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BRIEF COMMUNICATION

Relationships Between Sustained Sucrose-Feeding and Opioid Tolerance and Withdrawal

GEOFFREY M. SCHOENBAUM, R. J. MARTIN AND D. S. ROANE[1]

Department of Foods and Nutrition, Dawson Hall
University of Georgia, Athens, GA 30602

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SCHOENBAUM, G. M., R. J. MARTIN AND D. S. ROANE. *Relationships between sustained sucrose-feeding and opioid tolerance and withdrawal.* PHARMACOL BIOCHEM BEHAV **34**(4) 911–914, 1989.—This study examines the effect of sustained sucrose consumption on the development of tolerance to morphine analgesia (20 mg/kg IP injections) and subsequent, naloxone-precipitated withdrawal (2 mg/kg IP). Food intakes are also measured. Sprague-Dawley rats were allowed ad lib access to a 20% sucrose solution in addition to their normal diet. Pain thresholds and intakes were monitored for two weeks, then morphine tolerance was induced, followed by precipitated withdrawal. Tolerance was assayed by the tailflick method, and withdrawal was gauged by weight loss. The animals given access to sucrose developed lowered pain thresholds prior to tolerance induction relative to those of control animals, but they failed to exhibit any differences from controls in tolerance development of severity of withdrawal. The induction of tolerance first decreased, then increased sucrose consumption and steadily decreased chow consumption. Naloxone-precipitated withdrawal decreased chow consumption, but failed to affect the ingestion of the sucrose solution. It is concluded that changes in opioid function caused by sustained sucrose-feeding are insufficient to affect the development of tolerance to morphine analgesia; however, tolerance induction biphasically alters sucrose consumption.

Sucrose Morphine Naloxone Tolerance Withdrawal Pain Analgesia Feeding Nociception

AN overview of the opioid-food intake literatures shows that previous research can be divided roughly into two areas. The first is the effect that opioid agonists and antagonists have on regulating and maintaining food intake, while the second deals with the reciprocal relationship, i.e., the effect of food intake on opioid function. This present study, in which we examine the effect of sucrose feeding on the development of tolerance to morphine analgesia and subsequent withdrawal, and the effect of repeated morphine injection of sucrose consumption, addresses both areas.

Much systematic research has been done to investigate opioid modulation of food intake. This research has shown opioid agonists to both promote food intake (9) and alter food preference. Specifically, morphine has been demonstrated to decrease preference for carbohydrates at high doses (7), while lower doses increase carbohydrate preference (8). Additionally, the repeated injection of morphine ICV has proven to promote carbohydrate preference (1).

Studies exploring the effect of carbohydrates on opioid function have also indicated a strong relationship, particularly regarding the effects of simple sugars on opioid-mediated pain perception. The ingestion of simple sugars clearly has a profound effect on activity in the endogenous opioid system (EOS). For instance, both experimentally induced hyperglycemia (10) and brief exposure to a dextrose-sucrose cocktail (5) have been shown to reduce the antinociceptive potency of morphine. Evidence has also been found suggesting an immediate release of beta-endorphin from the hypothalamus in response to the consumption of a highly palatable food (4), while another study in rats has demonstrated that an oral infusion of sucrose causes an immediate, naltrexone-reversible analgesia of short duration (2).

Our recent research has focused on the long-term effects of ad lib sucrose-feeding on pain perception and morphine analgesia. We have found that long-term consumption of a high sucrose diet causes an apparent opioid-mediated decrease in pain thresholds and an increase in morphine potency (Roane and Martin, manuscript in review). Since morphine potency increased with sucrose-feeding, we considered it a natural extension to investigate the effect of a high-sucrose diet on the development of tolerance to

[1]Requests for reprints should be addressed to David Roane.

