Intake of High-Fat Food Is Selectively Enhanced by Mu Opioid Receptor Stimulation within the Nucleus Accumbens

MIN ZHANG, BLAKE A. GOSNELL and ANN E. KELLEY

Department of Psychology (M.Z.), University of Wisconsin-Madison, and Department of Psychiatry (A.E.K.), University of Wisconsin-Madison Medical School, Madison, Wisconsin; and Neuropsychiatry Research Institute (B.A.G.), Fargo, North Dakota

Accepted for publication January 2, 1998 This paper is available online at http://www.jpet.org

ABSTRACT

The present study was designed to further investigate the nature of feeding induced by opioid stimulation of the nucleus accumbens through an examination of the effects of intra-accumbens (ACB) opioids on macronutrient selection. In 3-hr tests of free-feeding (satiated) rats, intra-ACB administration of the mu receptor agonist D-Ala²,N-Me-Phe⁴,Gly-ol⁵-enkephalin (DAMGO; 0, 0.025, 0.25 and 2.5 μg bilaterally) markedly enhanced the intake of fat or carbohydrate when the diets were presented individually (although the effect on fat intake was much greater in magnitude). Intra-ACB injections of DAMGO, however, produced potent preferential stimulatory effects on fat ingestion with no effect on carbohydrate ingestion when both fat and carbohydrate diets were present simultaneously. Moreover, this selective stimulation of fat intake was independent of base-line diet preference and could be blocked by systemic injection of naltrexone (5 mg/kg). We also examined the effect of 24-hr food deprivation on the pattern of macronutrient intake in rats with access to both carbohydrate and fat. In contrast to the DAMGO-induced selective enhancement of fat intake, food deprivation significantly increased the intake of both diets to the same extent; however, in this case, only the stimulated fat intake was blocked by systemic naltrexone. Intra-ACB administration of DAMGO in hungry rats produced an effect similar to that observed in free-feeding rats; preference was strongly shifted to fat intake. Similarly, the opioid antagonist naltrexone (20 μg) infused directly into ACB preferentially decreased fat intake in hungry rats. These findings suggest that endogenous opioids within the ventral striatum may participate in the mechanisms governing preferences for highly palatable foods, especially those rich in fat.

Endogenous opioid peptides have been found to be involved in the modulation of feeding behavior in both humans and rats. Since the initial findings that morphine increased food consumption (Flowers et al., 1929; Martin et al., 1963), the role of endogenous opioids in different aspects of feeding behavior, such as caloric intake, taste reactivity, diet preference and the interaction with other neuropeptides, has been investigated extensively. Generally speaking, peripheral or central injections of opioid agonists, including mu, delta and kappa agonists, increase food intake and opioid antagonists decrease food consumption, at least in the short term, under various testing conditions (Holtzman, 1974; Reid, 1985; Levine and Billington, 1989). In addition to modifying total food consumption, opioid peptides influence macronutrient selection. Several studies with dietary self-selection paradigms showed that acute systemic morphine injections preferentially stimulate fat consumption while suppressing carbohydrate intake and having little modulatory effect on protein intake (Marks-Kaufman and Kanarek, 1980; Marks-Kaufman, 1982; Ottaviani and Riley, 1984). A similar pattern has been observed when rats were treated with morphine chronically (Ottaviani and Riley, 1984; Gosnell and Krahn, 1993). In contrast, the opioid antagonist naloxone selectively decreases fat intake when carbohydrate and protein are also available to rats (Marks-Kaufman and Kanarek, 1981, 1990). However, when base-line diet preference of rats was taken into consideration, Gosnell et al. (1990) found that morphine primarily increased preferred diet consumption rather than the intake of a specific macronutrient. Evans and Vaccarino (1990) also found that systemic morphine enhances intake of preferred food. These findings seem to support the currently favored hypothesis that opioids play a role in modulating the palatable aspects of food, making food more rewarding (Coo-per and Kirkham, 1993).

