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Endorphins and Food Intake: *Kappa* Opioid Receptor Agonists and Hyperphagia

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COOPER, S. J., A. JACKSON AND T. C. KIRKHAM. *Endorphins and food intake:* Kappa *opioid receptor agonists and hyperphagia.* PHARMACOL BIOCHEM BEHAV **23**(5) 889–901, 1985.—Evidence from studies which utilise either opiate receptor agonists and antagonists strongly indicate a role for endorphinergic mechanisms in the control of feeding responses. Two means by which these compounds may exert an effect on feeding can be singled-out. Firstly, emerging evidence suggests that the process of achieving satiety (terminating a meal, or choice of a commodity) may be accelerated following treatments with opiate receptor antagonists. Secondly, the preference for highly palatable solutions (sweet solutions have received most attention) in two-bottle tests is blocked after injection of opiate receptor antagonists. This finding has been interpreted in terms of the abolition of the reward or incentive quality associated with the particularly attractive flavour. These two mechanisms of action may represent two aspects of a single, fundamental process. Following an introduction to rat urination model of *in vivo kappa* agonist activity, the consistent effect of several *kappa* agonists (including the highly selective U-50,488H) to stimulate food consumption is described. Recognising that members of the dynorphin group of endogenous opioid peptides are *kappa* receptor ligands, some with a high degree of selectivity, and the evidence the dynorphins and neo-endorphins produce hyperphagia in rats is particularly interesting. Such lines of evidence lead to the hypothesis that peptides of the dynorphin group may act endogenously to promote the expression of normal feeding behaviour.

Dynorphin Hyperphagia *Kappa* agonists *Kappa* receptors Opiate antagonists Palatability Satiety Urination

THE last 10 years, beginning with the first identification of endogenous opioid peptides in the central nervous system [39], have seen remarkable progress in cataloguing the rich variety of opioid peptides which are now known to be present in central and peripheral tissues. In a recent review [1], Akil and her colleagues picked 1982 as an exceptionally good year in opioid peptide research. In that year, with the aid of recombinant DNA technology, it was discovered that the endogenous opioid products (and some non-opioid molecules) could be assigned to three distinct peptide families, each headed by its respective large precursor protein, which in turn was coded for by correspondingly distinct DNA sequences in the genome.

Less dramatically than this, some real progress has nevertheless been made in deriving the functional significance of endogenous opioid peptides, as they occur in the central nervous system and in peripheral tissues. Stemming from an early observation that the opiate receptor antagonist, naloxone, exerted an anorectic effect in hungry rats [38], interest has grown in a possible role for endogenous opioid peptides in the control of feeding responses. Several recent articles cover material published up to 1982 [95, 107, 108], and demonstrate the concerted efforts of many investigators to analyze the ways in which opiate receptor ligands can affect normal feeding behaviour, across many species, and under a variety of experimental situations. In the present article, we take the opportunity to concentrate on some recent developments, bearing two important questions in mind. If endogenous opioid peptides are involved in feeding behaviour, then a first question we can pose is by what mechanism(s) do opiate receptor antagonists modify or block their control over feeding? We consider two of the possible means, placing emphasis upon changes which occur in the process of achieving satiety, as well as on changes which affect the attractiveness, or incentive quality, of foodstuffs and fluids. The second question which concerns us is the identity of the endogenous opioid peptides which are presumed to be engaged in the mechanisms which determine the level of food consumption. More space is devoted to this latter question, and we consider the remarkable consistency with which *kappa* receptor agonists stimulate increased food consumption. Taking account of the evidence that peptides of the dynorphin group may act as endogenous ligands for the *kappa* receptor, we are led to the major working hypothesis that dynorphins and neo-endorphins have important functions to play in the control of food ingestion. Of course, equally interesting questions can be raised which deal with the involvement of endorphins in the control of water or salt intake [16], but it is not possible to consider them here. Our treatment of the feeding literature cannot be exhaustive, but we do intend to draw attention to promising lines of further enquiry.

OPIATE ANTAGONISTS AND SATIETY

Food consumption in some animals falls following acute or chronic treatment with opiate receptor antagonists. The anorectic effects of these drugs have been seen in rodents, carnivores, primates (including man), and in several additional species [36, 73, 94, 95, 107, 108, 124, 134]. The effect may not be limited to higher vertebrates, since a recent report has shown that food-deprived slugs consumed less puréed carrot after the injection of 1 mg/kg of naloxone [53]. In certain species, however, naloxone fails to affect food intake, e.g. [96]. It will be an interesting task to determine the extent to which the reduction of feeding following the administration of opiate receptor antagonists is a characteristic feature of only particular classes of animals. In one avian species, the pigeon, naloxone reduced food consumption but had no effect on water consumption [17,20], a finding which runs counter to many mammalian examples. Intracerebroventricular administration of β-endorphin enhanced food intake, in the pigeon, without changing water consumption [21]. The anorectic effect of naloxone, where it is present, can be modulated by other experimental manipulations. Thus, the effect in rats is attenuated after adaptation to a schedule of food-deprivation [30]. On the other hand, the sensitivity to the anorectic effect of naloxone is markedly increased in diabetic mice compared with controls [71]. Under appropriate experimental conditions, naloxone has been reported to have a dual effect on feeding in the rat, reducing the latency to initiate feeding whilst also hastening the termination of eating [56].

The anorectic effect of naloxone cannot be attributed to general motor disruption [3], or to a drug-induced aversion [68]. A number of years ago, it was suggested that naloxone may enhance the satiation of feeding [7]. According to this view, naloxone may block endorphin activity at opioid receptors which normally is effective in retarding the development of satiety, i.e., may block a feeding-maintenance function. A series of studies by Kirkham [55] is strongly supportive of the position that opiate receptor antagonists act to reduce food consumption by affecting the process of satiation. Having noted that naloxone and naltrexone affect the terminal stage of feeding to reduce meal size, Kirkham went on to use a runway paradigm [123] to show that these drugs enhanced satiation, measured in terms of the progressive decline in the approach speed to food and the amount of food consumption which occurs over repeated trials [55]. He concluded that naloxone and naltrexone advanced the onset of satiety. This brings us to the position that opiate receptor agonists may also influence the development of satiation. In a later section (Kappa Agonists Increase Palatable Food Consumption), evidence will be discussed which shows that *kappa* opiate agonists can induce a marked increase in food consumption in rats which are partially-satiated at the time of drug action.

