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Increased Fat Consumption Induced by Morphine Administration in Rats[1,3]

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MARKS-KAUFMAN, R. *Increased fat consumption induced by morphine administration in rats.* PHARMAC. BIOCHEM. BEHAV. 16(6) 949–955, 1982.—Patterns of caloric intakes and dietary self-selection of the three macronutrients, protein, fat and carbohydrate were examined in male rats following the administration of morphine sulfate (0.0, 1.0, 10.0 and 20.0 mg/kg, IP). Animals were given access to either ground Purina Chow or one of two dietary self-selection regimes, one with a high-fat ration (7.8 kcal/g) and the other with a fat ration isocaloric to the carbohydrate and protein rations (3.8 kcal/g). Animals received morphine injections at the beginning of a six-hour feeding period and nutrient intakes were measured at 1, 2, 4 and 6 hours postinjection. Similar patterns of macronutrient choice were observed for both animals maintained on the high-fat regime and animals with access to the isocaloric components following morphine injections. As a function of morphine injections, animals on both self-selection regimes increased fat intake while suppressing carbohydrate intake and exhibiting little modifications in protein intake.

Dietary selection Protein Fat Carbohydrate Morphine Endorphin

OPIOID agonists and antagonists have been found to modify feeding behavior in a variety of animals (e.g. [4, 9, 12, 21, 26, 30, 31]). In general, morphine has been found to increase food intake [13, 16, 26, 27, 29] while naloxone has been found to suppress feeding behavior [2, 3, 4, 5, 11, 12, 13]. In addition to modifying total caloric intakes, recent work has demonstrated that both morphine and naloxone selectively influence macronutrient intake in rats [18,19]. For example, following the administration of morphine, animals with access to the three macronutrients, protein, fat and carbohydrate, suppressed intakes of all three dietary rations for a two-hour period following morphine administration. While both protein and carbohydrate intakes remained suppressed for a six-hour feeding period after morphine injections, animals increased fat intake during the final four hours of a six-hour feeding period resulting in an overall increase in fat intake [18].

One possible reason for the differential effects of morphine in this situation may have been that while protein and carbohydrate were presented as solid rations, fat was presented in a liquid form. Morphine, therefore, may have influenced drinking behavior rather than feeding behavior. In the present experiment, the liquid fat component was replaced with a solid fat source. Aside from eliminating the question of whether observed alterations in fat intake were a consequence of feeding or drinking, this change provided the additional benefit of allowing for a more accurate measurement of fat intake.

Another possible reason for the observed differential effects of morphine on macronutrient intake was that the dietary rations varied in caloric density, with the fat ration being approximately twice as calorically dense as the protein and carbohydrate rations. Following the initial two-hour suppression in caloric intake, animals may have experienced a greater than normal energy deficit and sought the most immediate source of calories. Fat, having a greater caloric density than either protein or carbohydrate, would have provided this source. To determine if patterns of nutrient intake following morphine administration reflect general energy requirements or a specific need for fat, two self-selection regimes were used in the present experiment. The first regime consisted of the standard dietary components including a solid fat source. In the second regime, animals received a diluted fat source equal in caloric density to the carbohydrate and protein components.

METHOD

Animals and Diets

Twenty-two male Sprague-Dawley rats (CD outbred, Charles River Breeding Laboratories, Wilmington, MA), weighing approximately 275 g at the beginning of the experiment, were used. Animals were housed individually in hanging wire-mesh cages in a temperature-controlled room (21±1°C), maintained on a 12:12 hour light-dark cycle (lights on: 0800 hr).