Most of the studies described above have been conducted with the peripheral or intraventricular administration of morphine. Although a number of studies have demonstrated the involvement of the ACB in opioid-induced hyperphagia, little work has been done to investigate its role in macronutrient selection. In light of evidence implicating the accumbens in the processing of reward-related information, the investigation of how this structure modulates macronutrient preference could be particularly valuable for further understand-

ABBREVIATIONS: ACB, nucleus accumbens; DAMGO, D-Ala²,N-Me-Phe⁴,Gly-ol⁵-enkephalin.
standing of mechanisms underlying opioid-induced hyperphagia. Indeed, it is well documented that the ACB is a crucial brain area responsible for the establishment and maintenance of drug-seeking behavior induced by opiates, psychostimulants and alcohol (Wise and Bozarth, 1987; Koob and Bloom, 1988). Recently, evidence emerging from both clinical surveys and animal studies demonstrated parallels between drug or alcohol addiction and food cravings (Mitchell et al., 1985; Morabia et al., 1989; Krahn and Gosnell, 1991; Bell et al., 1994; Gosnell et al., 1995). Accordingly, it is possible that the ACBs may be involved in both drug reward and the subjective reward derived from food. This is consistent with our previous studies showing that in satiated rats, microinjections of mu and delta opioid receptor agonists into the ACB stimulate chow feeding and intake of liquid sucrose, effects both of which are blocked by pretreatment with naltrexone (Bakshi and Kelley, 1993a; Kelley et al., 1996; Zhang and Kelley, 1997). Furthermore, the phenomenon of conditioned feeding induced by multiple morphine microinjections into the ACB provides further evidence to suggest the involvement of reward mechanisms (Bakshi and Kelley, 1994; Kelley et al., in press). The current study extended these investigations to examining intra-ACB opioid effects on macronutrient selection. Because our past findings showed that the orexigenic effect of opioids seems to be mediated primarily by mu receptors (Bakshi and Kelley, 1993a; Zhang and Kelley, 1997), the current study was focused on the mu receptor. In this study, the relationship between base-line diet preference and the feeding stimulatory effect of opioids was investigated. We further compared the pattern of diet selection induced by opioid treatments with that induced by food deprivation. We assumed that intake in food-restricted rats is driven mainly by energy needs, with taste or palatability being relatively less important. In consideration of the notion that opioids facilitate feeding in satiated animals by enhancing the orosensory palatability of food, we predicted a difference in the profile of these two feeding paradigms.

Materials and Methods

Animals. A total of 54 male rats (Harlan-Sprague Dawley, Indianapolis, IN) weighing between 270 and 320 g were used in the present study. Animals were housed two or three to a cage with access to unlimited water and standard normal laboratory chow (Purina Chow) unless they were under specific food deprivation schedule (see details of experimental design). The lights were on at 7:00 A.M. and off at 7:00 P.M.

Surgery. Animals were handled for several days after arrival. For surgery, animals were anesthetized with a mixture of ketamine and xylazine (90 mg/kg ketamine and 9 mg/kg xylazine). Bilateral guide cannulae were secured to the skull with stainless steel screws and light curable dental resin (Dental Supply of New England, Boston, MA). Coordinates for the aimed sites were (in mm, with tooth bar 1.5 mm beyond the end of the guide cannula, for a final dorsoventral coordinate of −8.0 mm from skull. The rate of injection was 0.32 μl/min with the total duration of infusion being 1 hr 33 min. One additional minute was allowed for diffusion. Injectors then were removed, and the styles were replaced.

Behavioral testing and experiment design. After 2 to 3 days of recovery, the rats were brought into the testing room and provided daily with the testing diet (high-carbohydrate diet, high-fat diets or both, depending on the experimental design) for 3 hr in a testing cage. As indicated in table 1, both diets contained equal amounts of vitamins, minerals, choline chloride, fiber and protein, when equated on a caloric basis. Diets were obtained from Teklad Diets (Madison, WI). This period lasted for several days until stable food consumption across days was obtained. Except for the daily 3-hr testing period, animals were provided with standard laboratory chow, either ad libitum or with food restriction, depending on the experimental design (see below). Before the testing period began, a saline injection and a sham injection were given on separate days to habituate the rats to the injection procedure. Preweighed jars containing diets were attached to the testing cages. At the end of each testing period, the diet jars were removed and weighed, and the corresponding diet intake in calories was calculated and corrected for spillage. Water was available during the entire testing session.

