The Eating Disorders
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Chapter 3

Energy Balance and Opioid Receptors: Epsilons in the Periphery Promote Conservation; Kappa and Delta in the CNS Permit Expenditures

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Opium arrests life, anesthetises. Well being comes from a kind of death. Without opium I am cold, I catch cold, I do not feel hungry. I am impatient to impose what I invent. When I smoke I am warm, I do not know what colds are, I am hungry. My impatience disappears." "Opium leads the organism towards death in euphoric mood. The tortures arise from the process of returning to life against one's wish. A whole spring-time excites the veins to madness, bringing with it ice and fiery lava.

Jean Cocteau
Opium, The Diary of a Cure

OVERVIEW

In this chapter I present evidence that requires the revision and extension of my 1979 opioid theory [1] of the conservation of energy. Opioid peptides participate not only in hibernation-like phenomena that conserve energy, but also in the most intense of energy expenditures including arousal from hibernation and migration. The 1979 theory [1] did not propose a role for opioids in energy expenditure. Instead it focused on the many energy-conserving actions of morphine. Recent measurements of metabolic weight loss show that morphine, as predicted by the 1979 theory reduces the rate of such losses. Moreover this conservatory action can be blocked by an opioid antagonist that *does not* enter the brain. Therefore, the energy-conserving action of morphine must be localized to the body rather than to the brain. The body's opioid peptide responsible for energy conservation appears to be the specific ligand, beta endorphin. Also identified are the specific receptors where beta-endorphin acts to conserve energy; these receptors are known as the epsilon set. Apparently the epsilon receptors in the body act, more or less continuously to conserve energy until they receive either a kappa-receptor-mediated message or delta-receptor-mediated message from the brain that permits the expenditure of energy.

The evidence for kappa receptor control is based on two experiments: In one, a specific kappa agonist is shown to promote energy expenditure in a dose-related fashion. In the other, an energy-expending effect of morphine is unmasked by blocking morphine's conservatory actions in the body with an opioid antagonist that does not enter the brain. Additional experiments demonstrate that the unmasked energy-expending effect of morphine can be blocked by a specific kappa receptor antagonist that acts in the brain. The brain's kappa opioid system for the expenditure of energy contributes

to arousal from hibernation, reproduction, and other calorically expensive activities. In addition we have preliminary evidence that delta opioid receptors in the brain contribute to the linear running and perseverance involved in migration. Other aspects of migration such as social group formation may also involve opioids.

The revised theory has implications for understanding the eating disorders. Anorexia nervosa can be understood as an excess of kappa or delta receptor activity in the brain. Some forms of obesity can be understood not only in terms of excessive epsilon activity in the body but also in terms of insufficient kappa and/or delta receptor activity in the brain. The new theory can account for the excessive dynorphin reported to be present in the pituitary glands of obese mice. Such an accumulation could occur because of an inability of obese mice to release this peptide from storage sites. This idea is compatable with the well known supersensitivity of obese mice to drugs that block kappa-type opioid receptors in the brain. The theory also gives rise to an alternative explanation for the increase in feeding caused by kappa agonists in lean rodents. These increases may not be a direct effect of such drugs but secondary to caloric shortages produced by the increases that these drugs induce in metabolic weight loss.

The naturally-occurring opioid peptides have a major integrative role in energy balance [1,2,3]. I have presented evidence that some of these peptides, such as beta endorphin act to promote the conservation of energy [1]. In this chapter I discuss evidence that this action occurs primarily from epsilon receptors located in the periphery [4]. I also present evidence that other opioid peptides such as dynorphin act at kappa receptors in the brain to promote the expenditure of energy [4]. Moreover met-enkephalin acting at delta receptors in the brain may contribute to migration-like behavior of sufficient duration and intensity to allow very long and difficult journeys to be sustained until completion. Thus peptides that have a short form of the met-enkephalin sequence may contribute to the active rather than passive adaptation to famine. *These three types of opioid peptides work together to accomplish the delicate balance between conservation, expenditure, and behavioral adaptation to famine.*

They do this by coordinating a series of adaptive changes in many organ systems. For example, in man, morphine or beta-endorphin induces passivity, lowers respiratory rate and volume, lowers body temperature, reduces motor activity, induces constipation, reduces reactivity to sensory stimuli of arousal including pain, and reduces sexual urges [1]. The changes induced by morphine or beta-endorphin share a common theme: All of them move the organism toward the death-like state of hibernation. An organism faced with seasonal food shortages has two basic choices: hibernate or migrate. Reptiles and amphibians are cold blooded. They conserve energy by becoming stuporous in the cold.