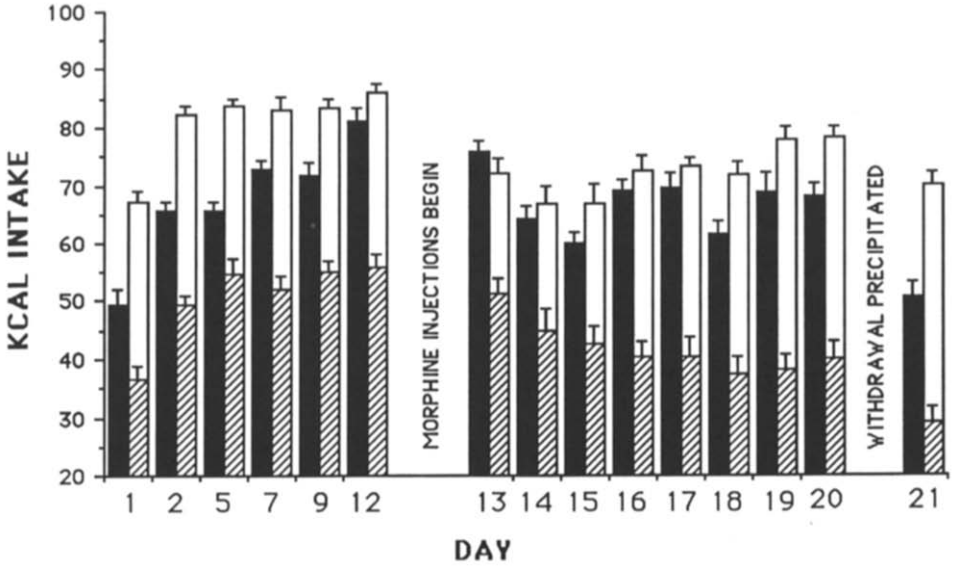

FIG. 1. Food intakes in kilocalories (kcal) for the 24 hours prior to the date of measurement for both the control and sucrose-fed animals. The black bars represent the kcal consumed in chow by the control group. The striped bars represent the kcal consumed in chow by the sucrose group, and the white bars represent the kcal consumed in sucrose by the sucrose group.

morphine analgesia and the severity of subsequent precipitated withdrawal. Preliminary findings have indicated that sucrose-feeding during opioid withdrawal lessens the severity of the withdrawal symptoms (3). As will be shown, our results failed to confirm these preliminary findings. Sucrose and chow intakes were also measured during the course of the experiment. Unexpectedly, these measurements, which were not the main focus of the study, produced the more interesting results.

METHOD

All animals were housed individually on a 12-hour light/12-hour dark cycle and allowed ad lib access to water and a semi-purified diet modified from American Institute of Nutrition (AIN) standards consisting of 20% casein, 0.35% DL-methionine, 65% corn starch, 5.15% fiber, 5% corn oil, 3.5% AIN minerals, and 1% AIN vitamins. The animals were given two days to acclimate to their diet and handling conditions. At 0800 hours, on day 0, the pain threshold of each animal was assessed by the tailflick method. In this method, the rat's tail is placed in a trough beneath a radiant heat source. The common "on" switch activates both the heat source and a timer. A photocell beneath the animal's tail senses removal of the tail and stops both timer and heat source, thereby determining the animal's latency to tailflick. For this experiment, a predetermined cut-off latency of 10 seconds was chosen to avoid tissue damage.

Following the determination of pain thresholds, thirty male Sprague-Dawley rats were divided into two equal groups so that the average weights and tailflick latencies were similar. One group of rats was given access to a 20% sucrose solution. The solution was placed on their cages at 1400 hours on day 0. The pain thresholds were measured by the tailflick method at 0800 hours on days 1, 2, 5, 10, 12, daily during the induction of morphine dependence, and again 18 hours after withdrawal was precipitated. Body weights and food and sucrose consumption were measured at 0830 hours on days 1, 2, 5, 7, 9, 12, daily during the induction of morphine dependence, and at 1.5, 3, and 18 hours after withdrawal was precipitated.