In experiments 1 and 2, non-food-deprived rats were treated with intra-ACB microinjections of DAMGO in doses of 0 (saline), 0.025, 0.25 and 2.5 μg/side in a counterbalanced order. There was at least 1 day spaced between injections. The testing session began immediately after the microinjections. For the first experiment, there were two groups of rats in which the effect of DAMGO on the consumption of high-carbohydrate diet and high-fat diet were evaluated separately (n = 10 for carbohydrate group, n = 14 for fat group). The diet was weighed every hour over the 3-hr testing period. For experiment 2 (n = 14), non-food-deprived rats had simultaneous access to both diets in the testing cage, and the position of diet jars was exchanged daily. After the rats were adapted to the testing diets, base-line intakes over 3 hr were measured for 3 consecutive days; thus, rats were divided into carbohydrate-prefering (CP) and fat-prefering (FP) groups on the basis of the ratio of the average of carbohydrate intake to fat intake. For CP group, the ratio was >1; otherwise, rats were assigned to the FP group. One day after the determination of

<table>
<thead>
<tr>
<th>TABLE 1 Composition of diets used in experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Carbohydrate</td>
</tr>
<tr>
<td>Corn starch</td>
</tr>
<tr>
<td>Dextrose</td>
</tr>
<tr>
<td>Sucrose</td>
</tr>
<tr>
<td>Casein*</td>
</tr>
<tr>
<td>DL-Methionine</td>
</tr>
<tr>
<td>Vegetable shortening</td>
</tr>
<tr>
<td>Safflower oil</td>
</tr>
<tr>
<td>AIN-76A vitamin mixb</td>
</tr>
<tr>
<td>AIN-76 mineral mixc</td>
</tr>
<tr>
<td>Choline chloride</td>
</tr>
<tr>
<td>Cellulose (Alphacel)</td>
</tr>
<tr>
<td>Weight (g)</td>
</tr>
<tr>
<td>Total energy (kcal)*</td>
</tr>
</tbody>
</table>

All components are expressed as weight (g). * Assuming a protein content of 90%. b The vitamin and mineral mixes contain 97% and 12% sucrose, respectively. c Based on energy values of 4, 9, and 4 kcal/g for carbohydrate, fat, and protein, respectively.
the base-line preference, rats were tested for the effect of DAMGO on diet preference. Immediately after the microinjections, the rats were put into the testing cages, which contained both of the diets. After the last injection of DAMGO, the rats underwent 1 additional test day in which an intraperitoneal injection of naltrexone (5 mg/kg) was given 15 min before an intra-ACB microinfusion of DAMGO at the dose of 2.5 \( \mu \)g. The intake of high-carbohydrate diet and high-fat diet was measured for 3 hr after DAMGO treatment.

In the first part of experiment 3 \((n = 16)\), the effect of mild food deprivation on diet selection was investigated. As in experiment 2, the rats were divided into FP and CP groups based on the same criteria. The rats had unlimited access to normal laboratory chow in the home cages except on the day on which the rats were deprived of food for 24 hr before the testing session. During the testing period, the hungry rats were put into the testing cages containing both high-carbohydrate and high-fat diets. Diet intake over the 3-hr session was measured. Four days later, the same procedure was conducted except that the rats received saline or naltrexone injections (5 mg/kg i.p.) 15 min before the access to carbohydrate and fat. Each rat received both intraperitoneal treatments, which were spaced by \( \geq 4 \) days.

The effect of DAMGO on carbohydrate intake

DAMGO peaked in the second hour (\( P < .01 \)). Subsequent planned mean contrasts demonstrated to result from the dose of 0.25 \( \mu \)g, 0.5 \( \mu \)g, 2.5 \( \mu \)g DAMGO; \( P < .01 \) for 0.025 and 2.5 \( \mu \)g DAMGO). The fat intake enhanced by 2.5-\( \mu \)g dose was still pronounced in the second hour (\( P < .01 \)).

