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Editorial

Endorphins: the basis of pleasure?

Specific opiate receptors were first described in mammalian nervous systems 19 years ago.¹ Two varieties of endogenous opiate agonists have been clarified in humans, the enkephalins and the structurally larger endorphins but the term endorphin is often used to encompass both types. Enkephalins are found diffusely in non-cerebellar brain, chiefly in the globus pallidus and spinal cord and outside the CNS in the gastro-intestinal tract, pancreas and adrenal glands. Beta-endorphin is found especially in the pituitary and hypothalamus. At least five separate opioid receptor types are known (μ , δ , κ , ϵ and σ). The distribution of these within the CNS varies from one species to another and in most instances it is not possible to relate a single receptor type to one particular function. The best studied compound, morphine, acts by definition on the μ receptor, whilst ketocyclazocine and dynorphin are the major agonists for the κ receptors. However, most opioid agents have mixed receptor activity.

Proposed functions for the endogenous opioid system are numerous but the best evidence relates to effects on analgesia, temperature regulation, appetite and thirst control, sexual behaviour and blood pressure regulation.² If β -endorphin is given exogenously it has addictive potential similar to opiates. For example, it was found³ that rats would work for a response contingent intraventricular injection when receiving relatively low amounts of this neuropeptide. The same phenomenon occurs with met-enkephalin.⁴ Few biological functions have not been related to endorphins at some time, but what is lacking is a cohesive model that gives some "purpose" to these diverse actions. Whilst it has been proposed previously that endorphins represent a "pleasure" system^{4,5} evidence for this has never been presented on a comprehensive basis. This review examines five varieties of enjoyable human activity and evaluates the role of opiates in each.

Opiate use

Evidence for opiate use dates back to the Assyrian "poppy" art from 4000BC and to studies of Egyptian, Greek and Persian cultures. The early use of opiates included analgesia but the extent of use for euphoria is not known. It is well documented,⁶ although not widely appreciated, that apart from euphoria, prolonged relaxation and sedation, opiates induce sensations comparable to sexual orgasm. One of the first to describe the orgasm-like quality of opioid administration was John Jones, an eighteenth century English physician describing acute oral

ingestion of Tinct Opium ("Laudanum")—"it has been compared not without good cause to a permanent gentle Degree of that Pleasure which Modesty forbids the name of."⁷ The acute effect of intravenous morphine injections was explicitly described as orgasm-like by one author⁸ who noted pleasurable sensations centred first in the pelvic and pubic area. Another author reported that nearly all of the patients being treated in his clinic for heroin addiction referred to it as an aphrodisiac.⁹ The mechanism by which opioids produce pleasure is not fully understood but it has been suggested that during the brief 30-60 second "rush" that follows intravenous heroin administration there is release of catecholamine both centrally and peripherally.⁶ Paradoxically long term abuse of opioids leads to decline of sexual behaviour.

Love and sex

There are no studies of endorphin release in humans during coitus but there is evidence from animal studies that sexual stimulation in rats and hamsters may lead to an increase in the activity of endogenous opioid systems. In male rats copulation progressively induces analgesia.^{10,11} Vaginal cervical stimulation of female rats has an analgesic effect.^{12,13} Plasma β -endorphin levels taken from male hamsters 30 seconds after their fifth ejaculation were 86 times higher than those of control animals.¹⁴ In one study¹¹ male rats were decapitated after 30 or 120 minutes of copulation but no difference in cerebral opioid content could be found between copulators and control animals at 30 minutes. The midbrain opioid content was significantly reduced in copulators after 120 minutes, which could indicate either inhibition of synthesis or a depletion due to increased turnover or metabolism. Although this report at first sight is contradictory¹⁴ it must be emphasised that Szechtman's rats had been exposed to repeated painful stimuli and there may be differences between rat and hamster responses. Furthermore, the central activity of β -endorphin cannot necessarily be inferred from the plasma concentrations. At a more anecdotal level, it is well recognised among migraine sufferers that intercourse can abolish headache.

There is less evidence incriminating endorphins with respect to passionate love and sexual desire. It was speculated¹⁵ that love brings on a giddy feeling comparable to an amphetamine high and that the crash which follows a breakup is like amphetamine withdrawal. Probably "love addicts" and drug addicts have much in common and the craving for romance is merely the craving for a particular

kind of "high".¹⁵ The euphoria associated with passionate love could be explained in terms of increased endorphin activity but in the absence of actual measurement this must remain a speculation.

Alcohol

The enjoyable effects of alcohol consumption need no elaboration but possible mechanisms of action have been elucidated only relatively recently. It was discovered¹⁶ that opiates and other drugs of abuse mediate their effects through the limbic system, reflecting the reward properties of these drugs. Alcohol like other addictive drugs may exert its reinforcing effect through the same pathway as natural reward transmitters.¹⁷ It is well known that ethanol and opiates have similar effects, for example, euphoria, development of tolerance and dependence as well as some aspects of withdrawal reactions following chronic exposure.

