Pharmacology Biochemistry & Behavior, Vol. 12, pp. 427–430. Printed in the U.S.A.

Morphine Selectively Influences Macronutrient Intake in the Rat[1]

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Received 19 October 1979

MARKS-KAUFMAN, R. AND R. B. KANAREK. *Morphine selectively influences macronutrient intake in the rat.* PHARMAC. BIOCHEM. BEHAV. 12(3) 427–430, 1980.—Dietary self-selection of the three macronutrients, protein, carbohydrate and fat, was examined in male rats following the administration of three doses of morphine sulphate: 10 mg, 15 mg, and 30 mg/kg body weight. Intakes of all three macronutrients were suppressed in a dose-dependent manner for a two-hour period following morphine administration. Both protein and carbohydrate intakes remained suppressed for a six-hour feeding period after morphine injections. In contrast, animals increased fat intake during the final four hours of the six-hour feeding period resulting in an overall increase in fat intake.

Dietary self-selection Morphine Feeding behavior Protein Fat Carbohydrate

OPIATE analgetic drugs have a biphasic effect on food intake in rats. For example, Thornhill, Hirst and Gowdey [14,15] found that heroin administration initially suppressed food intake for two to four hours. This suppression was followed by a period of vigorous feeding. Similarly, Kumar, Mitchell and Stolerman [6] reported that in comparison to a group of control animals, rats made tolerant to morphine by repeated daily injections immediately decreased food intake after drug administration. This decrease was followed by an increase in food intake two to three hours post-injection. As recent work has shown that drugs may have selective effects on the intake of specific nutrients [16], it would be interesting to determine if the period of increased feeding following administration of narcotic analgetics reflects a general increase in caloric intake or an increased need for a specific macronutrient.

In the present study, the effects of the acute administration of morphine on dietary self-selection of the three macronutrients, protein, fat and carbohydrate, were investigated.

METHOD

Animals and Diets

Six male Sprague-Dawley rats (CD outbred, Charles River Laboratories, Wilmington, MA), weighing approximately 400 to 420 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 to 2000 hr).

Animals were given access to three dietary rations: a protein ration, a carbohydrate ration and a fat ration. The protein ration (3.84 kcal/g) contained 960 g vitamin-free casein (ICN Pharmaceuticals, Cleveland, OH), 40 g minerals (U.S.P. XIV Salt Mixture, ICN Pharmaceuticals) and 22 g vitamins (Vitamin Diet Fortification Mixture, ICN Pharmaceuticals). The carbohydrate ration (3.84 kcal/g) was composed of 580 g cornstarch (Teklad Test Diets, Madison, WI), 280 g dextrin (Teklad Test Diets), 100 g commercial grade sugar, 40 g minerals (U.S.P. XIV Salt Mixture) and 22 g vitamins (Vitamin Diet Fortification Mixture). Both the protein and the carbohydrate rations were provided in Wahmann (Timonium, MD) LC-306-A food cups. The fat ration (8.2 kcal/ml), pure vegetable oil (Wesson), was presented in calibrated glass drinking tubes.

Procedure

Animals initially were given ad lib access to the three dietary components. Twenty-four hour baseline measurements of body weight and protein, carbohydrate and fat intakes were collected for 10 days. Access to the dietary rations was then restricted to a six-hour period during the day (0930 to 1530 hr). Animals were maintained on this restricted feeding schedule for the remainder of the experiment.

Animals were allowed to acclimate to the restricted feeding schedule for 30 days before testing for the effects of morphine on feeding behavior was initiated. On test days, animals were given intraperitoneal (IP) injections of morphine sulfate, generously supplied by the National Institute on Drug Abuse (Research Triangle Institute). Morphine was dissolved in 0.9% saline to a concentration that allowed the studied doses of morphine to be injected in volumes of 0.1 ml

[1]This research was supported by National Institute of Arthritis, Metabolism and Digestive Diseases Grant No. AM19821 to R. B. K. The authors would like to thank Lawrence J. Botticelli for his helpful comments on this manuscript.

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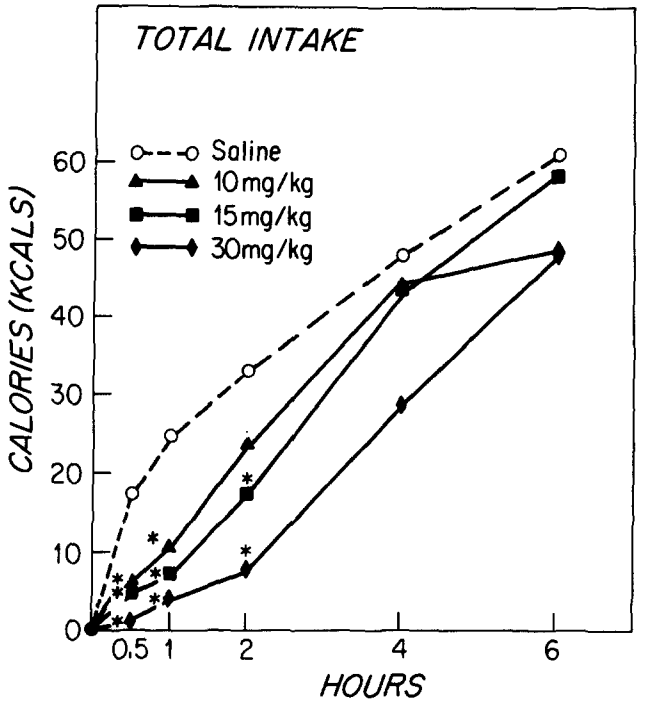

