International Journal of Obesity (2009) 33, S54–S58
 0307-0565/09 $32.00
www.nature.com/ijo

REVIEW

Reward systems and food intake: role of opioids

BA Gosnell[1] and AS Levine[1,2]

[1]*Department of Food Science & Nutrition, University of Minnesota, Food Science & Nutrition, St Paul, MN, USA and* [2]*Office of the Dean, College of Food, Agricultural and Natural Resource Sciences, University of Minnesota, St Paul, MN, USA*

Humans eat for many reasons, including the rewarding qualities of foods. A host of neurotransmitters have been shown to influence eating behavior and some of these appear to be involved in reward-induced eating. Endogenous opioid peptides and their receptors were first reported more than 30 years ago, and studies suggesting a role of opioids in the regulation of food intake date back nearly as far. Opioid agonists and antagonists have corresponding stimulatory and inhibitory effects on feeding. In addition to studies aimed at identifying the relevant receptor subtypes and sites of action within the brain, there has been a continuing interest in the role of opioids on diet/taste preferences, food reward, and the overlap of food reward with others types of reward. Data exist that suggest a role for opioids in the control of appetite for specific macronutrients, but there is also evidence for their role in the stimulation of intake based on already-existing diet or taste preferences and in controlling intake motivated by hedonics rather than by energy needs. Finally, various types of studies indicate an overlap between mechanisms mediating drug reward and palatable food reward. Preference or consumption of sweet substances often parallels the self-administration of several drugs of abuse, and under certain conditions, the termination of intermittent access to sweet substances produces symptoms that resemble those observed during opiate withdrawal. The overconsumption of readily available and highly palatable foods likely contributes to the growing rates of obesity worldwide. An understanding of the role of opioids in mediating food reward and promoting the overconsumption of palatable foods may provide insights into new approaches for preventing obesity.
International Journal of Obesity (2009) **33,** S54–S58; doi:10.1038/ijo.2009.73

Keywords: opioid; palatability; reward; sweet; feeding

It is generally recognized that energy intake and expenditure are regulated by a complex network of neurochemical systems. Studies indicating a role for opioids in the regulation of intake date back more than 30 years. The results of numerous studies have provided information about the receptor subtypes involved, the sites of action within the brain, the specific conditions under which opioids influence food intake, and the interaction of opioid systems with other systems that regulate energy balance. Space does not permit a discussion of all aspects of opioids in relation to food intake. Here we will concentrate on three areas of our ongoing research on opioids, with an emphasis on work from our laboratories: the issue of whether opioids stimulate intake of specific macronutrients or of preferred foods, the issue of whether they are primarily involved in the homeostatic or the hedonic aspects of feeding, and whether palatable food, partially through opioid mechanisms, may produce a condition that resembles drug addiction.

Correspondence: Dr AS Levine, Minnesota Obesity Center, University of Minnesota, 277 Coffey Hall, 1420 Eckles Avenue, St Paul, MN 55108-6074, USA.
E-mail: aslevine@umn.edu

Opioids and macronutrient intake

Several reports from the early 1980s indicated that when rats were allowed to self-select the macronutrient composition of their diets, injections of morphine, a preferential μ-opioid receptor agonist, caused an increase in fat intake and a decrease in carbohydrate intake[1] and the opioid antagonist, naloxone, preferentially decreased fat intake.[2] These studies supported a role for opioids in controlling the intake of specific macronutrients. In contrast, Gosnell *et al.*[3] performed a macronutrient self-selection study in which the baseline dietary preferences of the rats were considered. During adaptation to the self-selection regimen, it was noted that some rats displayed a preference for carbohydrate over fat, whereas others preferred fat over carbohydrate. When rats were given injections of morphine, it was observed that morphine primarily stimulated carbohydrate intake in the carbohydrate-preferrers, and stimulated fat intake in the fat-preferrers. Thus, morphine caused an increase in intake of the preferred food rather than of a specific macronutrient. Glass *et al.*[4] reported a complementary result with naloxone injections: the intake of the preferred diet was reduced by naloxone at lower doses than those required to reduce intake of the less-preferred diet.