Animals were divided into three groups matched on the basis of body weight. The first group of animals (N=8) was given access to the standard self-selection regime which

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TABLE 1

Protein Component (3.8 kcal/g)	
960 g	Vitamin-free Casein (ICN Pharmaceuticals, Cleveland, OH)
40 g	U.S.P. XIV Salt Mixture (ICN Pharmaceuticals)
22 g	Vitamin Diet Fortification Mixture (ICN Pharmaceuticals)
Carbohydrate Component (3.8 kcal/g)	
580 g	Corn Starch (Teklad Test Diets, Madison, WI)
280 g	Dextrin (Teklad Test Diets)
100 g	Commercial-grade sucrose
40 g	U.S.P. XIV Salt Mixture (ICN Pharmaceuticals)
22 g	Vitamin Diet Fortification Mixture (ICN Pharmaceuticals)
Fat Components	
Standard Fat Component (7.8 kcal/g)	
912 g	Hydrogenated vegetable fat (Crisco)
48 g	Safflower oil (Hollywood Health Foods, Los Angeles, CA)
90 g	U.S.P. XIV Salt Mixture (ICN Pharmaceuticals)
50 g	Vitamin Diet Fortification Mixture (ICN Pharmaceuticals
Isocaloric Fat Component (3.8 kcal/g)	
404 g	Hydrogenated vegatable fat (Crisco)
22 g	Safflower oil (Hollywood Health Foods)
267 g	Celluflour (ICN Pharmaceuticals)
267 g	Petroleum Jelly (Vaseline)
40 g	U.S.P. XIV Salt Mixture (ICN Pharmaceuticals)
22 g	Vitamin Diet Fortification Mixture (ICN Pharmaceuticals)

consisted of a protein ration (caloric density = 3.8 kcal/g), a carbohydrate ration (caloric density = 3.8 kcal/g) and a high-caloric fat ration (caloric density = 7.8 kcal/g) (see Table 1). The second group of animals (N=8) was given access to the standard protein and carbohydrate rations and a fat ration, isocaloric to the protein and carbohydrate rations (see Table 1). Salts and vitamins were added to each of the self-selection components to meet the requirements determined by the National Research Council [23]. The concentrations of these additives were calculated to be equal on a per kilocalorie basis. The third group of animals (N=6) was given access to ground Purina Rodent Chow no. 5001 (caloric density = 3.6 kcal/g). Purina Chow and the protein and carbohydrate rations were presented in Wahmann (Timonium, MD) LC-306A non-spill food cups. The fat components were presented in 75 ml glass cups. All animals had ad lib access to water throughout the experiment.

Procedure

To allow for adjustment to the dietary conditions, all animals initially received ad lib access to their respective dietary regimes. Body weights and nutrient intakes were measured daily for two weeks. Following this adjustment period, access to the nutrients was restricted to a six-hour feeding period during the light portion of the 24-hour cycle (0900 to 1500 hr). Following a two-week period of adaptation to the restricted feeding schedule, testing for the effects of morphine on energy intake and nutrient selection was initiated. Animals were given sham-injections for three days at the start of the feeding period and were handled at 1, 2, 4 and 6 hours after injections to accustom them to the testing procedure. Animals then received intraperitoneal injections of physiological saline for three days. Nutrient intakes were measured at 1, 2, 4 and 6 hours postinjection.

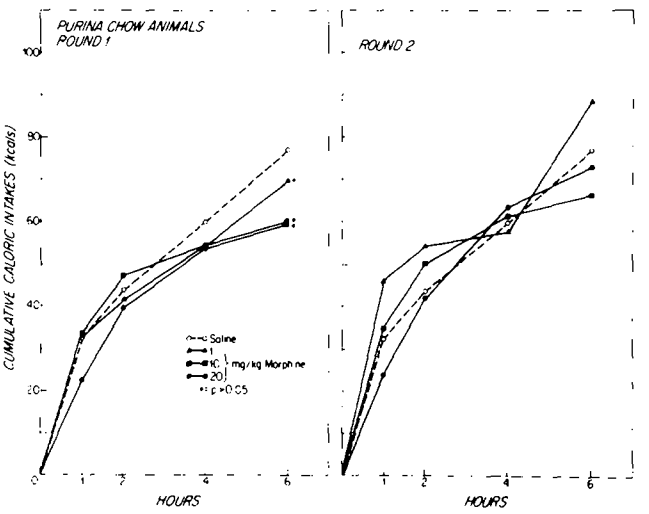

FIG. 1. Mean cumulative caloric intakes across a six-hour feeding period of animals maintained on Purina Chow, following (1) saline and the first round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections and (2) saline and the second round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from saline injections: $*p<0.05$.