Administration of morphine was begun on the evening of day 12 at 1730 hours. In order to induce morphine dependence, the animals were given IP injections of 20 mg/kg morphine sulfate at approximately 0730 and 1730 hours each day. Pain thresholds were measured each morning by the tailflick method thirty minutes postinjection. These values were used to assess the development of tolerance to morphine analgesia.

On day 20, at 1400 hours, withdrawal was precipitated by IP injection of 2 mg/kg naloxone. The severity of withdrawal was gauged by the measurement of weight loss at various time points in the 18 hour period following the injection of naloxone.

RESULTS

As expected, ANOVA with repeated measures showed the pain thresholds of the sucrose group to be significantly lower than those of the controls. Tukey's HSD and preplanned Student's *t*-tests were performed to evaluate differences between the groups on individual days. No differences were found by Tukey's HSD, but on both day 5 and 12, preplanned *t*-tests found the sucrose group to have significantly lower latencies than the controls, $p<0.05$. During the injections of morphine, the latencies of the two groups did not differ significantly at any individual time points, nor did the development of tolerance to morphine analgesia in the sucrose group differ significantly from that of the controls.

The food intakes are illustrated in Fig. 1. The intakes were considered in two parts: pre- and postinjection. In the preinjection phase, the animals on sucrose consumed a significantly greater number of kilocalories (kcal) each day than did the animals in the control group. The greatest differences in kcal consumption between the two groups were seen at the beginning of the test period, and these differences diminished over time, yielding a significant interaction [diet $\times$ days, $F(5,140)=5.360$, $p<0.001$]. Within the sucrose group during this period, the daily kcal consumed in sucrose did not change, but the daily kcal consumed in chow increased, $F(5,140)=20.344$, $p<0.001$.

During the induction of morphine tolerance, the total kcal consumed by the sucrose group was significantly higher than the

controls, $F(1,196)=5.586$, $p<0.05$. Within the sucrose group during this period, there was a highly significant interaction between morphine treatment and the source of the kcal being consumed, $F(7,196)=24.772$, $p<0.001$. As the morphine treatment progressed, the animals with access to sucrose steadily increased their daily consumption of the solution and steadily decreased their daily consumption of chow. Post hoc analysis by Dunnett's procedure showed that the sucrose intakes were significantly lowered from preinjections levels on day 13, the first day of morphine treatment. The same analysis also showed that by day 19, the seventh day of morphine treatment, the sucrose intakes had significantly surpassed their preinjection levels.

On day 20, following the injection of naloxone to precipitate withdrawal, the body weights were measured at 1.5, 3, and 18 hours postinjection. The rats in the control group experienced an average weight loss of 2.51%, 3.62%, and 5.42% at 1.5, 3, and 18 hours postinjection respectively, while the rats in the sucrose group lost an average of 2.54%, 3.91%, and 5.83% of their weight over the same time points. There were no differences in weight loss between the two groups at any of the time points. Total kilocalorie intakes decreased over this 18-hour period for both the control group, $p<0.001$, and the sucrose group, $p<0.02$, while the animals with access to the sucrose solution decreased only their consumption of chow, $p<0.02$, maintaining their consumption of the sucrose solution. The sucrose group consumed more kcal during withdrawal than did the control group, $p<0.001$.

The body weights of the two groups were similar throughout the course of the study. Both groups rose prior to the morphine injections, as expected with growing animals, then leveled off during tolerance induction (data not shown).

DISCUSSION

Based on previous evidence (3) we expected to find differences in the development of tolerance to morphine analgesia due to sucrose consumption. Our own research (Roane and Martin, manuscript in review) suggests that long-term sucrose-feeding decreases tailflick latencies and increases the analgesic potency of morphine through alteration of endogenous opioid function. Though differences in tailflick latencies were seen between the two diet groups prior to the morphine treatment, the data do not show any alteration of analgesic tolerance development due to diet. It is, therefore, concluded that any change in the functioning of the EOS caused by sustained sucrose consumption is insufficient to affect the development of tolerance to morphine analgesia.