The effect of DAMGO on carbohydrate intake. Infusion of DAMGO elicited an increase in carbohydrate intake (fig. 1). An overall significant dose effect was obtained \([F(3,27) = 5.176, P < .01]\), for which subsequent contrast analysis demonstrated to result from the dose of 0.25 \( \mu \)g (\( P < .01 \)) and 2.5 \( \mu \)g (\( P < .01 \)). Analysis of the time course of carbohydrate intake indicated a significant interaction between dose and time bin \([F(6,54) = 7.680, P < .01]\). In the first hour, both 0.025 (\( P < .05 \)) and 0.25 (\( P < .01 \)) \( \mu \)g enhanced carbohydrate consumption. The effect of 2.5 \( \mu \)g DAMGO peaked in the second hour (\( P < .01 \)).

In summary, when carbohydrate and fat diets were presented separately to rats, stimulation of \( \mu \) receptor systems within the ACB, combined with food deprivation, was investigated 7 days after the rats received the last intraperitoneal injection described above. The rats were administered an intra-ACB infusion of DAMGO (2.5 \( \mu \)g) or saline (injections spaced 2 days apart), in combination with the 24-hr food deprivation. One week later, the same group of rats were treated with intra-ACB microinfusion of naltrexone (20 \( \mu \)g) or saline. Diet intake over 3 hr was calculated as noted above.

All experiments used a within-subjects design; therefore, each rat received all dose treatments. All drug doses were administered in a counterbalanced order. The dose ranges used in these studies were chosen on the basis of previous work in the laboratory.

Data analysis. Data were analyzed initially using SuperANOVA software package (Abacus) on a Macintosh computer. The main dependent variable, food intake (in kcal), was analyzed with a two-factor (dose and time, or dose and diet) or one-factor (dose or treatment) analysis of variance followed by mean value comparison contrasts (Rosenthal and Rosnow, 1991). Planned contrasts compared each drug dose to its vehicle control. To determine the relationship between base-line diet preference and drug effect (experiment 2), difference scores were calculated for each diet and DAMGO dose by subtracting the intake of a particular diet intake after saline injection from the intake of the same diet after each DAMGO treatment. These difference scores were used to compute the correlations (Pearson’s \( r \)). The same method was used to determine the correlation between the base-line diet preference and the effects of hunger on nutrient intake, except that no difference scores were introduced for Pearson’s \( r \) (for details, see “Results”).

Histology. After the completion of all testing, rats were anesthetized deeply with sodium pentobarbital and perfused transcardially with a 0.9% isotonic saline solution followed by a 10% formalin solution. Brain were removed and stored in a 10% formalin solution for several days to allow for fixation. Before the cutting, the brain were transferred into the 10% sucrose-formalin overnight. For histological preparation, brains were cut into 60-\( \mu \)m sections, mounted and stained with cresyl violet. Sections were examined under the microscope to determine the placement of injector tips. Injections sites were well localized within accumbens approximately on the core/shell border. No animals were eliminated from any of the studies. (Photomicrographs of representative placements are shown in fig. 5.)

Results

Experiment 1: Effect of Intra-ACB Mu Opioid Agonist Infusion on Intake of High-Carbohydrate or High-Fat Diets Given Separately

The effect of DAMGO on fat intake. Two-way analysis of variance revealed a significant main effect of dose \([F(3,39) = 39.276, P < .01] \) and dose \( \times \) time bin interaction \([F(6,78) = 7.741, P < .01]\). Subsequent planned mean contrasts suggested that both the medium dose (0.25 \( \mu \)g) and high dose (2.5 \( \mu \)g) contribute to the significant dose effect (\( P < .01 \)) (fig. 1). Follow-up analysis of simple comparisons between saline and each dose of DAMGO treatment at each level of time bins (first, second and third hour) showed that all of the three doses enhanced fat intake in the first hour (\( P < .05 \)) for 0.025 \( \mu \)g DAMGO; \( P < .01 \) for 0.25 and 2.5 \( \mu \)g DAMGO). The fat intake enhanced by 2.5-\( \mu \)g dose was still pronounced in the second hour (\( P < .01 \)).