In contrast, relatively few mammals deal with food shortages by means of stupor. Instead most mammals have developed the energy-expending process of migration as a viable alternative. Migration requires extensive coordination of sensory information by the brain, whereas hibernation requires much less sensory processing.

The movement toward migration has encouraged the development of complex and sophisticated brain mechanisms capable for example, of navigation. In this chapter I present evidence that hibernation and migration have different opioid substrates. The more primitive one employing epsilon opioid receptors underlies hibernation. One way of studying these components uses opioid antagonists that block opioid receptors. For example, low doses of naloxone prematurely arouse Turkish hamsters from hibernation [5]. Thus, hibernation may represent a opioid-induced energy conservation. According to the theory presented here, hibernation may involve epsilon receptors. Energy conservation induced by beta endorphin also occurs in certain less-intense and less-prolonged forms, including sleep [6] and the psychological state known as learned helplessness [7,8]. The opioid receptors that contribute to learned helplessness are located in the brain [8] and these may be epsilon receptors.

In this chapter I extend the opioid theory of energy conservation to include certain cases of opioid-induced increases in energy expenditure that previously could not be incorporated by the theory. These effects of dynorphin do not occur at epsilon receptors. Instead, a new receptor known as the kappa receptor has evolved to handle dynorphin. Kappa receptors can be stimulated selectively by opiate drugs such as U50,488H or non-selectively by drugs such as morphine, which also stimulate epsilon receptors at similar doses. Kappa receptors may be blocked selectively by the kappa receptor antagonist MR2266. Naloxone or naltrexone may also be used to block kappa receptors, usually at doses higher than those that block epsilon receptors.

U50,488H increases reactivity to pain [9] in mice as well as increasing metabolic weight loss [4]. This suggests that opioid peptides that contain the leu-enkephalin sequence (i.e. dynorphin) act at kappa receptors involved in promoting arousal from cold-induced stupor. This would allow the organism to expend massive amounts of calories necessry for example to arouse itself from hibernation and/or to create an offspring. Delta receptors have evolved to handle certain

short met-enkephalin like opioids. Although it is difficult to selectively stimulate delta receptors, FK33824 is one of the better substances available at present for this purpose.

ENERGY EXPENDITURE

Met-enkephalin-containing peptides may participate in the sustenance of the motivational urge to migrate, thus allowing it to last long enough to complete trips of thousands of miles. Migration represents one of the most prolonged states of energy expenditure known. As such, it must involve its own kind of euphoria, for otherwise the organism would be distracted and would fail to persevere. Met-enkephalin may also participate in less-intense and less-prolonged states of energy expenditure such as arousal from sleep and certain learned behaviors [7]. Recently we reported that a met-enkephalin analogue FK33824 produces linear running in mice with obliviousness to environmental stimuli and undirectional movement. We showed that this migration like running was mediated by opioid receptors in the CNS [16,31]. These may be delta receptors concerned with certain aspects of migration such as navigation and perseverence.

Arousal from hibernation and migration are not the only massive energy-expending actions that involve opioid activity. Withdrawal from opiates precipitates a violent syndrome of energy-expending action, including lacrimation, vomiting, hyperthemia, diarrhrea, ejaculation, increased respiration, sweating, etc. The overreaction is due, in part, to hyperactivity in a brain pathway known as the ventral noradrenergic bundle. The evidence for this assertion is based on experiments employing selective lesions of this bundle made with 6-hydroxydopamine. The lesions deplete hypothalamic norepinephrine and also substantially reduce the symptoms of the withdrawal syndrome [10]. The ventral noradrenergic bundle contains a cotransmitter, dynorphin, released along with norepinephrine [11]. This suggests that the release of both excessive norepinephrine and excessive dynorphin contributes to the violence of the withdrawal syndrome. Accordingly, drugs that inhibit either transmitter should attenuate the withdrawal syndrome. This includes drugs like clonidine, an alpha 2 agonist, that already are known to attenuate the abrupt withdrawal symptoms [12]. This should also hold true for MR2266, a kappa receptor antagonist. Perhaps the combination of MR2266 and clonidine would be a supereffective treatment for the attenuation of the withdrawal syndrome.