On the other hand, Glass *et al*. found a more complex set of results when naltrexone, another opioid antagonist, was injected directly into either the amygdala (central nucleus, ACe) or hypothalamus (paraventricular nucleus, PVN).[5] The pattern of effects on preferred versus non-preferred food was dependent on the site of injection: ACe injections of naltrexone caused a decrease in intake of the preferred food, whereas PVN injections caused a decrease in the intake of both foods. The authors interpreted this difference as reflecting opioid effect on energy regulation in the PVN and on hedonic or affective processes in the amygdala. A more complex view of the role of opioids in the PVN was reported by Naleid *et al*.[6] When rats were given a choice of high-sucrose and high-fat diets, injections of [D-Ala2, N-Me-Phe4, Gly5-ol]-Enkephalin (DAMGO), a μ-opioid agonist, stimulated high-fat diet intake in fat-preferring rats, but sucrose-preferring rats did not increase their intake of either diet. Injections of naltrexone into the PVN reduced intake of the high-fat diet in both preference groups. The authors attribute the discrepancy of these results and those of Glass *et al*. (discussed above) as being on account of differences in the methods of statistical analysis, though there were differences in other procedural aspects as well. They suggest that the two preference groups may differ in the organization of opioid receptor systems in the PVN.

Studies with injections of opioids into the nucleus accumbens also provide some instances of either macronutrient or preference-specific effects on food intake. Woolley *et al*.[7] obtained results that support the idea that opioids influence food intake based on flavor preferences. Rats were given a choice of two foods that were nutritionally identical except for their flavoring. Injections of DAMGO into the nucleus accumbens preferentially increased intake of the food with the preferred flavor, whereas naltrexone reduced intake of the preferred flavor. When either food was offered alone, DAMGO stimulated the intake of each to the same degree. These results were interpreted as indicative of a role for opioids in flavor preference. On the other hand, Zhang *et al*.[8] found that injections of DAMGO into the nucleus accumbens preferentially stimulated the intake of a high-fat diet (versus a high-carbohydrate diet), regardless of the rats' baseline preferences.

Overall, the nature of the effect of opioids on diet selection remains unclear, as there are instances supporting either a selective macronutrient effect or a preference-based effect. Some discrepancies may be attributable to procedural differences, yet it is also likely that there are differences related to the injection site as well as the specific types of macronutrient being tested.

Hedonics and homeostasis

Regardless of the precise nature of the role of opioids in macronutrient selection, many studies clearly indicate a role for opioids in mediating palatability and the hedonic aspects of feeding. In an early study by Apfelbaum and Mandenoff,[9] the effect of naltrexone was measured in rats maintained on either standard chow or on chow plus a variety of additional palatable foods. Compared with the chow-only rats, the rats with access to additional palatable foods were hyperphagic and more sensitive to the intake-reducing effect of naltrexone. Similarly, Levine *et al*.[10] measured the effect of naloxone in rats fed standard chow or sweetened chow. After food restriction, the anorexic potency was greater in rats on sweetened chow than on standard chow. They concluded that naloxone blocked the portion of feeding driven by sweet taste.

Studies with the consumption of palatable fluids also indicate a role for opioids in taste reward. Kirkham[11] found that naloxone reduced the intake of sucrose solution in a manner similar to that produced by reducing the sucrose concentration. Antagonist-induced reductions have also been observed for saccharin solutions.[12,13] In non-deprived rats, increases in palatable fluid intake have been observed after injections of μ- and δ-opioid agonists injected into the lateral ventricles and into the nucleus accumbens.[13,14] In several human studies, opioid antagonism reduced the rated pleasantness of food and sucrose/fat mixtures (for example, Drewnowski *et al*.[15]; Yeomans and Gray[16]; Yeomans and Gray[17]). Notably, sensory evaluation and hunger ratings were not significantly affected. Rather, the effect appeared to be on processes involved in the maintenance and termination of feeding rather than on the initiation of feeding. Kirkham has reported results from animal studies that are consistent with this view. Naloxone reduced sham-feeding of sucrose solution in a dose-dependent manner, but had no effect on the initiation of sham-feeding.[11] Similarly, in repeated runway trials to measure both food consumption and food motivation, naloxone and naltrexone did not affect immediate performance, but reduced performance later in the blocks of trials, after some food had already been eaten.[18]