Although alcohol and opiates are not cross tolerant¹⁸ there is a notable resemblance between intoxication by each. Ethanol might function indirectly by activation of opiate receptors.¹⁹ Alcohol administered acutely to animals may be capable of raising cerebral endorphin levels, although not in every region where such peptides can be found. If rats are injected with ethanol 2.5 G/Kg intra-peritoneally a 20% increase in the concentration of met-enkephalin in the striatum and β -endorphin in the hypothalamus may be detected.²⁰ In another study similar doses of ethanol induced significant increases of met-enkephalin in rat striatum, midbrain and hypothalamus with a trend towards elevated levels of hypothalamic β -endorphin levels and reduced hippocampal met-enkephalin.¹⁹ No significant changes in pituitary β -endorphin concentrations were recorded. Slightly more ethanol (3.0 G/Kg) given intra-peritoneally to rats increased β -endorphin-like immunoreactivity in serum whilst brain levels showed little change, although the β -endorphin content of the hypothalamus and neurointermediate lobe of pituitary appeared to decrease possibly because of release of opiates into the blood.²¹ Conversely, chronic alcohol exposure produces lowering of endorphin level; 30 days exposure to 20% ethanol significantly lowered rat striatal and brain-stem met-enkephalin levels whilst β -endorphin concentration fell in pituitary especially the neuro-hypophysis.^{19, 20} Hypothalamic levels to both met-enkephalin and β -endorphin were unaltered. In human studies²² a four-fold increase of plasma opioid activity (but not β -endorphin) was reported in four volunteers following acute ethanol administration. Elevated β -endorphin (and cortisol) blood levels followed low doses of ethanol by mouth given to healthy non-alcoholic volunteers who had a strong family history of alcoholism.²³ Naloxone, the opiate antagonist in other human studies, has been shown to reverse alcohol-induced coma^{24, 25} and to prevent the effect of alcohol intoxication.²⁶

The major breakdown product of alcohol, acetaldehyde, is thought to combine with catecholamines to produce condensation products known as tetrahydro-isoquinolines (TIQ), for example, tetrahydro-papaverolin (THP) and salsolinol. These substances have marked opiate-like characteristics.²⁷ Interestingly benzyl-TIQs are essential intermediates in the biosynthesis of morphine in the poppy plant *Papaver Somniferum*.²⁷ It was suggested²⁸ that TIQ formed after ethanol ingestion could function as opiates, furthermore TIQs have been identified in rodent brain after chronic exposure to alcohol.²⁹ Rats given intraventricular injection of TIQ increase their alcohol consumption.³⁰ Salsolinol is a TIQ formed by condensation of acetaldehyde and dopamine. Human studies³¹ showed

higher urinary and CSF salsolinol levels in chronic alcoholics than controls with excess salsolinol in the hippocampus and limbic forebrain, that is, reward areas. However other studies³² demonstrated no correlation of salsolinol level in urine following withdrawal or alcohol loading even though aldehyde levels increased in blood. It was suggested that alcoholics might metabolise salsolinol more rapidly or that another unidentified TIQ might be formed. An added complication is that salsolinol is present in normal brain or urine as well as some alcoholic drinks and foodstuffs.³³ Despite some inconsistencies it remains possible that ethanol and TIQ may act as agonists at enkephalin and endorphin binding sites—particularly the δ receptor³⁴—where they could displace the natural compounds and induce a false sense of well being.

Food

Many affluent individuals eat more than their biological needs not for relief of hunger but for pure indulgence; if this becomes excessive it constitutes a pathological disorder—bulimia. According to classical theory there are two major regulatory areas for food intake, both located within the hypothalamus, one in the ventromedial zone (VMH) responsible for satiety and another ventrolaterally (VLH) which initiates feeding. It is significant that VLH is one of the most potent "reward" or "pleasure" centres of the brain. Animals or humans^{35, 36} will rapidly learn a response that produces electrical stimulation of this area, furthermore the same electrode that provides pleasure also induces eating.³⁷ It now appears more likely that the closely related paraventricular nucleus (PVN) and dorso-medial nuclei (DMN) are responsible for opiate related food regulation.³⁸ Many peptides are concerned with food regulation (cholecystokinin and corticotrophin releasing factor both of which inhibit intake)³⁹ but opiates could subserve the dual role of promoting ingestion and enjoyment. Morphine, β -endorphin, met-enkephalide and especially dynorphin all stimulate eating when micro-injected into PVN, whilst naloxone attenuates feeding.⁴⁰ Opiates given parenterally appear to stimulate especially the ingestion of fatty food.⁴¹ Dynorphin given centrally induces feeding in rats probably by activation of the κ receptor within PVN⁴² whilst κ -antagonist drugs inhibit feeding, more potently in fact than naloxone.^{40, 43–45} There is evidence of a second opioid feeding system within the amygdala which involves μ receptors, however, this is thought responsible for "foraging" whilst the κ system relates to food intake.^{46, 47} In humans opiate antagonists depress food intake over a single meal⁴⁰ as well as the size of a binge in bulimic subjects⁴⁸ but long term use of opiate antagonists are ineffective in this disease. Whilst plasma β -endorphin levels have been shown to rise in obese subjects,⁴⁹ they are also increased in anorexia nervosa.⁵⁰ Therefore, not all the human and animal data point in favour of a direct role for opiate peptides⁵¹ but the evidence is strong concerning dynorphin activated κ receptors in PVN and that the opioid system is active in humans.³⁹