Naturally, many opioids have the capacity to attenuate this syndrome in morphine-tolerant animals by restorating high levels of opioid receptor occupation. Dynorphin is no exception to this rule [13]. This could be explained if dynorphin or some related metabolite could occupy opioid receptors other than kappa during the state of withdrawal. Most conservative scientists agree that beta endorphin acts at epsilon, mu, and delta receptors. Perhaps dynorphin also acts at various opioid receptors. Furthermore there are subtypes of both mu and kappa receptors. All of these receptor types and subtypes occur in great numbers throughout the body and brain in remarkably diverse tissues including lung, gut, many endocrine glands, genitals, and also the central and peripheral divisions of the nervous system. Such complexity makes it difficult to unravel opioid functions. Certain theoretical considerations may provide a framework helpful in this endeavor.

HIBERATION MIGRATION AND BREEDING

From an evolutionary point of view it appears that the met-enkaphalin-containing opioid peptides evolved before the leu-enkaphalin-containing peptides. This was shown by demonstrations [14] in the South African clawed toad, *Xenopus laevis,* that neither of its two proenkephalin genes codes for a leu-enkephalin sequence. In constrast, the human proenkephalin gene contains the code for this sequence, as do the genes of other vertebrates that diverged from *X. laevis* some 350 million years ago. *X. laevis,* in common with most amphibians comes out of its hibernation-like behavior by absorbing heat from the environment rather than generating heat internally. This raises the possibility that the evolution of the gene coding for leu-enkephalin contributed to the capacity of organisms to generate all the heat necessary to arouse themselves from their cold induced stupor. Later in evolution with warm blooded animals, migration becomes an important adaptive response to famine. This may be connected with evolution of genes coding for met-enkephalin and the delta opioid receptor. Migration often brings animals together in groups, whereas hibernation is a solitary activity. This suggests that the met-enkephalin-coding gene may contribute to the social bonding associated with migration.

At the end of migration or hibration, animals often engage in seasonal breeding behavior to insure the reproduction of the species. Beta-endorphins of hypothalamic origin participate in the menstrual cycle. It is responsible for slowing down the luteinizing hormone (LH) pulse frequency from one an hour to one every five or six hours. This is necessary for the luteal phase of the cycle to occur. In contrast, naloxone is an effective stimulant for the release of LH at all times of the estrus cycle of rats. Moreover, chronic naloxone in primates accelerates the LH pulse frequency so that the ordinary slow luteal pulse frequency (one very five or six hours)

is speeded up to the faster rate of the follicular phase (one very hour).

Interestingly, leu-enkephalin also stimulates the release of LH [17]. It is not yet clear whether this is due to an action at kappa receptors. There also are some indications that delta-type opioid receptors may contribute to the increased amplitude of the LH pulse seen during the luteal phase of the cycle. Thus, beta endorphin could act at epsilon receptors to inhibit LH pulse frequency and delta receptors to increase LH pulse amplitude. This complicates the situation. Nevertheless, the LH stimulative action of leu-enkephalin fits the current theory quite well. Apparently, a balance occurs between the LH pulse-inhibiting action of epsilon receptors and the LH pulse-stimulating action of kappa receptors that modulates the pulsatile release of gonadotrophin-releasing hormone from the arcuate nucleus, thereby exerting a major influence on the menstrual cycle in females [18].

In males sexual desire is similarly influenced, at least insofar as beta-endorphin suppresses libido, and naltrexone increases the low libido of the male Zucker obese rat (fa/fa) sufficiently to turn this sexual "dud" into a sexual "stud" [3]. These lines of evidence suggest that the energy-expending activities regulated by opioid peptides include reproduction in both females and males.