OPIATE ANTAGONISTS AND FLUID PREFERENCE/ACCEPTANCE

A further line of enquiry which has commanded considerable experimental attention is that opiate receptor antagonists may attenuate the reward of palatable fluids, and thereby reduce the preference for these solutions in two-bottle tests, and their acceptance in one-bottle tests (see [22] for the preference/acceptance distinction). Studies which have been designed to address this point have yielded consistent findings. Le Magnen and his colleagues demonstrated that naloxone (1 mg/kg) markedly attenuated the consumption of a 0.05% saccharin solution in a two-bottle preference test [67]. At the same time, water intake was elevated, so that the naloxone-treated animals no longer expressed the preference for the sweet fluid. Comparable data have been seen in studies which have used nondeprived, food-deprived [76], or water-deprived animals [10,116], and which have used a range of saccharin concentrations [116], and have compared the effects of naloxone and naltrexone [10]. Rats' preference for the consumption of sweet solutions compared to water was consistently blocked by opiate antagonist treatments. The antagonists may have acted, therefore, to reduce the reward which normally derives from the palatable, sweet taste. This interpretation also accounts for a number of reports that opiate receptor antagonists dose-relatedly reduced the consumption of sweet solutions in one-bottle acceptance tests [9, 48, 72, 103, 112, 132].

One implication which has been drawn from these data is that there is an endorphinergic involvement in the mediation of the reward of gustatory stimuli [2, 10, 102, 112, 115]. Thus, experiments using opiate agonists would be of great value in trying to establish whether agonist activity at opiate receptors would be sufficient to increase the preference or the acceptance of a sweet solution. Some data are available and relate to the use of the *mu* agonist, morphine, but they are not consistent. For example, it has been reported that rats consume more saccharin solution following morphine treatments [102,115], but this effect did not occur in other cases in which saccharin preference [10], or acceptance [9], was measured. Hence, a central role for activity at *mu* receptors in relation to the reward of sweet solutions must remain in doubt, at least at the present time. In the light of recent evidence that *kappa* agonists stimulate the consumption of a highly palatable sweetened mash (see Kappa Agonists Increase Palatable Food Consumption), it would be instructive to assess the effects of *kappa* agonist treatments on the preference/acceptance functions of sweetened fluid consumption.

Most work concerned with the effects of opiate antagonists on preference and acceptance measures has employed sweet solutions. However, hypotonic and isotonic salt solutions are also palatable, and therefore it is as important to take account of the effects of opiate antagonists on the ingestion of these solutions. Thus, it has been shown that several opiate antagonists do reduce the consumption of a palatable 0.9% saline solution in a one-bottle test [18,72]. One recent study has investigated the effects of naloxone on the performance of water-deprived male and female rats in a two-bottle saline preference test [13]. This study showed that naloxone reduced overall fluid consumption in both sexes, but its effects on saline preference, although causing a reduction in some cases, were not entirely consistent. More work is necessary to determine if opiate antagonists act to reduce gustatory palatability or reward, in general, or act more specifically, to attenuate the response to sweet solutions, in particular.

Summary

Two important ideas have been advanced to account for the effects of opiate receptor antagonists on food and palatable fluid consumption. The first suggests that the size and duration of a meal is reduced, because the opiate antagonists bring forward feeding satiety as distinct from weakening the initiation of feeding [55]. Naloxone and other antagonists can therefore be said to impose a "satiety signal." An inference

to be drawn from this description is that the antagonists may achieve their effect on food consumption by blocking an endogenous opioid peptide which promotes feeding and maintain meal size. This line of reasoning will be taken up later with regard to the actions of dynorphin peptides. The second idea is that stimulus features which are associated with high incentive quality of foodstuffs may interact in their effects in a particularly relevant sense with endogenous opioid mechanisms. Tests using attractive, sweet solutions consistently show that opiate receptor antagonists block the high preference for, and acceptance of, these solutions. Once again, one can infer that endogenous opioid peptides may enhance the attractive quality, or incentive value, of palatable fluids. The two ideas can be drawn together when it is recognised that the development of satiety is associated with a loss in the "reward" of a foodstuff. As a meal proceeds, an initially preferred, attractive food, generally becomes less so. Furthermore, recent evidence indicates that rather than considering "satiety" to occur in some general way, we should recognise that satiety can occur more specifically for the food commodity offered [57]. Future work on endorphinergic involvement in the control of food consumption will need to use experimental designs which take account of the commodity-specificity of satiation processes.

THE DIURETIC EFFECT OF KAPPA AGONISTS

On the basis of their work using the nondependent and opiate-dependent chronic spinal dog, Martin and his colleagues [26,27] distinguished between three types of opiate receptor, and referred to them according to prototypic ligands: the *mu* receptor (after morphine), the *kappa* receptor (after ketocyclazocine), and the *sigma* receptor (after SKF 10,047, N-allynormetazocine). Before we consider the effects of several *kappa* agonists, morphine and SKF 10,047 on food consumption, we are devoting this section to a review of the diuretic effects of *kappa* agonists. Recent data show that a simple test of urinary output can successfully discriminate between full and partial *kappa* agonist activity, and between *kappa* and *mu* activity. The *in vivo* characterization of drugs as *kappa* agonists will therefore serve as a very useful basis for comparison, when, in the next section, we come to consider feeding experiments.

Slizgi and Ludens [117] studied the effect of ethylketocyclazocine (EKC), a benzomorphan analogue which serves as a prototype *kappa* agonist [26,77], on urinary output in conscious rats. They showed that subcutaneous injections of EKC at doses from 0.01 to 3.0 mg/kg had a dose-related effect on urine formation over a 5 hr period. Although EKC had a pronounced effect to increase urinary output, the level of sodium excretion remained unchanged, except for a significant decrease at 3.0 mg/kg. Slizgi and Ludens [117] showed that in association with the pronounced water diuresis there was a fall in plasma vasopressin (ADH) levels. They suggested that the EKC-induced diuresis may be linked, at least in part, to an inhibition of vasopressin secretion, although they also considered the possibility of an action of EKC at the kidney to interfere with the renal response to vasopressin. Their work in the rat has been extended recently by Huidobro-Toro and Parada [42], who have demonstrated dose-dependent diuretic effects of not only EKC, but also of the *kappa* agonists, bremazocine [104], and U-50,488H [128]. At the same time, the urine of rats treated with the *kappa* agonists showed dose-dependent reductions in sodium and potassium excretion. Bremazocine was most potent, and produced a copious diuresis at a dose as small as 0.05 mg/kg. They also noted that naloxone, a nonspecific opiate receptor antagonist, did not significantly modify urinary output or electrolyte excretion in doses up to 4.0 mg/kg. However, the putatively more selective *kappa* antagonists, WIN 44,441 and MR 2266, produced dose-dependent antidiuresis. Bremazocine-induced diuresis was competitively antagonized by both WIN 44,441 and MR 2266 [42]. The diuretic effect of the highly selective *kappa* agonist, U-50,488, has also been studied in the anaesthetized dog [118]. Dose-dependent increases in urine formation occurred with intravenous administration of U-50-488H, although its effects on urinary sodium and potassium excretion were neither dose-related nor consistent. Interestingly, the diuretic response to 5.0 mg/kg U-50,488H was abolished completely when ADH (2 pmol/min/kg) was added to the infusion. These data obtained in the dog confirm the production of a water diuresis by a highly selective *kappa* agonist, and further suggest that the diuresis resulted from an effect on ADH.