Experiment 2: Effect of Intra-ACB Mu Opioid Agonist Infusion on Diet Preference in Nondeprived Rats

In this test with the two macronutrient-specific diets simultaneously available, free-feeding rats given an intra-ACB infusion of DAMGO displayed a strong preference for fat compared with the carbohydrate diet (fig. 2). Significant effects of dose condition \([F(3,39) = 22.029, P < .01]\), diet \([F(1,13) = 9.851, P < .01]\) and diet \( \times \) interaction \([F(3,39) = 14.141, P < .01]\) were found. As shown in figure 2 (top), the 0.25- and 2.5-\( \mu \)g doses of DAMGO significantly increased total caloric intake (the sum of fat intake and carbohydrate intake) (\( P < .01 \)) and fat intake (\( P < .01 \)), whereas carbohydrate consumption remained unchanged. Furthermore, the enhancement induced by 2.5 \( \mu \)g DAMGO was completely blocked by naltrexone treatment (\( P < .01 \)).

![Fig. 1](image-url)
The correlation between the intake of each diet and baseline diet intake was shown in table 2, which suggested increased fat intake elicited by the 2.5-μg dose was positively correlated with base-line fat intake (P < .01) and negatively correlated with base-line carbohydrate intake (P < .05). To investigate the relationship between drug effect and baseline preference in detail, the data were reanalyzed after dividing the rats into CP and FP groups based on the criteria mentioned earlier. As demonstrated in figure 2 (middle and bottom), the 0.25- and 2.5-μg doses significantly facilitated fat feeding in both CP and FP groups. In contrast, no effect was observed on carbohydrate intake in both groups. Moreover, the effect on fat intake induced by the 2.5-μg dose was blocked by naltrexone pretreatment (P < .01). These results indicated that DAMGO exerted a pronounced preferential influence on fat intake, regardless of preexisting diet preference.

Experiment 3: Effect of Food Deprivation Alone and Food Deprivation in Combination with Intra-ACB Mu Agonist or Antagonist on Diet Selection

**Food-deprivation alone.** The mean value of intake across 3 consecutive days before the first test day was calculated and served as base-line intake in the satiated condition. The cumulative 3-hr diet intake was analyzed with two-way analysis of variance: feeding condition (satiation vs. hunger) × diet (fat vs. carbohydrate). In contrast to the results in experiment 2, only the main effect of feeding condition was found significant [F(1,15) = 82.819, P < .01], with no interactions or effects of diet content. This profile indicates that 24-hr food deprivation produced a significant increase in caloric intake compared with the satiated feeding condition but, more importantly, that the magnitude of this increase was similar across both diet conditions as shown in figure 3 (top). Similarly to experiment 2, however, only enhanced fat intake was blocked by intraperitoneal injection of naltrexone (P < .01).

In contrast to the selective effect of DAMGO on fat preference demonstrated in experiment 2, food deprivation produced no preferential alterations in macronutrient consumption in relation to base-line preference. Food-deprivation-induced diet consumption was significantly correlated with corresponding base-line diet preference (table 3). As shown in figure 3 (middle and bottom), food deprivation increased consumption of both diets to the same degree in both FP (P < .01 for both diets) and CP groups (P < .01 for carbohydrate; P < .05 for fat).

**Diet selection induced by intra-ACB DAMGO or naltrexone in hungry rats.** As for the effects of DAMGO on diet choice after food deprivation, two-way analysis of variance showed significant main effects for dose [F(1,15) = 13.536, P < .01], and diet [F(1,15) = 9.367 P < .01]. There also was a significant dose × diet interaction [F(1,15) = 7.552, P < .05]. Further analysis of simple comparisons showed that the selective stimulatory effect of DAMGO on fat consumption (P < .01) was responsible for the interaction (fig. 4).

An intra-ACB infusion of naltrexone suppressed food intake, shown in figure 4. Analysis of variance revealed a significant main effect of drug treatment [F(1,15) = 54.219, P < .01] and a significant drug × diet [F(1,15) = 13.593, P < .01] interaction. Follow-up simple comparison between drug and saline treatment at each level of diet demonstrated that naltrexone treatment dramatically inhibited fat consumption (P < .01) while producing less effect on carbohydrate intake (P < .05).

**TABLE 2**

Correlation coefficients (Pearson's r) for the relationship between base-line diet intake and the effect of DAMGO on diet intake

<table>
<thead>
<tr>
<th>Effect of DAMGO on the intake of each diet (difference from control intake)</th>
<th>Fat</th>
<th>Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-line intake (μg)</td>
<td>0.025</td>
<td>0.25</td>
</tr>
<tr>
<td>Fat</td>
<td>0.137</td>
<td>0.231</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>−0.096</td>
<td>−0.426</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < .01 and <sup>b</sup> P < .05 indicate significant correlation.