WEIGHT LOSS: PERIPHERAL AND CENTRAL RECEPTOR SITES OF ACTION

Metabolic weight loss is another energy-expending activity regulated by opioid peptides. We used metabolic weight loss as a model system to establish the roles of epsilon and kappa receptors. Henry et al [4], made measurements of metabolic weight loss in mice under the influence of various doses of morphine or U50,488H, a selective kappa receptor agonist. This work helped establish that opioid receptors participate in energy expenditure. All animals lose weight over time because of the cost of metabolic processes: heat production, muscle activity, and the generation of CO_2 and gaseous H_2O. This weight loss can be measured by the use of a computer-controlled balance capable of weighing live animals accurately to the nearest 10 mg [4]. By effectively trapping urine and feces in a granulated clay bedding weighed along with the animal, we were able to obtain weight loss values that correlated highly with other measures of metabolism such as oxygen consumption. Our findings were as follows: Morphine produced a dose-related decrease in the rate of metabolic weight loss (figure 1). Neither DAGO nor morphiceptin, fairly specific mu receptor agonists, had this effect.

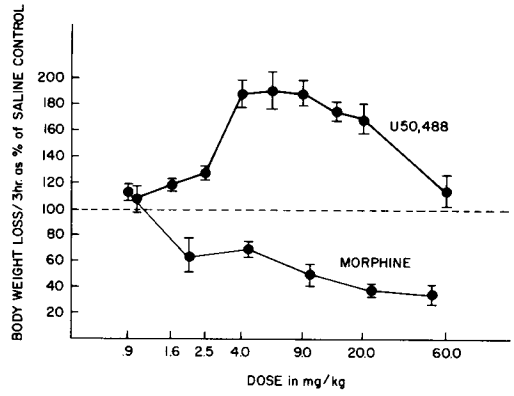

Figure 3.1 Opioid receptors: an epsilon set in the body acts to conserve energy until a kappa set in the brain permits energy expenditure.

These findings directly confirm the opioid theory of conservation. They also eliminate the mu receptor as a possible site and leave two possibilities: delta or epsilon receptors. The energy-conserving action of morphine had some specificity, because it was completely blocked by the opioid antagonist, naltrexone, at low doses. Naltrexone does not usually block delta receptors at low doses. Thus, by a process of elimination we are left with epsilon receptors as the most likely candidates for morphine's energy-conserving action.

The evidence for the kappa-receptor-induced increase in energy expenditure is more straightforward. U50,488H increased metabolic weight loss in a dose-related manner (figure 1). The shape of the dose-response curve was an inverted U function. At the maximum effective dose (between 4 and 9 mg/kg U50,488H produced a doubling of the metabolic weight loss. This action of U50,488H was blocked by 6 mg/kg of MR2266, a specific kappa receptor antagonist, but it was only slightly reduced (from 190 to 170% of saline controls) by 6 mg/kg of naltrexone. This indicates that the U50,488H-induced increase in metabolic weight loss has some specificity; it is blocked selectively by kappa opioid receptor antagonists.

In order to obtain information about the site of these opioid actions, we decided to antagonize their actions with an opioid antagonist that does not enter the brain known as MR2663BR (naltrexone methobromide). This substance had no effect on the U50,488H-induced increase in metabolic weight loss [4]. This suggests that U50,488H increases metabolic weight loss by actions at kappa receptors located in the brain. In contrast, MR2663BR completely reversed the direction of metabolic weight loss for the morphine-injected mice, producing a 151% ± 13 increase over saline controls [4]. Thus, the combination of morphine plus MR2663BR

revealed, or unmasked, an effect just like that of U50,488H. This could be due to kappa receptor activity. In support of this idea, the increase in metabolic weight loss induced by morphine plus MR2663BR was completely blocked by the kappa receptor antagonist MR2266 (6 mg/kg) [4]. These results suggest that morphine has two antagonistic actions: a peripheral energy-conservation effect at epsilon receptors, and a central energy-expenditure effect at kappa receptors. Apparently the conservation action is large enough to completely mask the expenditure action, and this explains why morphine alone produces a decrease in metabolic weight loss. Blockade (by means of MR2663BR) of the peripheral opioid receptors, however, allows the central kappa action of morphine to manifest itself without opposition from the peripheral epsilon system. In order to test further the idea of antagonism between these two systems, we showed that increasing amounts of morphine caused increasing inhibition of metabolic weight loss induced by a constant amount of U50,488H [4].