A systematic study of the effects of a variety of opioid compounds on urinary output in the normally hydrated rat has been conducted by Leander. He, too, showed that the *kappa* agonists, bremazocine, EKC and ketazocine produced a marked dose-related increase in urination, with bremazocine being the most potent compound in its diuretic effect [50]. An increase in urinary output was clearly discernible following 0.02 mg/kg of bremazocine. The opiate receptor antagonist MR 2266 was about twice as potent as naloxone in antagonizing the diuretic effect of 0.08 mg/kg of bremazocine, which is further evidence consistent with a *kappa*-receptor mediation of the diuretic effect. The mixed agonists/antagonists, butorphanol, cyclazocine and nalorphine, increased urination but to a lesser extent than bremazocine or EKC [61]. Morphine, *l*-methadone and pentazocine did not increase urinary output. Further studies have confirmed that other *kappa* agonists, U-50,488H and proxorphan [60], and tifluadom [62], produce marked diuretic effects.

On the basis of these, and additional, data, Leander [63, 64, 65] distinguishes between three classes of drugs with *kappa* agonist activity. (1) The first class are described as full *kappa* agonists without *mu* agonist activity and comprises bremazocine, proxorphan, U-50,488 and tifluadom. For each of these compounds, the cumulative urinary outputs measured at 2 hr and at 5 hr are monotonically related to the dose (potency relationships: bremazocine > proxorphan > tifluadom > U-50,488. (2) The second class are described as full agonists with *mu* agonist activity and include MR 2033, ketazocine and EKC. The *mu* agonist action of EKC was demonstrated in rats which were water-loaded (3 ml/100 g of body weight) simultaneously with administration of the drug. Five mg/kg EKC produced a profound antidiuretic effect at 1 and 2 hr following the injection and water-loading. The antidiuretic action of EKC was completely blocked by pretreatment with 20.0 mg/kg of the irreversible *mu* receptor antagonist β-funaltrexamine (β-FNA) [130] 18 hr before the water-loading and EKC administration. Compounds in the second class are defined in terms of an inverted, U-shaped dose-effect curve for cumulative urination at 2 hr after drug injection [65]. (3) The third group are categorized as partial *kappa* agonists, and consist of nalorphine, butorphanol and oxilorphan, which produce less than the maximal diuresis which is associated with the full *kappa* agonists. In contrast to the diuretic effect of *kappa* agonists, morphine, other *mu*

agonists, and β-endorphin exert antidiuretic effects [40, 41, 59, 60].

A study using two strains of mice compared the effects of several opiates on urinary output over a 5 hr period [101]. Bremazocine, EKC and morphine markedly increased urination, and their results led the authors to suggest that *kappa* agonist activity in mice can be identified by measuring urinary output, and furthermore, that morphine, in this species, may have some *kappa* agonist activity.

These studies on the diuretic effects of *kappa* agonists provide a useful basis for comparison with the data derived from feeding experiments. The experiments on the measurement of urinary output first of all establish potency relationship between *kappa* agonists, and secondly, allow a classification of drugs into full *kappa* agonists, *kappa* agonists with *mu* agonist activity, partial *kappa* agonists, and *mu* agonists. They also provide a yardstick by which to judge the consistency of the data which implicate *kappa* receptor-mediation in the control of food intake.

THE HYPERPHAGIC EFFECT OF KAPPA AGONISTS

Since the discovery that opiate receptor antagonists will reduce food consumption in some species, investigators anticipated that stimulation of feeding responses should follow opiate agonist activity. This prediction has now been amply substantiated, and there has been a recent concentration of interest on the hyperphagic effects of *kappa* agonists. In this and the following sections, the data for several *kappa* agonists will be considered, and comparisons will be drawn between their effects and those of morphine, a prototypic *mu* agonist and with N-allylnormetazocine (SKF-10,047), a *sigma* agonist, in order to assess the receptor specificity of the opiate-induced increases in food consumption. In addition, preliminary work on the possible physiological and behavioural mechanisms of action of *kappa* agonists will be introduced with regard to potential sites and modes of action.

EKC and Ketocyclazocine

Sanger and McCarthy [110] studied the effects of EKC, administered by subcutaneous route in doses of 0.1–10.0 mg/kg, to rats with free access to food and water. The experiments were carried out during daylight hours. Over the 6 hr period of observation, saline-treated rats consumed cumulatively about 2 g food and drank about 3 ml water. During the first hour of the test, EKC at doses of 0.1 and 0.3 mg/kg significantly increased food consumption, the effect being of the order of a 1 g increase in intake. This hyperphagic effect was maintained into the second hour of the test but was then not significantly present throughout the remaining 4 hr of observation. Water consumption was not concurrently affected at these two smallest doses of EKC. Hence, the data revealed a specific increase in food consumption occurring early in the test, which followed treatments with small doses of EKC. But it is also interesting to consider the effects of larger doses. A significant increase in cumulative food intake was noted at the end of the second hour after injection of 1.0 mg/kg EKC, and occurred by the end of the fourth hour following injection of 10.0 mg/kg EKC. Thus, the larger the EKC dose, the longer the delay before a significant increase in food consumption could be detected. The consequence of this relationship was that at 2 hr, there was an inverted U-shaped dose-effect relationship with a peak effect at 1.0 mg/kg, whilst at 4 hr and 6 hr, food consumption was less clearly related to the dose of EKC, although the peak effect occurred at 10.0 mg/kg EKC (see Fig. 1 [110]). The similarity between these results and those obtained with EKC in the rat diuresis test (see Fig. 1 [65]) should be noted. If EKC is considered a full *kappa* agonist with *mu* agonist activity (see The Diuretic Effect of Kappa Agonists), then the inverted U-shaped dose-effect relationship described early in the feeding test may reflect a hyperphagic effect mediated by activity at *kappa* receptors and an opposing effect occurring with larger dose treatments and mediated by activity at non-*kappa* receptors. Before leaving this study [110], it is worth considering the long latency increase in water consumption which was obtained with an injection of 1.0 mg/kg of EKC (Fig. 2 [110]). The authors pose the question of whether the increase in water intake is secondary to the increases in food consumption. Our own data [126] suggests that this may not be the explanation, since normally hydrated rats drink more when given access to water but not to food following EKC treatments (see Fig. 1 [126]). Since this effect may represent polydipsia which was secondary to polyuria, we are inclined to interpret Sanger and McCarthy's data [110] in terms of a direct hyperphagic effect of EKC treatments, but a delayed, secondary polydipsia which arises from the established *kappa*-induced diuretic effect.