FIG. 1. Total cumulative caloric intake following the administration of saline, 10 mg/kg, 15 mg/kg and 30 mg/kg morphine sulfate. Significantly different from saline injections: *=$p<0.05$.

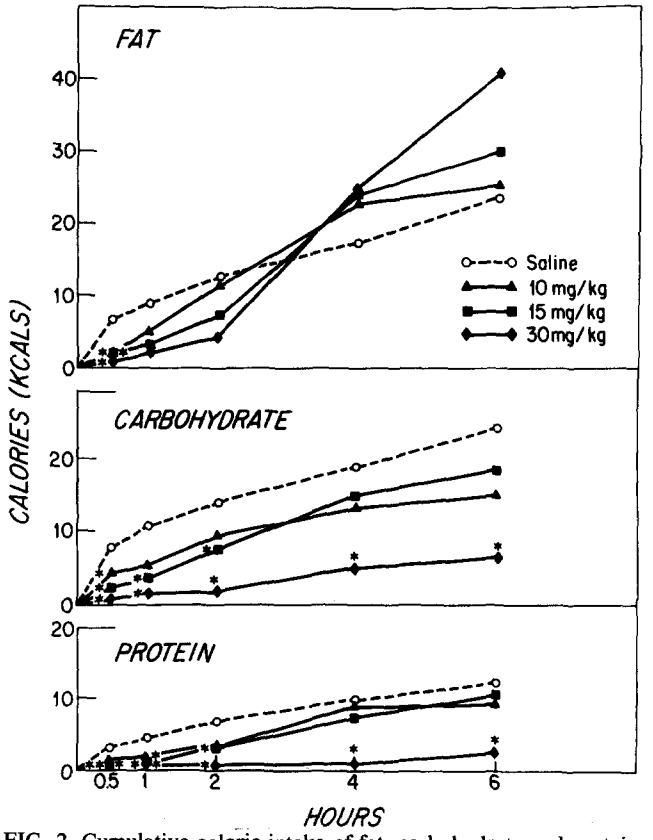

FIG. 2. Cumulative caloric intake of fat, carbohydrate and protein over a six-hour period following the administration of saline, 10 mg/kg, 15 mg/kg and 30 mg/kg morphine sulfate. Significantly different from saline injections: *=$p<0.05$.

per 100 g of body weight. Three doses of morphine, administered in the following order, 10 mg/kg, 15 mg/kg and 30 mg/kg body weight, were used. Morphine injections were separated from each other by a minimum of seven days. To control for conditioning to the injection procedure, animals received IP injections of physiological saline on the days immediately preceding morphine administration. Protein, fat and carbohydrate intakes were measured at 0.5, 1, 2, 4 and 6 hours following both morphine and saline injections.

Data were analyzed using one-way analyses of variance followed by a posteriori multiple comparisons of within-group means [13].

RESULTS

Animals consumed less calories when restricted to a six-hr feeding schedule than when provided with ad lib access to food. However, while animals initially lost weight when given food for only six hours a day, animals began to regain weight within ten days of being placed on the restricted feeding schedule. At the time of testing for the effects of morphine on feeding behavior, mean body weight of the animals was approximately 105% of the pre-restriction value. Also, although restricting animals to a six-hour feeding schedule resulted in a decrease in caloric intake (to approximately 75% of ad lib intake), restriction did not lead to any major alterations in the percentage of calories taken from each of the three macronutrient components. On both the 24-hr and six-hr feeding schedules, animals took approximately 20% of their calories as protein, 40% as carbohydrate and 40% as fat.

Neither caloric intake nor nutrient selection were modified when saline injections were given at the beginning of the six-hour feeding period. As there were no differences in intakes across saline injections, mean data for saline administration are presented.

When morphine was administered at the beginning of the six-hr feeding period, an initial dose-related suppression of caloric intake (calculated as the sum of caloric intakes from each of the three macronutrients) was observed (Fig. 1). Caloric intake was significantly suppressed at 0.5 hours post-injection for all doses of morphine. Intake remained suppressed for up to 2 hours after injection for the two higher doses of morphine. During the period from 2 to 6 hours after morphine administration, animals increased caloric intake above saline levels. As a result of this biphasic response in feeding behavior, total caloric intake during the six-hour feeding period did not vary as a function of drug administration.