Round 1. On test days, animals in each dietary group received intraperitoneal injections of morphine sulfate. Three doses of morphine were used: 1, 10 and 20 mg/kg body weight. Each animal received each dose of morphine with a minimum of seven days intervening between drug injections. To minimize temporal order effects, drug injections were given in a counterbalanced order to animals within each dietary condition. Nutrient intakes were measured at 1, 2, 4 and 6 hours postinjection. Water intakes were measured at the beginning and end of the six-hour feeding period throughout the experiment.

Round 2. One week later the procedure followed in Round 1 was repeated in Round 2. All animals again received injections of all three doses of morphine in a counterbalanced order. Drug injections were separated by a minimum of seven days and nutrient intakes measured at 1, 2, 4 and 6 hours postinjection.

As there were no differences in intakes across the days when saline was given, mean data for saline for each group of animals are presented.

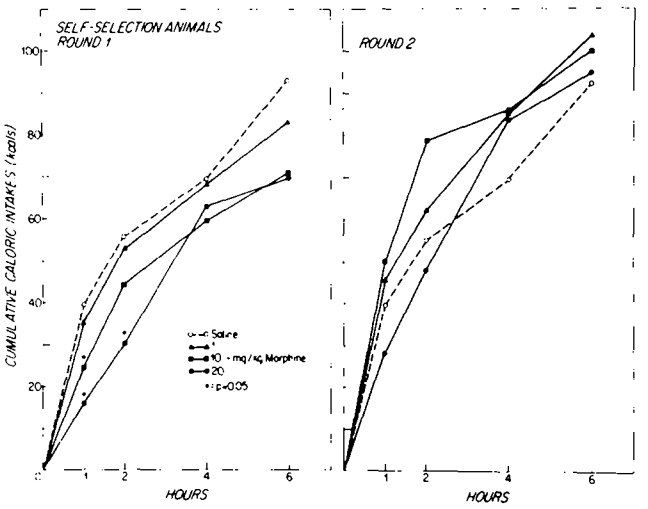

FIG. 2. Mean total cumulative caloric intakes (calculated as the sum of caloric intakes from each of the three macronutrients) across a six-hour feeding period of animals maintained on the self-selection regime, following (1) saline and the first round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections and (2) saline and the second round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from saline injections: $^*p<0.05$.

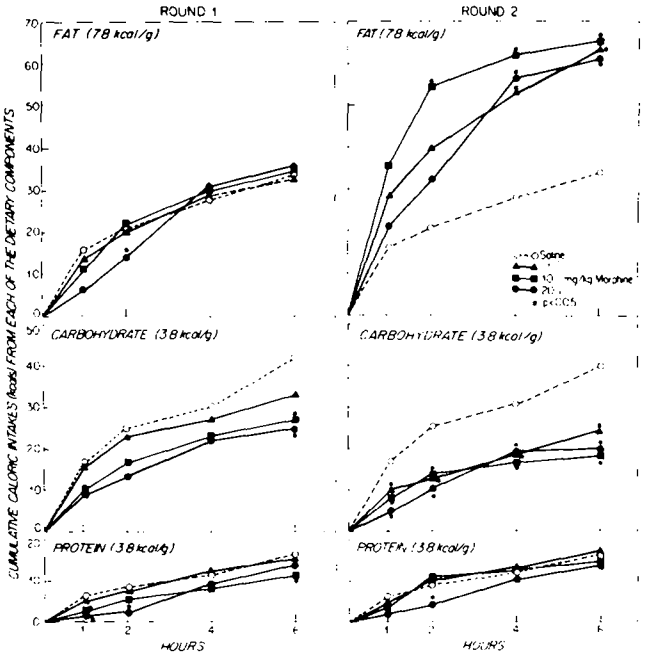

FIG. 3. Mean cumulative caloric intakes across a six-hour feeding period of fat, carbohydrate and protein, following (1) saline and the first round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections and (2) saline and the second round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from saline injections: $^*p<0.05$.