A second report which helped to stimulate interest in the role of the *kappa* opiate receptor in feeding behaviour was that of Morley, Levine and their associates [90]. They, too, examined the effects of *kappa* agonists treatment on the food consumption during daylight hours of rats which had been maintained on free access to food and water. Ketocyclazocine administered in a dose of 1.0 mg/kg produced a significant increase in food consumption during the first hour of the test, the effect being about 1 g more than the control level. Following the administration of 10.0 mg/kg of ketocyclazocine, cyclazocine or EKC, there were significant increases in the 4 hr and 6 hr cumulative food intake values. It seems likely that these larger dose treatments produced some early suppression of feeding behaviour, so that the hyperphagic effect only became evident later in the observation period. In favour of this interpretation, their data showed that rats given 10 mg/kg of ketocyclazocine failed to eat during the first 60 min access to the food (see Fig. 4 [90]). Furthermore, in rats which were feeding in response to 25 hr food-deprivation, ketocyclazocine at 10.0 mg/kg abolished food consumption in the first hour of the test; the animals only began to eat during the second hour of the test (see Fig. 7 [110]). In agreement with the Sanger and McCarthy data [110], therefore, we see that a small dose of a *kappa* agonist can exert an early hyperphagic response, but that following the injection of larger doses, the hyperphagic effect is apparently delayed. Morley *et al.* [90] suggested that the increased food consumption followed agonist activity at the *kappa* receptor, whereas the 'sedative' effect of the larger dose treatments which initially inhibits or prevents feeding may depend on *mu* receptor activation. This idea is consistent, as we have seen, with the classification of EKC and ketocyclazocine as full *kappa* agonists with some *mu* agonist activity, which was derived from the urination experiments.

Using a different feeding paradigm, Locke *et al.* [73] investigated the effects of *mu* and *kappa* agonists, as well as the partial agonist buprenorphine, in both the rat and the squirrel monkey. In this case, non-deprived animals were given access to a palatable sweetened milk solution for a 30 min test. An interesting aspect to their data is that the results differed for their two test species. In rats, EKC in a dose of

0.03 mg/kg (but not in larger doses of 0.1–1.0 mg/kg), and ketocyclazocine in doses of 0.1–1.0 mg/kg, both produced significant increases in milk consumption. Etorphine (0.0003–0.1 mg/kg), buprenorphine (0.03–10.0 mg/kg), and morphine (0.1–10.0 mg/kg) did not increase milk consumption, and instead, following administration of either 0.01 mg/kg of etorphine or 10.0 mg/kg of morphine, there was a major suppression of milk consumption. In the rat, therefore, the *kappa* agonists EKC and ketocyclazocine, but not the *mu* agonists, etorphine, buprenorphine or morphine, produced a hyperphagic effect. This effect was obtained using small doses of *kappa* agonists, and occurred with short latency. The squirrel monkeys responded differently. None of the opiates increased milk consumption, but they all significantly attenuated intake. Hence, *kappa*-induced hyperphagia was not observed in this species. Additional work using more specific *kappa* agonists (see below) and several feeding paradigms will be necessary before it can be concluded that *kappa* receptors play no part in the control of feeding responses in squirrel monkeys.

A further species difference has been reported by Lowy and Yim [75]. First they confirmed that ketocyclazocine in small doses (0.5–4.0 mg/kg) produced a significant stimulation of 3 hr food intake in nondeprived rats in a daytime test, a finding which was consistent with earlier results [110]. In contrast, nondeprived male hamsters did not show a hyperphagic response to ketocyclazocine (0.25–16.0 mg/kg), or to morphine or meperidine. The authors suggest that hamsters may lack an opiate-sensitive feeding system, a conclusion which finds support in their earlier finding that feeding responses in the hamster were unaffected by naltrexone treatments [74]. However, it would be premature, at this stage, to rule out the possibility that *kappa* agonists can stimulate food consumption more generally across species, in the absence of studies with the more specific receptor agonists.

There are several reports that *kappa* agonists act to stimulate food consumption in mice. In a recent study, the effects of ketocyclazocine and morphine on the spontaneous feeding of young (1–2 months) and old (24–30 months) male CF-1 mice were investigated [52]. Both opiates caused an increase in food consumption, but the effects were more marked during dark period testing, compared with measures taken during the light period. Furthermore, the increase in food intake in the older mice following injection with ketocyclazocine was less than that observed in the younger mice. The authors remark on the observation of Przewłocki and co-workers [100], who have demonstrated that there is a marked nocturnal increase in immunoreactive-dynorphin (an endogenous ligand for the *kappa* receptor) in rat hypothalamus. Circadian variation in endogenous opioid peptides may account for circadian variation in sensitivity to the hyperphagic effect of opiate agonists.

The phase of the light-dark cycle in which food tests are conducted may be relevant to a discrepancy in the literature, concerning the responses of obese and lean mice to *kappa* agonist treatments. In one study, reported by Ferguson and co-workers [23], genetically obese *(ob/ob)* and lean *(?/+)* female mice were injected with EKC (0.03–10.00 mg/kg, SC), and their food and water intakes were measured during the beginning of the dark period. The lean animals showed an increase in food intake following injection of 10.0 mg/kg of EKC. On the other hand, the obese females showed an elevation of food intake at 1.0 mg/kg, with a severe depression of feeding occurring after treatment with a 10.0 mg/kg dose. The authors concluded that obese animals were more sensitive to the *kappa* agonist treatment than lean mice. In a second study, Morley and colleagues [88] examined the effects of three *kappa* agonist (ketocyclazocine, butorphanol, tifluadom) in obese *(ob/ob)* and lean *(ob/−)* male mice on their spontaneous food consumption in tests carried out during the daytime. They found that lean animals were more sensitive to the hyperphagic effects of tifluadom and butorphanol treatments. Clearly, the two studies yield results which are not altogether consistent, and, indeed, one group concluded that obesity is associated with changes in *kappa* receptors and their ligands [23], whereas the other concluded the opposite [88]. The sex of the animals differed between the two studies, as did the time of testing (daytime [88] as opposed to nighttime [23]). Either one or both of these factors could interact with obesity to determine the final observed pattern of feeding response.