While a biphasic effect on energy intake was found after morphine administration, this effect was not representative of the pattern of intake found for the individual macronutrients (Fig. 2). Decreased consumption of each of the three macronutrients contributed to the initial decrease in caloric intake. However, intake of the individual components during the final 4 hours, did not parallel total caloric intake. Both protein and carbohydrate intakes were initially suppressed in a dose-related manner and remained suppressed for the entire six-hr period. In contrast, while animals initially suppressed fat intake, they increased fat consumption above

saline levels during the final 4 hours. This later increase in consumption resulted in a greater intake of fat for the entire six-hr period following morphine than after saline injections.

DISCUSSION

Opiate analgetics selectively affected macronutrient consumption. Intakes of protein and carbohydrate were suppressed throughout a six-hr feeding period following morphine administration. In contrast, morphine produced a biphasic effect on fat intake.

Several alternative explanations exist to explain morphine's selective action on nutrient intake. First, as fat was presented in a liquid form, it might be argued that with respect to fat intake, morphine influenced drinking behavior rather than feeding behavior. This explanation seems unlikely, as Frenk and Rogers [2] recently reported that water-deprived rats reduced fluid intake in a dose-related manner following the administration of morphine. Additionally, we have found that during a six-hr feeding period following morphine injections, rats given a choice of a 32% sucrose solution and a standard laboratory diet suppressed intake of the sucrose solution to a greater extent than intake of the standard diet. These data suggest that morphine depresses fluid intake rather than stimulating it. Further evidence that morphine was influencing feeding behavior rather than drinking comes from experiments comparing nutrient selection of a liquid source of fat to a solid source (hydrogenated vegetable oil with the addition of 2% vitamins and 4% minerals). In these experiments, no differences in nutrient selection were observed as a function of the type of fat offered to animals.

A second possibility is that following the initial two hour suppression of caloric intake animals experienced a greater than normal energy deficit and sought the most immediate source of calories. Fat, having a greater caloric density than protein or carbohydrate, would provide this source. Presently, we are investigating this possibility by using sources of fat diluted with non-nutritive materials.

Third, the selective effects of morphine on nutrient intake may be mediated by endocrine mechanisms. It is well-established that morphine affects both pituitary and pancreatic hormones. Acute morphine administration stimulates release of growth hormone (GH), prolactin (PRL) and adrenocorticotropin (ACTH), while inhibiting release of thyrotropin (TSH) [1,11]. Also, morphine has been reported to facilitate the release of insulin and glucagon from the endocrine pancreas in vitro in the presence of glucose [4]. Both these pituitary and pancreatic hormones have been reported to have substantial influences on feeding behavior. For example, insulin administration leads to increased food intake, with prolonged treatment resulting in significant elevations in body weight [7,12]. While the effects of these hormones on specific nutrient intake have not been fully elucidated, it seems likely that they may play an important role in determining diet selection. Supportive evidence for the role of endocrine mechanisms in the action of morphine on nutrient intake comes from observations of the effects of the opiate antagonist, naloxone, on pituitary hormones and diet selection. Naloxone produced the opposite effects from morphine on pituitary hormone release [11]. Interestingly, while morphine (administered at the doses used in the present experiment) and naloxone both depress caloric intake [3,8], we have found that naloxone produced the opposite effect from morphine on diet selection. Over a six-hr feeding period, naloxone administration led to a dose-dependent reduction in fat intake. While naloxone resulted in a slight initial depression of both carbohydrate and protein intake, total six-hr intake of these two nutrients did not vary as a function of drug administration. Thus in contrast to morphine, naloxone suppressed fat intake, but had no overall suppressive effect on either protein or carbohydrate intake.

The importance of endogenous opioid peptides in feeding behavior has recently been reported. In comparison to lean littermates, increased levels of pituitary β-endorphin are observed in genetically obese mice (ob/ob) and rats (fa/fa) [9]. It is interesting to note that diet choices made by genetically obese mice are similar to the changes observed in choice behavior after morphine. Obese mice select lower proportions of their diets as protein and carbohydrate, and higher proportions as fat than lean controls [10]. Recent research has indicated that animals with other forms of experimental obesity display, not only, different modifications in brain and pituitary β-endorphin levels from genetically obese mice, but also, different patterns of diet selection. For example, Krieger *et al.* [5] reported that animals made obese by neonatal monosodium glutamate (MSG) administration have reduced levels of brain β-endorphin with no change in pituitary levels. We have found that rats with MSG-induced obesity choose a higher percentage of their daily calories as carbohydrate and lower percentages as fat and protein than control animals (Kanarek and Marks-Kaufman, unpublished results).

The results of the present experiment demonstrate the importance of examining dietary self-selection in studies of feeding behavior. While increased caloric intake is a common characteristic of most forms of experimental obesity, patterns of diet selection vary significantly among different models of obesity. These differences in diet selection may be correlated with differences in patterns of endogenous peptides.

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