Drugs

Morphine sulfate, generously provided by the National Institute on Drug Abuse (Research Triangle Institute) was dissolved in 0.9% saline to concentrations that allowed studied doses to be administered in volumes of 0.1 mg/100 g body weight.

Statistical Analyses

Cumulative nutrient intakes were analyzed across the six-hour feeding period using one-way analyses of variance followed by a posteriori multiple comparisons of within-group means.

RESULTS

Purina Chow

Effects of Morphine on Intake of Animals Given Purina Chow

Round 1. Caloric intakes of animals given Purina Chow were significantly suppressed only at the six-hour measurement period for all three doses of morphine (Fig. 1).

Round 2. During the second round of injections, caloric intakes of animals given Purina Chow did not differ as a function of morphine administration (Fig. 1).

Standard Dietary Components

Effects of Morphine on Total Caloric Intake of Animals on the Standard Self-Selection Regime

Round 1. Total caloric intakes (calculated as the sum of caloric intakes from each of the three macronutrient components) of animals given the standard self-selection regime were suppressed in a dose-related manner at both one and two hours following morphine injections. By four hours following injections, no significant differences in cumulative total caloric intakes were found (Fig. 2).

Round 2. In Round 2, self-selection animals slightly increased cumulative caloric intakes above saline values by four hours postinjection, following the administration of all three doses of morphine (Fig. 2).

Effect of Morphine Administration on Nutrient Intake of Animals on the Standard Self-Selection Regime

Round 1. Intakes of each of the individual macronutrient components across the six-hour feeding period did not parallel total caloric intake (Fig. 3). During the first round of drug administration, protein intake was suppressed across the six-hour feeding period by the two higher doses of morphine. Carbohydrate intake was decreased in a dose-related manner throughout the six-hour feeding period, with a significant reduction at six hours postinjection. Fat intake was significantly suppressed by the highest dose of morphine (20 mg/kg) two hours postinjection. Other than this initial suppression, fat intake did not vary as a function of drug administration.

Round 2. During the second round of drug administration, different patterns of nutrient selection were observed (Fig. 3). The only significant decrease in cumulative protein intake occurred following 20 mg/kg morphine at two hours postinjection. At all three doses tested, animals decreased carbohydrate intake to a greater extent in Round 2 than in Round 1. While animals did not exhibit significant modifica-

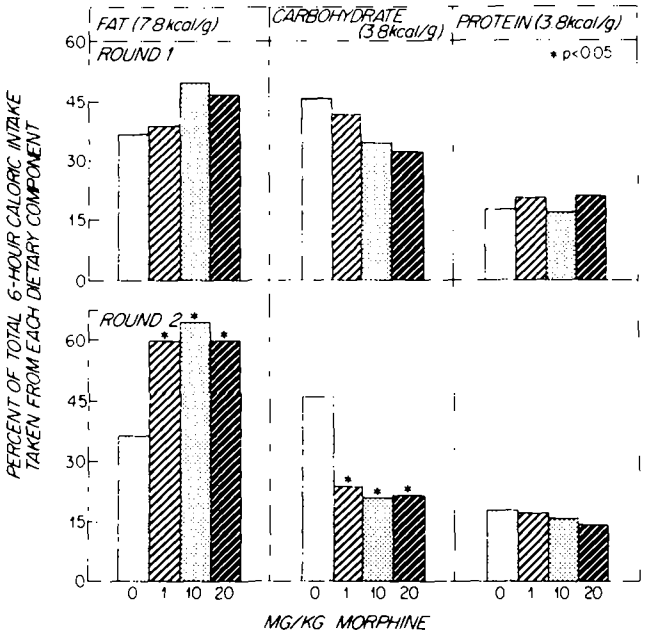

FIG. 4. Mean percent calories taken from the fat, carbohydrate and protein components of the dietary self-selection regime over a six-hour feeding period, following the first and second round of 0.0, 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from 0.0 mg/kg: $*p<0.05$.