OBESITY AND ANOREXIA NERVOSA

These results have important implications for understanding obesity and anorexia nervosa. They suggest the following scenario: The periphery contains a opioid system (epsilon type) for energy conservation that functions only to conserve and store calories. It cannot engage in caloric expenditure unless a message comes from the brain to allow this. The brain message involves, in part, a kappa-type and/or delta type opioid receptor for energy expenditure. In obesity there may be either insufficient central kappa or delta opioid message for expenditure and/or too much peripheral epsilon message for conservation. This suggests that the treatment of obese subjects with a combination of a kappa agonist and a peripheral antagonist such as MR2663BR would optimize their chances of losing weight. This prediction is quite counter-intuitive from the point of view of the literature indicating that kappa agonists stimulate feeding [19]. Yet, from the data reported here, kappa agonists should work as an anti-obesity treatment. In support of this possibility, kappa agonists increase urination [20] and also increase metabolic weight loss [4].

The theory described above also has implications for the treatment of anorexia nervosa. Here the problem may be too much kappa or delta message of expenditure from the brain and/or an insufficient opioid message of conservation in the periphery. The theory predicts that treatment with drugs that block kappa receptors, such as MR2266 should help anorexics to eat more. They could further be encouraged to eat with a form of opioid that activated epsilon receptors in the periphery alone. Some evidence already exists that anorexia nervosa does indeed have an opioid component [21]. Finally, our recent work with delta receptors in the brain suggests that the well known sloth of the obese may be due in part to a lack of delta opioid receptor activity. Moreover, hyperactivity of delta receptors in the brain could contribute to behavioral hyperactivity in anorexia nervosa.

The theory has implications for understanding genetic obesity, which has been identified most definitively in mutant rodents (ob/ob mice and fa/fa rats). These animals are heavily biased toward energy conservation. They seek and accumulate excessive calories. Moreover, their efforts at energy expenditure and reproduction are marginal. In this chapter, I review evidence that this bias toward energy conservation is due, in part, to the combination of excessive activity from beta-endorphin systems, diminished activity from dynorphin systems and diminished activity from met-enkephalin systems. Some evidence supports this hypothesis in one subgroup of the human population, obese hirsute women, who have excessive beta-endorphin in their blood [22]. Other forms of human obesity have not been investigated extensively.

The changes responsible for environmental obesity are likely to be more subtle than those involved in genetic obesity. Nevertheless, the opioid mechanism involved in environmental obesity may be fundamentally the same as that of genetic obesity. In support of this idea, an opioid peptide involvement was established in ordinary rats that had their obesity induced by a highly palatable diet [23]. Thus, the opioid theory of obesity has been extended to an environmental type of obesity. If this work can be extended to humans, it would expand considerably the possible role of opioids in the etiology of obesity. This has proved difficult to accomplish. Most of our information is on the genetic forms of obesity. These forms involve relatively long-lasting changes in opioid peptides that should induce relatively long-lasting changes in the opioid receptors.

RECEPTOR SENSITIVITIES AND REGULATION IN OBESITY

I will now consider new evidence on the question of receptor subsensitivity and supersensitivity underlying opioid actions in obese mutants. Three precursors for opioid peptides have been identified: pro-opiomelanocortin, pro-enkephalin, and pro-dynorphin. Members of all three families occur in excess in the pituitary of genetically obese rodents [24,25] and beta-endorphin occurs in excess in their blood [26]. Beta-endorphin in the pituitary, for example, becomes elevated as early as four weeks of age in obese mice (C57BL/6J

ob/ob) [26,27] and remains elevated throughout their lifespan [27]. In old age the pituitary beta-endorphin levels reach new highs [27]. Leu-enkephalin in the posterior pituitary also rises sharply between the ages of five weeks and three months in the *ob/ob* mouse [28]. These genetically obese mutants therefore represent an animal model with a lifetime of multiple opioid excesses. Other peptide excesses, such as hyperinsulinemia, often induce a decrease (downregulation) in the binding of the peptide by its receptors. Therefore, opioid excesses should produce similar changes. Conversely, opioid shortages should induce an upregulation in opioid receptors. Indeed, upregulation of mu receptors from chronic treatment with naltrexone has been demonstrated [29]. Is this true for opioid peptides in the genetically obese? If so, certain opioid receptor types should show such upregulation. Conversely, other opioid receptor types should show downregulation if their ligand is in excess supply.