Bremazocine

On the basis of the urination test, bremazocine [104] is a particularly potent *kappa* agonist [63, 64, 65]. Unfortunately, very little work has been done in relation to its effects on ingestional responses. Some of our own work will be discussed later, but mention is made here of a study using rats and mice reported by Hartig and Opitz [35]. Female rats were deprived of food and water during the 12 hr light period, and bremazocine was injected intraperitoneally 30 min before the beginning of the dark period and the return of their food and water. Bremazocine (1.0–8.0 mg/kg) increased 12 hr water intake but produced slight, overall reduction in food consumption, particularly when injected at a dose of 8.0 mg/kg. The increase in water intake may, of course, have been secondary to bremazocine-induced polyuria. The decrease in food intake is more difficult to explain, although three relevant factors need to be taken into consideration. Firstly, given the great potency of bremazocine, the range of doses used in the study represent relatively high values. Secondly, the measurement of intake after a period of 12 hr may not reflect much shorter-term changes in food consumption. Thirdly, the animals had been deprived of both food and water prior to drug administration, and this manipulation is known to affect feeding and drinking responses following treatments with opiate agonists [109]. It is possible, therefore, that a hyperphagic effect of bremazocine occurs in rats which may be revealed by changes in the experimental conditions. This is a crucial point to clarify, since the hypothesis that all *kappa* agonists can produce a stimulation of feeding responses would fall, were bremazocine to remain ineffective. In nondeprived female NMRI mice, bremazocine (1.0–8.0 mg/kg, SC) did stimulate both food and water consumption over a 24 hr measurement period [35]. This limited evidence suggests that in mice there may be some involvement of *kappa* receptors in the control of feeding responses. Since *kappa* agonists are diuretic in mice [101], the enhanced water consumption over 24 hr may, in part at least, reflect a polydipsia which is secondary to a polyuria.

Tifluadom

Tifluadom is an interesting compound which has the structure of a 1,4-benzodiazepine, but which has been characterized as a selective *kappa* agonist [105,106]. In receptor binding assays, tifluadom had a 25 times higher affinity for an opiate site in guinea pig brain homogenates labelled with [^{3}H](−)bremazocine, but showed no affinity for a ben-

zodiazepine site in rat brain homogenates labelled with [^{3}H]-flunitrazepam [105,106]. Tifluadom exhibits analgesic activity, and like bremazocine, the analgesic activity of tifluadom was more sensitive to MR 2266, an opiate antagonist which is reputedly selective for *kappa* receptors, than to naloxone. The reverse was the case for morphine. As noted earlier, tifluadom exhibits *kappa* agonist activity in the rat urination model [62].

Tifluadom has also been shown to stimulate food consumption in non-deprived rats during the daytime [92]. Following the subcutaneous administration of tifluadom in a dose of 5.0 mg/kg, the rats exhibited a significant increase in food intake 2 hr after the start of the measurement period. The hyperphagic effect was then maintained throughout the remainder of the 6 hr period. The effect was specific in that water ingestion did not increase at any time following tifluadom administration [92]. These data are consistent with the view that tifluadom is a *kappa* agonist, and that *kappa* agonists can stimulate food consumption. However, a complication arises because 1,4-benzodiazepines which are active at benzodiazepine receptors also stimulate food consumption [6,12]. Hence, the data do not in themselves exclude a possible benzodiazepine receptor-mediated effect of tifluadom to enhance food consumption. This point has been addressed in a recent report by Jackson and Sewell [46]. They demonstrated that the hyperphagic effect of 5.0 mg/kg (+)-tifluadom was antagonized by the opiate receptor antagonists, naloxone, naltrexone, MR 1452 and MR 2266, but not by the specific benzodiazepine receptor antagonist RO15-1788 [44]. Furthermore, intracerebroventricular administration of ICI 154,129, a selective antagonist at *delta* opiate receptors [114], also failed to block tifluadom's hyperphagic effect. The authors concluded that the effect of tifluadom to enhance food consumption may include activity at opiate receptors of the *kappa* and/or *mu* sites, but their data exclude the involvement, directly or indirectly, of *delta* opiate receptors or benzodiazepine receptors.

Tifluadom has been reported to enhance food intake, without change in water intake, in both the genetically obese mouse *(ob/ob)* and its lean littermate *(ob/−)* [88]. Tifluadom (0.0–5.0 mg/kg, SC) significantly increased 4 hr and 6 hr cumulative food intake in nondeprived *(ob/−)* mice, which were tested in the daytime. A smaller effect of 0.5 mg/kg of tifluadom was found in the obese mice, but other doses were without effect on food intake.

Butorphanol

According to the urination test for *kappa* activity, butorphanol can be characterized as a partial *kappa* agonist [61]. Levine and Morley demonstrated that butorphanol increased food consumption in rats [69]. Interestingly, in a study using Fischer-344 rats, older animals (22 and 28 months) appeared to be less sensitive to butorphanol in their hyperphagic response compared with younger animals (2 and 12 months) [30]. Adrenalectomy has been reported to enhance the effect of butorphanol on food intake in rats [70], while hippocampal lesions and pinealectomy had no effect [32,33]. Pharmacologically, the purines, adenosine and inosine, have been reported to suppress the feeding induced by butorphanol [129]. A number of peripherally-administered satiety-inducing peptides (e.g., CCK, somatostatin) were relatively ineffective in suppressing the feeding which follows butorphanol treatments [93]. Butorphanol has also been shown to stimulate food intake in mice [88].

U-50,488H

U-50,488H (trans-3,4-dichloro-N-methyl-N[2-(pyrrolidinyl)-cyclohexyl]-benzeneacetimide methanesulphonate) is one of a number of structurally novel compounds [120], which acts as a highly selective *kappa* agonist [128]. In addition to its analgesic activity [99], it causes water diuresis in rats and dogs [118,128], and can elevate rat plasma corticosteroid levels [58]. U-50,488H allows an excellent test of the hypothesis that activity at *kappa* receptors stimulates increased food consumption. Recently, a hyperphagic response to subcutaneous administration of U-50,488H has been described in nondeprived rats tested during the daytime [85]. Following 1.0 mg/kg of U-50,488H, food consumption was significantly elevated by about 1 g in the first 2 hours of a six-hour observation period. Significant increases in the cumulative food intake were observed after 6 hours, following the administration of 5.0 or 10.0 mg/kg U-50,488H [85].