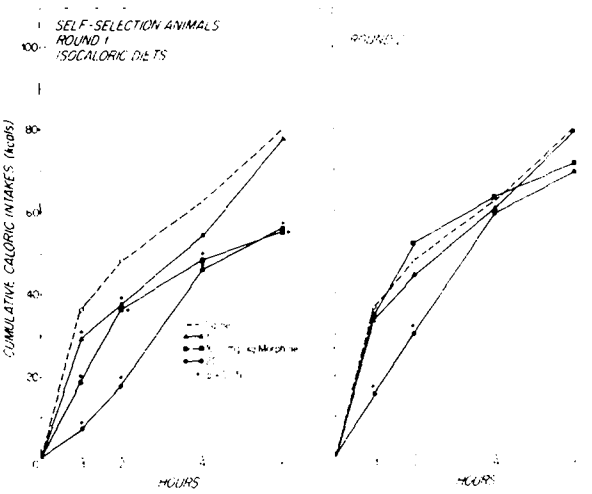

FIG. 5. Mean total cumulative caloric intakes (calculated as the sum of caloric intakes from each of the three macronutrients) across a six-hour feeding period of animals maintained on the isocaloric self-selection regime, following (1) saline and the first round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections and (2) saline and the second round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from saline injections: $*p<0.05$.

tions in fat intake during the first round of morphine injections, in Round 2 animals consumed significantly more fat following morphine injections than following control injections.

Effects of Morphine on Percent Nutrient Intake of Animals Given the Standard Self-Selection Regime

Percent of nutrients selected over the six-hour feeding period was modified by morphine injections. Percent protein intake was not altered as a function of drug administration. A slight suppression in percent carbohydrate intake was apparent during the first round of morphine administration, and became significant following the second round of exposure to the drug. In contrast to percent carbohydrate intake, percent fat intake was elevated during Round 1 and became significantly elevated during Round 2 at all three doses of morphine tested (Fig. 4).

Isocaloric Dietary Components

Effects of Morphine on Total Caloric Intake of Animals on the Isocaloric Self-Selection Regime

Round 1. Self-selection animals with access to the three isocaloric diets reduced total cumulative caloric intakes in a dose-related manner following morphine injections (Fig. 5).

Round 2. During the second round of morphine administration, total caloric intake was only decreased at one and two hours following the administration of the highest dose of morphine (20 mg/kg) (Fig. 5).

Effects of Morphine on Nutrient Intake of Animals with Access to the Isocaloric Self-Selection Regime

Round 1. Animals with access to the isocaloric fat source exhibited patterns of nutrient selection similar to animals with access to the standard self-selection regime (Fig. 6). Protein intake was significantly suppressed across the six-hour feeding period by the two higher doses of morphine. Animals displayed a dose-related suppression of carbohydrate intake at all measurement times. No modifications in fat intake were observed as a function of morphine injections.

Round 2. Animals with access to the isocaloric dietary components displayed different patterns of nutrient selection from Round 1 during the second round of access to the drug (Fig. 6). Protein intake was suppressed at only the highest dose of morphine tested, with the greatest decreases noted during the first two hours postinjection. Carbohydrate intake was significantly suppressed at the highest dose throughout the six-hour feeding period. Again, as was observed with animals on the standard self-selection regime, following morphine, self-selection animals with access to the isocaloric fat source significantly increased fat intake above control values across the six-hour feeding period.