We also had reason to expect differences in the severity of precipitated withdrawal exhibited by the two groups. It has been reported that sucrose-feeding (3) decreases the severity of precipitated withdrawal. Our data failed to show that sustained sucrose consumption affects opiate withdrawal when compared to a control group. It has been suggested the protective effect of sucrose might be better evaluated by comparison with a control group denied access to sucrose only during withdrawal. This design will be utilized in future experiments.

Perhaps the most notable finding in this study is the indication that the chronic administration of morphine in large doses caused the animals to increase their sucrose consumption, apparently at the expense of chow intake. The sucrose consumption of these animals had remained at a steady level throughout the period prior to the injections. In research relevant to this finding, Marks-Kaufman (7) has shown morphine injections to decrease consumption of a sucrose-containing carbohydrate ration in a dose-dependent manner over a six-hour feeding period postinjection. Over time, repeated applications of morphine ICV are reported to increase consumption of sweetened milk (1). Small doses (1 mg/kg) of morphine also promote carbohydrate preference (8). In our study, the development of tolerance to morphine analgesia significantly affected sucrose ingestion. Our results parallel the observations of Belluzzi and Stein regarding the consumption of sweetened milk following repeated morphine injection ICV (1). Daily sucrose intakes decreased with the first morphine injection, then rose over time to surpass the preinjection levels, even though morphine injection was still seen to have an analgesic effect. The biphasic effect on sucrose intake was not accompanied by appreciable change in body weights. These findings support the assertion that acute injection of morphine in large doses will decrease sucrose ingestion, but require recognition that repeated injections of morphine eventually promote sucrose consumption, even to the exclusion of other nutrients.

During precipitated withdrawal, both groups greatly decreased their chow intake, but the sucrose group maintained its consumption of sucrose essentially unchanged. This finding of sustained sucrose ingestion following naloxone is somewhat novel in view of previous studies in normal animals indicating that naloxone decreases consumption of sweet solutions (6). Although it is possible that a single injection of naloxone was not sufficient to suppress sucrose ingestion over the entire 18-hour period, it seems more likely that naloxone's effect on the ingestion of sapid solutions is altered in morphine-dependent animals, since a significant reduction in chow intake was still observed in both groups over the same 18-hour period.

The results of our experiment mesh well with much of the research on the relationship between the ingestion of simple sugars and endogenous opioid function. We do not feel our data contradict the previous research showing that endogenous opioid activity is increased immediately following sucrose-feeding. Indications that sucrose-feeding produces a brief period of analgesia (2) through a release of beta-endorphin (4) lead to the conclusion that short-term sucrose administration causes activation of endogenous opioid function. Our own studies use a longer-term paradigm and have shown that sustained sucrose consumption produces a greater sensitivity to painful stimuli (Roane and Martin, manuscript in review). The increase in sensitivity appears to be opioid-mediated, since the difference between sucrose and control groups is abolished by naloxone.

Overall, much of the data considering both the short- and long-term effects of sucrose-feeding on opioid function are consistent with a two-phase response to sucrose ingestion. The first phase in the response to sucrose-feeding is short-term, involving the release of beta-endorphin immediately after sucrose administration and resulting in a brief period of analgesia (2,4). The second phase seems to occur in response to continued sucrose consumption and may involve a gradual decrease in endogenous opioid function, perhaps due to the extension of a refractory period following the initial activity.

Our present study shows that sustained sucrose consumption is affected by both the induction of morphine dependence and withdrawal precipitated by naloxone. If the two phase response to sucrose ingestion proposed is correct, the increase and maintenance of sucrose consumption during dependence induction and withdrawal may be an effort to support the high level of activity in the EOS initiated by morphine injections. Clearly, our speculation in this area requires much future research and is intended as a suggestion in that context.

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