This raises two interesting possibilities for receptor changes in the obese mice. Kappa receptors in the brain may be upregulated in response to a shortage of dynorphin. This hypothesis is based on the assumption that obese mice have accumulated opioid peptides such as dynorphin in storage sites instead of releasing them. There is no direct evidence in support of this hypothesis. However, indirect evidence indicates that obese mice are supersensitive to the feeding- and drinking-increasing action of a kappa agonist [25,26]. Such supersensitivity is compatible with upregulation of kappa receptors. The situation with the epsilon receptors in the body should be quite the opposite. We know that beta-endorphin in obese mice is released from storage, because we find beta-endorphin in excess in the blood. This should lead to a downregulation of epsilon receptors in the periphery. This hypothesis remains to be tested.

A large body of evidence shows that genetically obese rodents have substantial supersensivity to opioid antagonists including naloxone, naltrexone, and MR2266 [24,25]. Their feeding and drinking behavior, for example, is suppressed by opioid antagonists at doses one tenth of those required to do this in lean controls [24]. In other words, they are supersensitive to the symptoms of the withdrawal syndrome precipitated by an opioid antagonist. The withdrawal syndrome also occurs spontaneously in subjects that have developed tolerance to morphine after the effects of an opiate such as morphine wears off.

We have shown [30] that obese mice have an exaggerated set of symptoms to withdrawal from morphine compared with their lean controls. For example, obese mice lose more body weight than lean mice. Ordinarily female obese mice (five to six months old) gain 0.16 g/day compared with 0.002 g/day for lean controls. Withdrawal from morphine abolished their gain and produced a dose-related loss in body weight in the obese mice. The lean mice had to be in withdrawal from doses of morphine five times greater than those of the obese mice in order to show the same effect on body weight loss.

The obese mice also showed sharper drops in food and water intake due to morphine withdrawal than the lean mice. This effect was particularly dramatic for the drop in water intake, which dropped so steeply that the obese mice, who ordinarly take about 1.3 ml of water for every gram of food eaten, lost this polydipsia entirely and required only 0.8 ml of water for each gram of food. The abnormally high water- to-food ratio of obese mice was restored to the level of lean mice by withdrawal from morphine. The restoration was a linear function of the log of the dose of morphine that the mice were being withdrawn from (1 to 16 mg/kg). Thus, the *ob/ob* mouse has both supersensitivity to withdrawal from morphine and supersensitivity to the withdrawal precipitated by opioid antagonists. This data has encouraged us to embark on a major investigation of receptor-binding characteristics (affinity and number) in obese and lean rodents. We hope to characterize upregulation and downregulation for the various receptor types and test some of the predictions of this revised theory of opioid function in the conservation and expenditure of energy.

HETEROGENIETY OF RECEPTOR TYPES

The idea of differential and sometimes opposite reactions in receptors for different opioid types has an important parallel with the glucocorticoid system of obese mice. We have shown that genetically obese mice (ob/ob) are hypersensitive to glucocorticoid-induced stimulation of feeding but dramatically insensitive to glucocorticoid-induced losses in body weight [32]. These different actions of glucocorticoids would act in tandem to promote obesity. Steroids as well as peptides have significant roles in the etiology of obesity and anorexia. Moreover there appears to be the same heterogeniety of steroid receptor types, particularly in glucocorticoid receptor types as there is in opioid receptor type. We have found reduced binding and activation of glucocorticoid receptor complexes in whole brain liver, cerebral cortex, hippocampus and hypothalamus of genetically obese and diabetic mice (mdb/mdb) as compared to their lean control [33].

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