Effects of Morphine on Percent Nutrient Intake of Animals Given Access to the Isocaloric Self-Selection Regime

Modifications in patterns of nutrient selection were evident during the second round of drug administration (Fig. 7). Percent protein intake did not vary as a function of morphine administration in either of the two test rounds. Percent carbohydrate intake was very slightly suppressed in Round 1. During Round 2 percent carbohydrate intake was significantly suppressed relative to saline values. While percent fat intake was only slightly elevated during the first round of

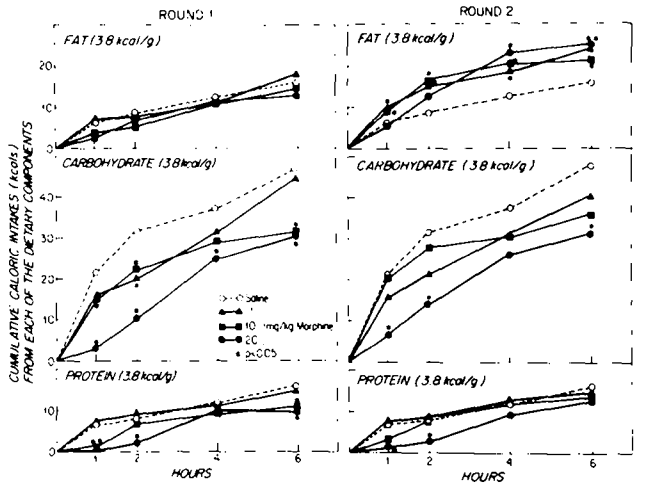

FIG. 6. Mean cumulative caloric intakes across a six-hour feeding period of fat, carbohydrate and protein, of animals maintained on the isocaloric self-selection regime, following (1) saline and the first round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections and (2) saline and the second round of 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from saline injections: $*p<0.05$.

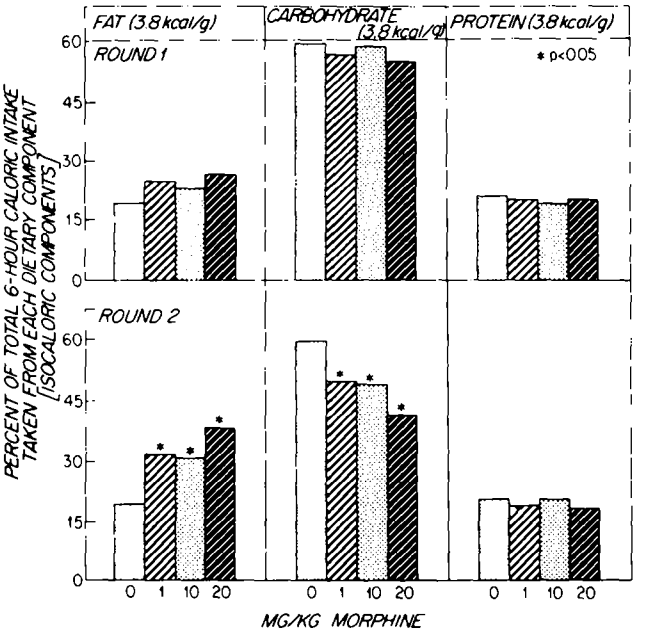

FIG. 7. Mean percent calories taken from the fat, carbohydrate and protein components of the isocaloric dietary self-selection regime over a six-hour feeding period, following the first and second round of administration of 0.0, 1.0, 10.0 and 20.0 mg/kg morphine sulfate injections. Significantly different from 0.0 mg/kg: $*p<0.05$.

drug administration, it was significantly elevated during the second round of morphine injections.

No modifications in water intake were observed over the six-hour feeding period as a function of morphine administration.

DISCUSSION

As previously reported [18], the acute administration of morphine resulted in selective modifications in macronutrient choice. In the present study, following morphine administration, animals maintained on both dietary self-selection regimes, increased intake of the fat components, while suppressing carbohydrate intake and exhibiting little modification in protein intake. While these effects were evident during the first round of morphine administration, they became more pronounced with repeated exposure to the drug.