---

Accumbens Opioids and Food Intake 911

---

**Accumbens Opioids and Food Intake 911**
The main purpose of this study was to investigate the role of ACB mu opioid receptors in macronutrient preference and to obtain further information concerning the mechanisms underlying opioid-induced feeding. Our data demonstrate that within this brain area, stimulation of mu receptors exerts a powerful preferential facilitory effect on fat consumption. Furthermore, this effect is independent of preexisting diet preference and is blocked by cotreatment with naltrexone. Finally, the difference in the profiles between DAMGO- and food deprivation-induced diet selection suggests that endogenous opioids, at least within the ACB, may play a key role in the factors that govern food intake other than energy deficits, particularly palatability.

There is some debate with regard to the nature of opioid-induced feeding in terms of whether such feeding is nutrient specific or rather specific to individual base-line preferences. A selective increase in fat intake was reported by several studies with rats undergoing acute (Marks-Kaufman and Kanarek, 1980; Marks-Kaufman, 1982; Romsos et al., 1987) or chronic treatment with morphine under different feeding conditions (Ottaviani and Riley, 1984; Marks-Kaufman and Kanarek, 1990; Gosnell and Krahn, 1993). Consistent with the present results, naltrexone or naloxone selectively decreased fat intake in a self-selection paradigm (Marks-Kaufman and Kanarek, 1980; Marks-Kaufman, 1982). On the other hand, some researchers have argued that opioid-induced feeding is preference specific rather than macronutrient specific, finding that the effects of morphine on nutrient intake were modified when base-line preference was taken into consideration. Three studies provide evidence to support the preference-related hypothesis. The most direct evidence is provided by the study of Gosnell et al. (1990), who found that systemic injection of morphine preferentially increased fat intake in fat-preferring rats and carbohydrate intake in carbohydrate-preferring rats. They concluded that morphine causes a selective increase in the intake of preferred foods. Several differences may account for the discrepancies between that study and the present data. First, in the study of Gosnell et al., morphine was administered systemically, therefore stimulating many regions and subtypes of opiate receptors. Second, rats were allowed 24-hr access to the different diets compared with only 3-hr access in the present experiments. Consequently, the restricted base-line tests may be more strongly influenced by taste preference or palatability. Furthermore, it is noteworthy that in the study of Gosnell et al., although no significant effect was found on carbohydrate intake in fat-preferring rats, morphine still produced a significant stimulatory effect on fat intake, even in the carbohydrate-preferring rats. This finding suggests that morphine tends to produce a relatively greater effect on fat intake, although the size of the effect may be dependent on base-line preference. An additional study reported that systemic administration of morphine facilitated intake of carbohydrate in carbohydrate-deprived rats and protein in protein-deprived rats (Evans and Vaccarino, 1990). Furthermore, Glass et al. demonstrated that the anorexic effect of naloxone on

**Table 3**

Pearson’s $r$ for the relationship between base-line diet intake and the effect of food deprivation on diet intake.

<table>
<thead>
<tr>
<th>Effect of food deprivation on diet intake</th>
<th>Fat</th>
<th>Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-line intake</td>
<td>0.806$^a$</td>
<td>-0.496$^b$</td>
</tr>
<tr>
<td>Fat</td>
<td>-0.555$^a$</td>
<td>0.546$^b$</td>
</tr>
</tbody>
</table>

$^a$ $P < .01$ and $^b$ $P < .05$ indicate significant correlation.

**Discussion**

The main purpose of this study was to investigate the role of ACB mu opioid receptors in macronutrient preference and to obtain further information concerning the mechanisms underlying opioid-induced feeding. Our data demonstrate that within this brain area, stimulation of mu receptors exerts a powerful preferential facilitory effect on fat consumption. Furthermore, this effect is independent of preexisting diet preference and is blocked by cotreatment with naltrexone. Finally, the difference in the profiles between DAMGO- and food deprivation-induced diet selection suggests that endogenous opioids, at least within the ACB, may play a key role in the factors that govern food intake other than energy deficits, particularly palatability.