Morphine

Using morphine as the prototype *mu* agonist, it is possible to assess the degree to which increased food consumption is specifically related to opiate activity at the *kappa* receptor. Sanger and McCarthy [109] reported that following the administration of morphine (1.0–30.0 mg/kg), the food and water consumption of food-deprived rats was significantly reduced. A significant first-hour reduction in food intake occurred following either 10.0 or 30.0 mg/kg morphine. Water intake during the first hour was significantly reduced following the injection of 3.0 mg/kg morphine and above. By contrast, morphine produced some increases in food and water consumption in nondeprived rats [109]. Intakes during the first hour of the observation period were not affected, but by the end of the second hour, food intake was elevated in the case of 1.0 and 3.0 mg/kg morphine treatments. The size of the increase in food consumption was of the order of 1 g. A very similar study was carried out using nondeprived rats which were tested during the dark phase of the daily light cycle [8]. In this experiment, morphine (0.25–8.0 mg/kg) did not enhance food intake at any stage during a 6 hr test period. Following 8.0 mg/kg morphine, indeed, food intake was almost completely suppressed for the first two hours of the test [8]. The reason for the inconsistency between the results of the Sanger and McCarthy study [109] and the Cooper study [8] is not clear. One possibility could be the higher control level of food intake during the nighttime testing [8] compared with the daytime test [109]. A point of agreement between the studies, however, is the hyperdipsic effect of morphine which occurred during the second hour of observation.

N-allylnormetazocine (SKF-10,047)

SKF-10,047 is considered the prototype *sigma* agonist [77]. A recent study by Gosnell and colleagues [29] showed that following its administration in doses of 0.1 and 1.0 mg/kg (SC), SKF-10,047 produced an increase in food intake in nondeprived rats, which were tested in the daytime. In contrast, food intake was not enhanced during nocturnal testing, when the only significant effect reported was a suppression of feeding after the injection of 10.0 mg/kg of SKF-10,047 [29]. This pattern of results is reminiscent of those obtained with morphine, which were described in the previous section. In food-deprived dogs, SKF-10,047 has been reported to decrease food intake [127].

Summary

Evidence reviewed in this section indicates that *kappa* opiate receptor agonists, ketocyclazocine, EKC, cyclazocine, bremazocine, tifluadom, butorphanol, and the highly-selective compound, U-50,488H, stimulate increased food consumption in rodents. The consistency of the results strongly suggests that *kappa* opiate receptors are involved, in an important sense, in the control of feeding responses [87]. With little exception, the data have been collected in daytime or nighttime tests of spontaneous feeding, using standard rodent food in the consumption tests. Furthermore, the food intake data have been limited to measures of the amount of food consumed. Additional work is urgently required to assess the generality of *kappa* receptor involvement in the control of feeding processes, and should include research which takes account of multiple factors involved in the arousal and satiation of feeding; the palatability, variety, and nutritional content of diets; meal pattern analysis of food intake; microstructural analysis of feeding responses. Increases in food consumption following treatment with the *mu* agonist, morphine, occur but not entirely consistently. The *sigma* agonist, SKF-10,047, has been shown to stimulate food intake in rats, but not in dogs.

KAPPA-RELATED FEEDING EFFECT: SITES AND MECHANISMS OF ACTION

Although the phenomenon of increased food consumption in rodents following treatments with *kappa* agonists is well-established, we do not at the present time have a clear understanding of how the increase is brought about. One theoretical account of the controls of feeding lays great emphasis on the interaction of central neural and endocrine mechanisms [84,86]. Viewed within this framework, it is interesting that adrenalectomized and adrenal demedullated rats showed an enhanced feeding response to EKC and butorphanol treatments, in a test of spontaneous food consumption during the daytime [70]. Since corticosterone replacement had no effect on food intake following the injection of EKC, the authors suggest that the adrenal medulla may have an important part to play in *kappa*-induced feeding [70]. In female rats, the hyperphagic response to ketocyclazocine was attenuated by ovariectomy and estradiol treatment [91]. The addition of progesterone reversed the effects of ovariectomy and estradiol. The data were taken to indicate some modulation of opioid functions in relation to feeding control by female gonadal steroids [91]. Taken together, these two pieces of evidence suggest ways in which peripheral endocrine systems may affect *kappa*-induced feeding.

Centrally, bilateral electrolytic lesions of the globus pallidus or the striatum attenuated the effect of ketocyclazocine to stimulate the food consumption of nondeprived rats measured in the daytime [31]. Gosnell *et al.* [31] suggest that these two structures may be sites of action for the stimulatory effects of exogenous opiates on food intake. Since these regions are densely innervated by dopaminergic terminals, they also suggest that the feeding response to *kappa* agonists involves an interaction between central dopamine and opioid systems [31]. Additional experimentation by the same group indicates that the increase in feeding response after *kappa* agonist treatments does not depend on the integrity of the hippocampus [32], or of the pineal gland [33]. These important, albeit preliminary, studies do provide a guide to central structures which may be involved in the hyperphagic effect of *kappa* agonists. Further research will determine the degree to which the postulated interaction between dopaminergic and opioid peptide mechanisms are involved in the physiological and behavioural controls of feeding behaviour [86].

KAPPA AGONISTS INCREASE PALATABLE FOOD CONSUMPTION

Research in our laboratory has been directed towards a pharmacological analysis of the mechanisms which are involved in the control of palatable food consumption in nondeprived rats. The diet we use in the feeding studies is made up of a mixture of powdered standard rat food, sweetened condensed milk and water [14, 15, 45]. Nondeprived rats consume it avidly, and show a high baseline level of consumption in the course of a 30 min test period carried out in the daytime. In this case, the feeding response is clearly under the control of a potent incentive to eat, and contrasts sharply with the low levels of spontaneous feeding during the daytime in nondeprived rats given access to their normal diet. The results that we have so far accumulated favour strongly an involvement of *kappa* receptors in the feeding response to the highly palatable diet.