Olszewski and Levine[19] have argued that one mechanism that may be involved in the opioid-mediated overconsumption of palatable foods is the delay or blunting of satiety systems; they suggest that two possible systems are the melanocortin and oxytocin systems. Centrally administered oxytocin and α-MSH (an agonist at melanocortin receptors) inhibit food intake, and seem to play a role in mediating satiety.[20] Oxytocin-deficient mice show increased intake of carbohydrate solutions (sweet and non-sweet); this effect was interpreted as support for a role of oxytocin in carbohydrate-specific satiety.[21] Naloxone potentiated the effects of cholecystokinin and lithium chloride (LiCl) on oxytocin secretion and feeding,[22] and butorphanol, a mixed μ/κ-opioid agonist, reduced the number of c-Fos-positive oxytocin cells in the PVN at a time associated with the termination of feeding.[19] Naltrexone increased c-Fos immunoreactivity in rat arcuate nucleus α-MSH neurons,[23] and chronic morphine administration reduced proopiomelanocortin gene expression and α-MSH levels in the medial basal hypothalamus.[24] These studies support the possibility that

palatability-related increases in food intake may be, in part, because of an opioid-related reduction in the activity of satiety systems. Through similar mechanisms, opioids are also capable of preventing the formation of a conditioned taste aversion. Injections of LiCl were given to rats after a brief exposure to a novel saccharin solution,[25] a procedure that typically leads to conditioned taste aversion. Treatment with morphine, butorphanol or nociceptin/orphanin FQ (N/OFQ) at the time of the initial saccharin presentation prevented or blunted the formation of a taste aversion, as measured in a separate saccharin exposure given 3 days later. N/OFQ is the endogenous peptide ligand for the NOP receptor that has some similarity to opioid peptides but does not act directly on opioid receptors.[26] It does, however, cause a naloxone-reversible increase in food intake, which suggests that it may interact at some level with opioid systems.[27] In an immunohistochemical experiment that was parallel to the taste aversion study, groups of rats were given the same pharmacological treatments (but not in the conditioned taste aversion paradigm). Injections of LiCl increased the number of c-Fos-positive oxytocin and vasopressin neurons in the paraventricular and supraoptic hypothalamic nuclei. Morphine, butorphanol, and nociceptin blocked or blunted this effect of LiCl, though having little effect when given alone.[25] Opioids, therefore, seem to reduce activity in oxytocin (and possibly other) systems that contribute to satiety and aversion. In both cases, one consequence would be an increase in feeding.

Interactions between palatability and drugs of abuse

If opioids are involved in the hedonic or rewarding aspects of feeding, it might be expected that food reward has some similarity to other types of reward, such as that produced by many drugs of abuse. Some of the observed similarities include sugar-induced upregulation of μ-opioid and D_1 dopamine receptors,[28] an increase in the transcription factor, ΔfosB, in the nucleus accumbens[29] and an increase in the release of dopamine in the nucleus accumbens.[30] With regard to this latter effect, Hajnal *et al*.[30] reported that sham-drinking of sucrose produced concentration-related increases in extracellular dopamine in the nucleus accumbens that were independent of the amount of sucrose ingested. It should be noted, however, that increases in dopamine release caused by sucrose ingestion are typically much smaller than those that are observed after intravenous cocaine self-administration.[31] In spite of this difference, it has been shown that when given a mutually exclusive choice between intravenous cocaine and saccharin, rats generally preferred the saccharin solution; sucrose solution was also chosen over cocaine.[31]