There is some debate with regard to the nature of opioid-induced feeding in terms of whether such feeding is nutrient specific or rather specific to individual base-line preferences. A selective increase in fat intake was reported by several studies with rats undergoing acute (Marks-Kaufman and Kanarek, 1980; Marks-Kaufman, 1982; Romsos et al., 1987) or chronic treatment with morphine under different feeding conditions (Ottaviani and Riley, 1984; Marks-Kaufman and Kanarek, 1990; Gosnell and Krahn, 1993). Consistent with the present results, naltrexone or naloxone selectively decreased fat intake in a self-selection paradigm (Marks-Kaufman and Kanarek, 1980; Marks-Kaufman, 1982). On the other hand, some researchers have argued that opioid-induced feeding is preference specific rather than macronutrient specific, finding that the effects of morphine on nutrient intake were modified when base-line preference was taken into consideration. Three studies provide evidence to support the preference-related hypothesis. The most direct evidence is provided by the study of Gosnell et al. (1990), who found that systemic injection of morphine preferentially increased fat intake in fat-preferring rats and carbohydrate intake in carbohydrate-preferring rats. They concluded that morphine causes a selective increase in the intake of preferred foods. Several differences may account for the discrepancies between that study and the present data. First, in the study of Gosnell et al., morphine was administered systemically, therefore stimulating many regions and subtypes of opiate receptors. Second, rats were allowed 24-hr access to the different diets compared with only 3-hr access in the present experiments. Consequently, the restricted base-line tests may be more strongly influenced by taste preference or palatability. Furthermore, it is noteworthy that in the study of Gosnell et al., although no significant effect was found on carbohydrate intake in fat-preferring rats, morphine still produced a significant stimulatory effect on fat intake, even in the carbohydrate-preferring rats. This finding suggests that morphine tends to produce a relatively greater effect on fat intake, although the size of the effect may be dependent on base-line preference. An additional study reported that systemic administration of morphine facilitated intake of carbohydrate in carbohydrate-deprived rats and protein in protein-deprived rats (Evans and Vaccarino, 1990). Furthermore, Glass et al. demonstrated that the anorexic effect of naloxone on
neuropeptide Y-induced feeding of carbohydrates and fats was dependent on diet preference. In these cases, however, the base-line preference of the given nutrient was determined by either nutrient deficit or neuropeptide Y-induced stimulation, both of which introduce a variety of factors that could mask the pure effects of opioids on nutrient selection.

The data from the present experiments help to clarify this debate. They suggest, at least for the ACB, that μu receptor stimulation preferentially enhances intake of foods that have inherently high palatability, such as fat. This effect is mostly clearly observed when animals have a choice of macronutrients or foods. When given a choice between carbohydrate and fat, ACB opioid stimulation enhanced only fat intake. Similarly, when rats are presented with both sweetened water and unsweetened water, only intake of the sweetened solution is enhanced (Zhang and Kelley, 1997), and when given a choice between chow and sugar, only sugar intake is enhanced (Evans and Vaccarino, 1996). However, because all foods that rats eat naturally have some inherent palatability, such as rat chow or carbohydrate, DAMGO also is able to stimulate intake when such foods are present alone. Furthermore, intra-ACB administration of DAMGO not only increases sucrose drinking (Zhang and Kelley, 1997) but also enhances the intake of salt solution (unpublished observation). It has also been reported that morphine suppresses aversive reactions to a bitter solution such as pure quinine (Doyle et al., 1993). Taken together, these experiments suggest that ACB opioids are involved in modulating the palatable response to food across a broad range of macronutrients and tastes. This idea may appear somewhat at odds with our present finding that the opioid effect was relatively fat specific. However, it is highly likely that the extent of enhanced palatability is correlated with the content of the fat and sugar because in general, highly preferred foods contain combinations of fat and sugar (or fat and salt) (Drewnowski et al., 1992b). In support of this notion, there is evidence of a correlation between taste palatability and activation of endogenous opioid systems. For instance, consumption of highly palatable food rich in fat and sugar causes an increase in the release of β-endorphin (Brennan et al., 1994; Welch et al., 1996). Additionally, an interesting interaction has been found between drug self-administration and food or taste preference. For example, fat-preferring rats consume more ethanol than carbohydrate-preferring rats (Forsander, 1982; Krahn and Gosnell, 1991). In an earlier study, it was found that the rats with high preference for fat ultimately became morphine drinkers, whereas those with low preference for fat did not consume the drug (Marks-Kaufman and Lipeles, 1982). Rats that have a high preference for sweet taste show a greater tendency to self-administer morphine (Gosnell et al., 1995). These lines of evidence suggest the existence of a close relationship between the opioid reward system and neural circuits processing taste reactivity and palatability. More specifically, we hypothesize that opioid systems within the ACB are the major region in which this processing occurs; stimulation of opioid receptors in this region results not only in hyperphagia but also in reinforcing effects as demonstrated in the place preference paradigm or intracerebral self-administration (Van der Kooy et al., 1982; Goeders et al., 1984; Mucha and Iversen, 1986; Zhang and Kelley, 1997).