Tifluadom and U-50,488H are, as we have seen, highly selective *kappa* agonists. Both significantly increase the ingestion of the high-incentive diet at doses of 0.3 and 3.0 mg/kg U-50,488H and 2.5–10.0 mg/kg tifluadom [25]. The magnitude of the increase in food consumption is impressive, from a baseline level of about 15 g food consumed in 30 min to between 20 g and 25 g food consumed in 30 min. Hence, the increase in food intake following *kappa* agonist treatments can be of short latency, and can involve large increments in the amount of food which is consumed. *Mu* receptors do not appear to be involved in the hyperphagic response, since morphine (0.01–3.0 mg/kg, SC) did not enhance the consumption of the palatable food [45].

A particularly interesting point to arise from the work is that some *kappa* agonists appeared not to stimulate food consumption, unless a modification was introduced into the test procedure, as described later. Thus, EKC and bremazocine did not enhance consumption; instead they produced an initial suppression of feeding when administered at relatively low dose levels (3.0 mg/kg EKC and 0.1 mg/kg bremazocine). These reductions may have been due to some degree of motor incapacitation, and it has been similarly noted that both drugs will reduce water consumption in water-deprived rats [63,126]. It seems probable that the decrements in ingestional responses associated with treatments using EKC and bremazocine are due to activity at non-*kappa* sites. On the basis of urination studies, it has been suggested that EKC has both *kappa* and *mu* agonist activity [65], and therefore the behavioural decrements may reflect activity at *mu* receptors. This suggestion requires further investigation, particularly since bremazocine was not characterized in the same way.

Nevertheless, significant increases in palatable food intake have been detected following small dose treatments with bremazocine (0.01 mg/kg) and EKC (0.1 mg/kg). The test procedure required a modification to reveal the hyperphagic effects of these two compounds. The rats were allowed to ingest a preload of the palatable diet to achieve a degree of feeding satiety before administration of the drugs. Following the preloading procedure, the baseline level of palatable food consumption was reduced to between 5 g and 10 g in the 30 min test period [45]. When EKC and bremazocine were administered to partially-satiated rats, in-

TABLE 1

SEQUENCES OF OPIOID PEPTIDES IN THE DYNORPHIN/NEO-ENDORPHIN PRECURSOR PROTEIN [50]

(H) . . .-LYS-ARG-TYR[175]-GLY-GLY-PHE-LEU-ARG-LYS-PRO-LYS-ARG[185]- . . .

β-NEO-ENDORPHIN

α-NEO-ENDORPHIN

-TYR[209]-GLY-GLY-PHE-LEU-ARG-ARG-ILE[216]-ARG-PRO-LYS-LEU-LYS-TRP-ASP-ASN-GLN-LYS-ARG[227]-

DYNORPHIN A-(1–8)

DYNORPHIN A

-TYR[228]-GLY-GLY-PHE-LEU[232]-ARG-ARG-GLN-PHE-LYS-VAL-VAL-THR[240]-ARG-SER-GLN-GLU-ASP-PRO[246]-

DYNORPHIN B

-ASN[247]-ALA-TYR-TYR-GLU-GLU-LEU-PHE-ASP-VAL[256](OH)

DYNORPHIN B-29

verted U-shaped dose-effect functions were obtained for the measure of palatable food consumption in a 30 min test. Thus, 0.01 mg/kg bremazocine significantly enhanced food consumption in partially-satiated rats, whereas 0.03 and 0.1 mg/kg bremazocine produced a marked suppression of feeding. Likewise, in the case of EKC, 0.1 mg/kg significantly elevated food intake, while 1.0 mg/kg abolished feeding [45]. It is interesting that in an earlier report on sweetened milk consumption by nondeprived rats, 0.03 mg/kg EKC (but not larger doses) produced a significant increase in intake [73]. These data are probably best interpreted in terms of actions of bremazocine and EKC at multiple opiate receptors. The evidence obtained with the highly selective *kappa* agonists U-50,488H and tifluadom suggests that the hyperphagic response is mediated by activity at *kappa* receptors. The suppression of feeding which follows larger doses of bremazocine and EKC depends, it seems, on activity at non-*kappa* sites.

In order to gain greater insight into the effects U-50,488H on the behaviour of feeding rats, we have recently conducted a videorecording study on partially-satiated animals (Jackson and Cooper, unpublished results). Food intake was increased by U-50,488H treatments, in a 30 min test which was conducted with rats which were partially-satiated before drug administration. Analysis of the videotapes indicated that the increase was not due to an increase in the rate of food consumption but arose because the duration of feeding was extended, with corresponding reductions in the time devoted to grooming and activity about the test box. The results appear to be consistent with a reversal of the satiation of feeding, following administration of the specific *kappa* agonist.

DYNORPHIN GENE PRODUCTS AND KAPPA OPIATE RECEPTORS

It is now known that the many endogenous opioid peptides which have been identified in brain and peripheral tissue can be grouped into three genetically distinct peptide families [1]. The opioid peptides derive from three precursor proteins, proopiomelanocortin (POMC), pre-pro-enkephalin and pre-pro-dynorphin (pre-pro-enkephalin B), respectively. The dynorphin group will be considered here, because of the selective affinity of the products of the pre-pro-dynorphin precursor for *kappa* receptors, and because we wish to emphasize the role of *kappa*-mediated effects in relation to the control of feeding behaviour.

The amino acid sequence of pre-pro-dynorphin was deduced from the nucleotide sequence of cloned DNA complementary to mRNA for the protein [50]. The precursor is a protein of 256 amino acids, and contains the sequence of dynorphin A, a heptadecapeptide which was isolated by Goldstein and his group [27,28] and by Tachibana and colleagues [121]. It occupies positions 209–225 (see Table 1). The peptide dynorphin A-(1–8) [82,113] occupies positions 209–216. Following dynorphin A is a second dynorphin-like peptide, dynorphin B, which was first described by Fischli and colleagues [24] as part of a 32-residue peptide, consisting of dynorphin A and dynorphin B linked by Lys-Arg. Dynorphin B (called "rimorphin") was independently isolated from bovine posterior pituitary [54]. An extended dynorphin B of 29 residues, called "leumorphin" has been described by Suda *et al.* [110]. Residues 175–183 of the precursor correspond to the opioid peptide β-neo-endorphin [81], and extension of β-neo-endorphin by a single Lys produces α-neo-endorphin [51].

