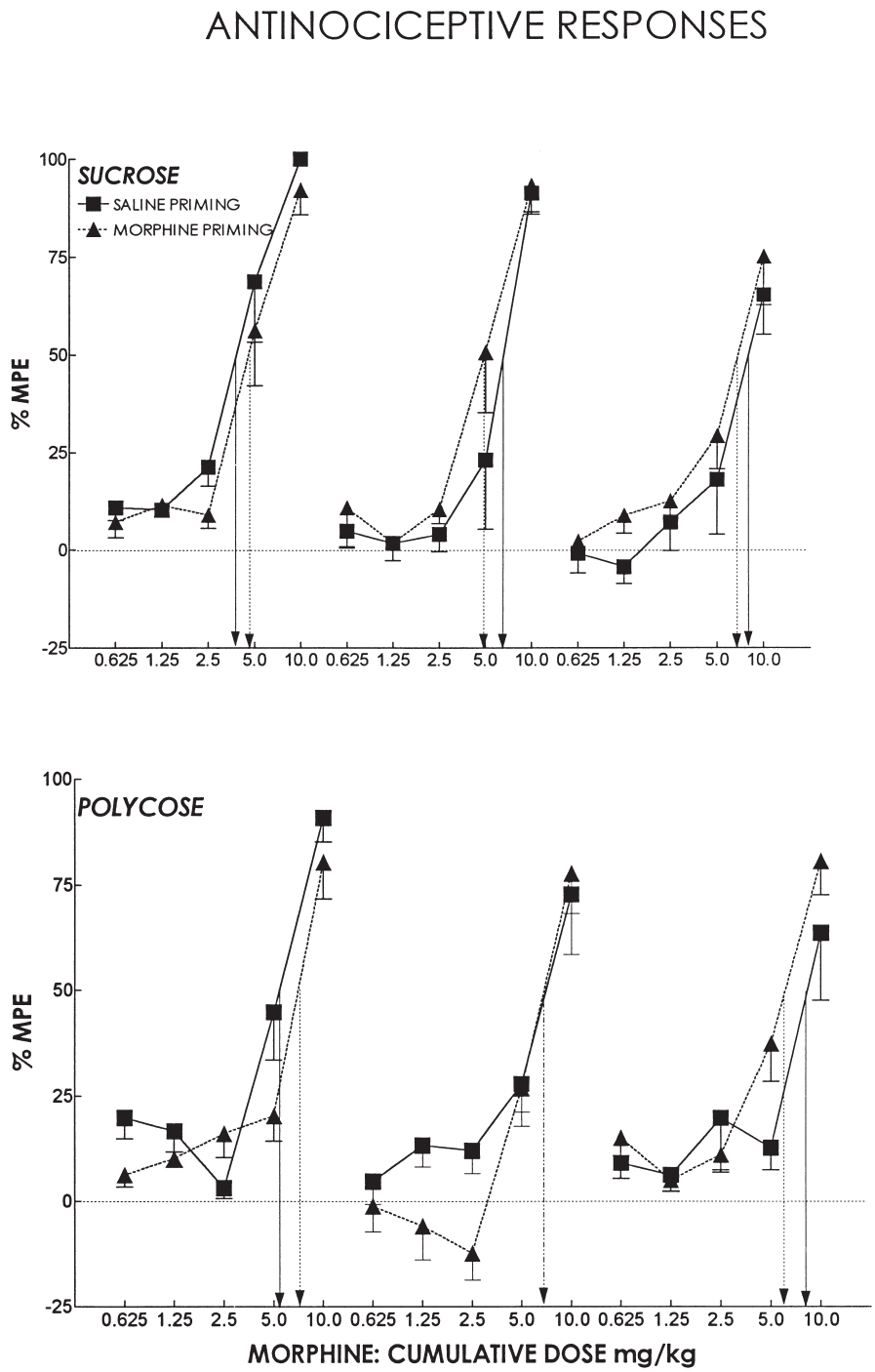

FIG. 4. Antinociception data for rats given sucrose or Polycose are expressed as mean (SEM) %MPEs. Downward arrows indicate mean IED_{50}s for each priming group. Data are presented across 3 weeks of nociceptive testing. %MPEs did not vary significantly over the 3-week test period, indicating that tolerance did not develop to morphine's analgesic properties.

ity to opioid drugs, or that alterations in morphine-induced antinociception stem from vitamin or protein deficiencies. The former concern was investigated in earlier experiments examining dietary mediation of morphine-induced antinociception among rats fed sucrose, Polycose, saccharin, or water. We demonstrated that differences in body weight, percent body fat, or caloric intake were not correlated with analgesic responses (11). The latter concern was addressed in recent studies that show that morphine-induced antinociception is not altered by either protein or vitamin and mineral deficiencies

(17). Another factor that could influence the effects of diet on opioid tolerance is that the metabolic fate of morphine could have been altered by different diets, thus changing the bioavailability of morphine. However, unpublished data from this laboratory demonstrate that brain levels of morphine were similar in rats maintained on a palatable diet that increased morphine-induced antinociception and in chow fed controls (Kanarek, Kream, and Cohen, unpublished data).

Tolerance to opioids can be discerned via alterations in receptor sensitivity (24,35) or density (42) or changes in protein kinase activity (28,30). Long-term intake of sucrose is associated with increased β-endorphin levels as well as increased whole-brain opioid receptor binding affinity (25), whereas long-term saccharin intake is associated with decreased opioid receptor binding affinity (12). Further, supporting the impact of feeding behaviors on the endogenous opioid system, both food restriction and streptozotocin-induced diabetes decreased opioid receptor binding capacity in rats (39,40). It is possible that long-term intake of palatable nutritive solutions results in conformational changes in the opioid receptor system, resulting in increased morphine-induced antinociception and a reduction of opioid tolerance. The exact mechanism for these effects is not known. Currently this laboratory is investigating the effects of palatable fluid intake on mu-opioid binding capacity and binding affinity in rat brain.

In conclusion, the present experiments demonstrate that nutritive, palatable solutions alter the development of tolerance to the analgesic properties of morphine. Long-term sucrose intake, in particular, seems to be most effective in attenuating the development of tolerance to morphine-induced antinociception. It is important to note that analgesic tolerance is a small component of the effects of repeated morphine exposure. The effects of long-term intake of palatable fluids on tolerance to other physiological changes associated with morphine administration, such as thermoregulation and locomotor activity, are unknown. Current investigations in this laboratory will determine whether differences in tolerance develop to the hyperthermic and locomotor effects of morphine following long-term intake of a palatable sucrose solution.

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