It is of interest to note the difference in the profiles of DAMGO-induced and food deprivation-induced diet intakes. In nondeprived rats with diets presented concurrently, DAMGO augmented only fat consumption without an effect on carbohydrate intake. However, 24-hr food deprivation enhanced feeding of both diets to the same degree. When base-line intake of the two diets was taken into consideration, the effect of DAMGO on fat intake was positively correlated with base-line fat intake, whereas no correlation was found between DAMGO-induced carbohydrate intake and base-line carbohydrate preference. In contrast to the DAMGO-induced selective change in diet preference, food deprivation produced no effect on diet preference; indeed, the degree of intake of each diet after deprivation corresponded to the initial base-line preference in the nondeprived state. Support for this idea is provided by the finding that naltrexone infusion was able to decrease both fat and carbohydrate intake when infused into the ACB in hungry rats. Granted, the effect of intra-ACB naltrexone was less potent on carbohydrate than on fat, and in the initial part of that experiment, systemic naltrexone did not affect deprivation-induced carbohydrate intake. This discrepancy may be accounted for by the higher concentration of antagonist in the intracerebral injection. Because naltrexone is not entirely selective, it may also be possible that blockade of δ receptors accounts for the decrease in carbohydrate intake. A number of studies, including our own, have shown that infusion of δ agonists into ACB or ventral tegmental area enhances food intake (Majeed et al., 1986; Bakshi and Kelley, 1993a; Noel and Wise, 1995; Zhang and Kelley, 1997).

These data also raise the question concerning the relationship between hunger and palatability. Although many foods have inherent high palatability and are consumed for their pleasurable effects, rather than to relieve an energy deficit, hunger clearly increases palatability of all foods. Thus, it is important to note that opioids likely play a role in palatability both in the nondeprived and food-deprived states. This hypothesis is consistent with clinical studies in control and obese patients, which show that opioid antagonists decrease the intake of foods, especially those rich in sugar and fat, even though hunger and satiety ratings are not affected (Yeomans et al., 1990; Drewnowski et al., 1992a; Yeomans and Gray, 1996). In these reports, the finding that naloxone preferentially decreases intake of sweet and/or high-fat food...
by reducing the “pleasantness” rating of these food items lends support to the hypothesis that opioids play an important role in palatability.

Foods containing fat and sugar have high caloric density, and thus the preferential effect of opioids on consumption of these foods might have an adaptive significance from the standpoint of evolution. Throughout evolution, famine or food scarcity, rather than obesity, was likely to be a problem. To survive in these conditions, organisms would have to develop strategies to prepare for impending food shortages due to seasonal or climatic variations or, at times, starvation. Because calorie-dense food (especially fats, which are beneficial for long-term energy storage) has a highly rewarding taste, this would ensure that animals obtain and store energy whenever such food might be available. This notion is consistent with our findings that in hungry rats, DAMGO and naltrexone preferentially increased and suppressed the intake of fat, respectively. In modern Western societies, however, in which the food supply is abundant and overweight rampant, overactivation of the endogenous opioid peptides may contribute partly to human obesity, binge eating and uncontrollable craving for sweet and high-fat foods. The present data suggest that in particular, activation of µ opioid receptors within the ventral striatum may participate in the selection and consumption of highly palatable foods.

References