From the point of view of the involvement of *kappa* receptors in the control of feeding responses, it is of considerable interest that dynorphin A shows a highly selective affinity for the *kappa* receptor [5, 43, 98, 133, 136]. Furthermore, other peptides derived from the same precursor show affinity for *kappa* receptors: dynorphin A- (1–8) and dynorphin A-(1–9) [4,19]; α- and β-neo-endorphin [97]; leumorphin [119]. A recently-synthesized analogue [D-Pro_{10}] dynorphin A(1–11) is a highly potent and selective ligand for *kappa* receptors [25]. In a comparative study, using the guinea pig-ileum bioassay, it has been shown that dynorphin A is the most potent *kappa* agonist; dynorphin-32, dynorphin B, dynorphin B-29 and α-neo-endorphin are about equipotent, and about 10–20 times less potent than dynorphin A; dynorphin A- (1–8) and β-neo-endorphin are about 200 times less potent

[49]. It appears likely that peptides of the dynorphin group are endogenous ligands for *kappa* opiate receptors. This suggests that one important function of endogenous dynorphin peptides may have to do with the control of feeding responses. Preliminary evidence which supports this hypothesis is considered in the next section.

The distributions of immunoreactive dynorphin B, immunoreactive dynorphin, and immunoreactive α-neo- and β-neo-endorphin in the central nervous system of the rat has been described recently by Zamir and colleagues [137, 138, 139, 140]. In most brain areas the levels of dynorphin B are much higher than those of dynorphin A, even though there is a 1:1 ratio of the two peptides in the precursor module. The widespread distribution of immunoreactive pro-dynorphin peptide products suggests that these opioid peptides may participate in many physiological functions, of which the control of feeding may be one.

It is interesting that the Brattleboro strain of rats which are homozygous for diabetes insipidus, are deficient in vasopressin but show normal levels of dynorphin [60]. Furthermore, *kappa* agonists did not increase urination in the Brattleboro rat [60], even though low doses of clonidine were effective in increasing urination. Hence, *kappa* agonists may act by inhibiting vasopressin release, perhaps by acting at an autoreceptor. In magnocellular neurons of the hypothalamus (in supraoptic and paraventricular nuclei), there is a common localization of dynorphin and vasopressin [131]. During co-release of dynorphin and vasopressin, dynorphin may exert an inhibitory effect on the further release of vasopressin. There is also evidence to indicate that in extra-hypothalamic brain tissue, dynorphin-containing neurons may be independent of vasopressin-containing neurons [80]. A dynorphin-vasopressin link may not necessarily be involved in feeding responses. Experiments with the Brattleboro strain should prove informative on this point.

DYNORPHINS INCREASE FOOD INTAKE

A major argument for the involvement of opioid peptides in the controls of feeding processes is that exogenous peptides stimulate food consumption. Intracerebral administration of either β-endorphin [34, 66, 78] or enkephalin analogues [47, 79, 122] has been shown to produce hyperphagia in nondeprived rats. However, at this point we note that drugs which act as *kappa* agonists increase food intake, and that dynorphins may be endogenous ligands for *kappa* receptors, and draw the inference that dynorphins should also stimulate feeding. The prediction has been confirmed in the work of Morley and his colleagues. They have shown that after intracerebroventricular injection of dynorphin-(1–13), nondeprived rats display a hyperphagic response during daytime testing [83]. The response to dynorphin-(1–13) was antagonized by naloxone, and also by the dopamine antagonists, haloperidol and metoclopramide [84,89]. The latter result suggests possible interactions between dopaminergic and dynorphinergic mechanisms in the control of feeding responses [84,86]. The feeding produced by ICV injections of dynorphin-(1–13) was reduced by subcutaneous administration of bombesin (10 μg/kg), but not by cholecystokinin-octapeptide (10 and 20 μg/kg, SC), thyrotropin-releasing hormone (10 and 20 μg, ICV), or calcitonin (1 unit, ICV) [89]. It is interesting to note that the dynorphin-induced feeding was accompanied by excessive grooming. In a later group of experiments, the same investigators showed that ICV injection of 20 μg dynorphin-(1–17) produced a robust hyperphagic effect; increases in food intake were also detected following administration of dynorphin-(1–10), -(1–11), and -(1–13). Dynorphin B (rimorphin) also increased feeding. The effect of dynorphin-(1–17) was reversed by naloxone and was shown to be specific to feeding; drinking responses were not enhanced [85].

These data are consistent with the notion that stimulation at central *kappa* sites by peptides of the dynorphin group results in increased feeding in the rat. Such data imply that endogenous dynorphinergic activity may be important in the normal controls of feeding responses. Since rats are predominantly nocturnal feeders it is interesting that levels of immunoreactive-dynorphin increase in rat hypothalamus during the night [100]. By contrast, pituitary immunoreactive-dynorphin decrease during the night [100]. Circadian variation in levels of immunoreactive-dynorphin would be expected to occur if endogenous dynorphin is instrumental in the control of ingestional responses.

Dynorphin may also have a part to play in the hyperphagic response to 2-deoxy-D-glucose (2-DG). Forced consumption of a 2% NaCl solution has the effect of markedly reducing pituitary levels of immunoreactive-dynorphin [37]. Yim and his colleagues have shown that rats which were maintained on the solution for 5 days displayed an attenuated feeding response following 2-DG treatment, but did not affect the response to insulin administration [135]. Apparently the feeding induced by the *kappa* agonist, ketocyclazocine, remained intact [134].

CONCLUSIONS

A robust finding which emerges from this survey is that a range of drugs which share an action as *kappa* receptor agonists can stimulate the increased consumption of food. The hyperphagic effect is opiate receptor-mediated since it can be antagonized by naloxone and other specific opiate antagonists. Their site of action may be restricted to certain specific regions of the brain, on the evidence of some recent lesion studies. Neuropeptides of the dynorphin family may represent the endogenous ligands for the *kappa* receptor. Consequently, the release of dynorphin and neo-endorphin peptides may be instrumental in the control of feeding responses. We can have some confidence in this inference because it has been shown that intracerebroventricular administration of these peptides can enhance feeding behaviour. A physiological role for dynorphinergic peptides in relation to the consumption of food has yet to be demonstrated, but we can obtain some clues about possible mechanisms by which food intake is stimulated from the evidence of studies which have employed opiate antagonists. These antagonists reduce food intake, perhaps by reducing the incentive value of food commodities and by accelerating the process of satiety. Both effects could derive from a common action, since satiation is associated with the loss of incentive to eat particular foodstuffs. The experimental finding that *kappa* agonists will enhance food intake in partially-satiated animals hints that the maintenance of feeding behaviour may be under dynorphinergic control, which weakens as satiation proceeds. Future research will no doubt reveal if the hint is a valuable clue to a solution, or no more than a red herring. The next 10 years may tell.

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