Behavioral studies also indicate overlap and interactions between sweet taste and drugs of abuse. Jewett *et al*.[32] used a drug discrimination assay to measure the effects of sucrose ingestion on the discriminative stimulus effects of the low-efficacy μ-agonist, nalbuphine. The rats were trained to discriminate nalbuphine from saline in an operant choice procedure. When subsequently tested at lower doses of the drug, there was a dose-dependent generalization to nalbuphine-appropriate responding. Chronic access to a sucrose solution caused a leftward shift in the nalbuphine dose–response curve, indicating an effect of sucrose on the μ-opioid system. Sucrose intake has also been shown to potentiate the locomotor effects of amphetamine (an indirect dopamine agonist that increases dopamine release), cocaine (a dopamine reuptake blocker) and quinpirole (a dopamine D_2 receptor agonist).[33–35] Furthermore, the rats either selected or bred for high or low sweet intake show corresponding differences in the acquisition or amount of self-administered amphetamine, cocaine, and morphine.[36–39] In humans, opiate-dependent subjects on methadone maintenance report higher consumption of sweets than control subjects,[40] and subjects diagnosed with alcohol dependence or cocaine abuse/dependence tend to prefer sweeter sucrose solutions than controls.[41,42]

After reviewing the similarities between the effects of sugar ingestion and those related to drug addiction, Avena *et al*.[43] conclude that under some circumstances, sugar can be addictive. Among the behavioral evidence supporting this view is the observation of signs of opioid withdrawal after naloxone is given to the rats maintained on a cyclic regimen of access to a glucose solution.[44] In the first experiment, the rats were food-deprived daily for 12 h, and then provided food and a 25% glucose solution for 12 h. A control group was fed chow *ad libitum*. After 8 days on this schedule, all rats were given injections of a high dose of naloxone (20 mg kg^{-1}, intraperitoneally) or saline. In the cycled glucose/chow group, naloxone precipitated some of the somatic signs typically associated with opiate withdrawal: teeth chatter, forepaw tremor, and head shake. During spontaneous withdrawal (termination of glucose access and 24–36 h food deprivation), some of these withdrawal signs were evident in the cycled glucose/chow group but not in the *ad libitum*-fed group. Although this experiment did not include control groups for the effect of food deprivation or for the effect of cyclic access to glucose, additional experiments in this report and in other reports from these authors have included such controls, such as groups receiving *ad libitum* sugar and chow, cyclic chow, and cyclic sugar/*ad libitum* chow. Generally, the effects that are described as being similar to those observed with drug addiction are limited to the condition in which food deprivation (12 h) is cycled with 12 h access to chow and a sugar solution.[43] Although there are intriguing parallels to drug addiction, it is important to note that the conditions under which they are observed (which also produce alterations in activity, drinking, and meal patterns) are a critical aspect of sucrose 'addiction'.

In contrast to the review by Avena *et al*.,[43] Drewnowski and Bellisle[45] focused primarily on human studies that addressed

whether the excessive intake of sweets, or other palatable foods, can be considered as meeting the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) criteria for substance dependence. They argue that sweet foods and beverages do not meet the tolerance and withdrawal criteria of the DSM-IV diagnosis of substance dependence with physiological dependence. Another criterion for substance dependence is that other aspects of life are given up because of substance use. Drewnowski and Bellisle point out that the ease of availability of fast foods and sweet-containing foods makes it unlikely that this criterion would be met. They do suggest, however, that some of the criteria for dependence (using larger amounts than intended, having a persistent desire to cut down, and spending a great deal of time obtaining, using, and recovering from the substance) may apply to some cases of bulimia nervosa.

Although it is debatable whether there is a scientific or heuristic basis for considering sugar as potentially addictive, it is clear that there has been a large increase in the worldwide use of energy-containing sweeteners,[46] as well as a continuing growth in obesity rates.[47] An understanding of the role of opioids in mediating food reward and promoting the overconsumption of palatable foods may provide insights into new approaches for preventing obesity.

Conflict of interest

BA Gosnell and AS Levine have received grant support from NIDA.

Acknowledgements

The writing of this paper was supported in part by the National Institute of Drug Abuse (R01DA021280), and the National Institute of Diabetes and Ingestive and Kidney Diseases (P30DK50456).

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