The present experiment addresses two of the issues raised by previous work on morphine and diet selection. First, the fact that increased intakes of the solid fat components were observed in the present experiment eliminates the possibility that the increases in fat consumption observed in a previous study [18] in which fat was presented in a liquid form, was solely a function of drinking rather than feeding behavior. Second, it had been proposed that after the initial two-hour suppression of total caloric intake following morphine injections, animals might have experienced a greater than normal energy deficit and sought the most immediate source of calories. As the fat component employed in the prior study had a greater caloric density than the protein and carbohydrate components, it would have provided the most immediate source of calories. However, in the present experiment animals significantly increased their consumption of the isocaloric fat source as well as the standard fat source following morphine injections. This occurred even though animals on the different self-selection regimes started from very different baselines of fat intake. Prior to drug administration, animals given access to the standard self-selection components consumed almost 40% of their calories from their fat ration, while animals with the isocaloric components consumed less than 20% of their calories from fat. Despite starting from very different baselines, both groups of animals significantly increased consumption of the fat component of their respective dietary regimes following morphine injections. Therefore, the possibility that animals were increasing intake of the fat ration following morphine injections on the basis of caloric density alone appears unlikely.

While modifications in diet selection following morphine administration were evident during the first round of drug injections, they became more apparent during the second round of morphine injections. Alterations in feeding behavior associated with repeated exposure to morphine have been previously reported. For example, while Riley *et al.* [24] did not observe modifications in food intake following one week of daily morphine injections, they did note a dose-related hyperphagia three to six hours postinjection during the second week of drug administration. This period of increased food intake occurred progressively sooner with repeated drug administration. Further research is necessary to better understand the importance of repeated exposure to morphine to patterns of food intake and diet selection.

Recent experimental evidence has suggested that the effects of opioid agonists and antagonists on feeding behavior may be a function of the action of these drugs on endogenous opioid systems [22]. Evidence to support the involvement of an endogenous opioid system in diet selection comes from the different actions of morphine and naloxone on nutrient

choice [18,19]. Morphine is believed to facilitate the activity of an endogenous opioid system (e.g., [10,32]) while naloxone is thought to inhibit the activity of this system (e.g., [1]). Interestingly, even though naloxone and morphine led to very different patterns of diet selection, these drugs had similar actions on total caloric intake. While naloxone administration reduced fat intake, morphine injections resulted in an increase in consumption of this nutrient. In contrast, while total six-hour consumption of carbohydrate was not significantly modified by naloxone administration, six-hour carbohydrate intake was suppressed following injections of morphine [18,19]. The opposite effects of these two pharmacological agents on patterns of nutrient choice strongly suggest a role for endogenous opioid activity in the regulation of macronutrient intake.

Further support for the involvement of endogenous opioid systems in the regulation of food intake comes from studies examining animals with different forms of experimental obesity. For example, while genetically obese mice (ob/ob) and rats (fa/fa) are reported to have elevated levels of pituitary β-endorphin in comparison to their lean littermates [6, 7, 8, 17, 25], animals made obese by the neonatal administration of monosodium glutamate (MSG) are reported to have reduced levels of brain β-endorphin, with no changes in pituitary levels [15]. Interestingly, animals with different forms of experimental obesity not only have different levels of brain and pituitary β-endorphin but also display different patterns of diet selection. For example, the genetically obese mouse is reported to select a higher proportion of its diet as fat, and lower proportions as protein and carbohydrate when placed on a self-selection regime [20]. This pattern of intake resembles that observed following the administration of morphine. In contrast, rats with MSG-induced obesity choose a higher percentage of their calories as carbohydrate and lower percentages as fat and protein than control animals [14]. This pattern of intake is similar to the pattern of intake observed in neurologically-intact animals following naloxone injections [19].

The preceding studies demonstrate how experiments employing dietary self-selection regimes may provide information, not only on quantitative, but also qualitative adjustments in feeding behavior following pharmacological manipulations. More detailed examination of patterns of dietary self-selection following the administration of opioid agonists and antagonists may provide a greater understanding of the mechanisms involved in the regulation of food intake.

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