Does hunger stimulate opiate secretion which in turn activates feeding or does feeding *per se* cause opiate secretion? Probably both mechanisms operate. If endogenous opiate levels increased with feeding this would provide an explanation for much of the pleasure associated with eating. The following gives evidence that opiates could be involved: a) Hypothalamic β -endorphin secretion is increased when highly palatable food is given to rats⁵² although secretion is also elevated by starvation; b) Patients with bulimia often describe their binging and purging as pleasurable;⁵³ c) Stress induced eating can be

evoked by tail pinch or swimming in laboratory animals and has been found to activate endorphin secretion.^{54 55} On suspension of stress-provoked eating in rats a withdrawal syndrome is seen similar to that observed after opiate addiction,⁵⁴ from which it has been suggested that obesity may result from auto-addiction to endogenous opioids.⁵⁶ The obvious drawback with these explanations is that both pain and exercise are suspected to cause increased endorphin release in their own right; d) Enkephalin is found in all areas of human gut, especially the antrum,⁵⁷ both in neurons and open-ended secretory cells. It has been proposed⁵⁸ that in states of obesity the duodenal receptor secretory cells overproduce and release excess enkephalin (or fail to degrade it rapidly enough), and that this would have an effect comparable to morphine; e) It has been reported⁵⁹ that hydrolysates of wheat gluten and α -casein contain peptide fragments with opioid activity. Some of these fragments, sometimes called "exorphines", are likely to be produced normally within the stomach, and are protease resistant, and they might therefore reach the brain.⁶⁰

Exercise

Exercise produces a sense of well being and at least three exercise related phenomena may involve endorphins; the athlete's "high", increased pain tolerance, and addiction to exercise. The runner's "high" is a well recognised phenomenon sometimes compared to the state of euphoria and enthusiasm experienced after opiate consumption. In the rat, endorphin-receptor occupancy increases after acute exercise^{61 62} whilst there is elevation of plasma β -endorphin⁶³⁻⁶⁸ and leu-enkephalin.⁶⁹ In human studies, mainly in trained runners, β -endorphin, ACTH, prolactin and growth hormone levels all increase.^{65 67 70} It appears that high intensity exercise substantially elevates plasma β -endorphin in 30-60 seconds^{71 72} but moderate exercise for up to one hour may have no effect.^{73 74} There is less agreement concerning endorphin levels and adaptation to chronic exercise.⁷⁵ One study⁷⁶ confirmed an increased β -endorphin after a marathon run, but found that the levels did not elevate so much in subsequent races, as if some form of adaptation had taken place. Mood elevation is well documented, particularly in depressed patients⁷⁷⁻⁷⁹ and because of this, exercise programmes have been used with some success in the treatment of depression.^{80 81} Conversely, naloxone administration before exercise abolishes the sense of well being.⁸² There is no doubt that exercise has mood elevating effects but whether this is entirely endorphin-related is uncertain. During exertion there is release of noradrenaline, dopamine, serotonin and prolactin.⁸³⁻⁸⁵ Corticosteroids are also secreted and could have mood elevating effects presumably independent of endorphin.

Exercise induced analgesia has a well defined relation to opioids. There is strong evidence from animal⁸⁶ and human⁷⁰ studies of an increased pain threshold after exertion. Naloxone reverses the "suppressed" ischaemic pain of exercise.^{70 87} Addiction to exercise may be defined as a pleasurable activity associated with tolerance and withdrawal—then exercise and running would appear to comply.^{78 81 88 89} Morgan⁹⁰ described eight cases of running addiction where devotion to jogging assumed a higher priority than commitment to work, family, interpersonal relations and medical advice. Those forced to stop running became depressed, anxious and extremely irritable. It has been suggested that the psychological profile of addicts of either type—narcotic or exercise—have many similarities.⁷⁸ Unfortunately there are no studies of endorphin levels during exercise withdrawal but it is very likely they

would fall. Because plasma β -endorphin levels have universally been shown to increase with exercise, especially running, Steinberg⁷⁹ concludes that exercise has reward value and its effects mimic those of acute or chronic opiate exposure.

Although endorphins are probably major agents in promoting exhilaration other neurotransmitters probably participate in the process—particularly catecholamines such as noradrenaline and dopamine^{4 91}—hence the common observation of heightened sexual sensation when associated with either fear of discovery or amphetamine-like drugs.

The functions of adrenaline and nor-adrenaline were probably viewed as highly complex until Cannon proposed a fundamentally simple "fight and flight" model. By the same token endorphins have diverse functions but this does not detract from what appears to be a major function as "pleasure peptides". Other well established endorphin related functions which are not directly enjoyable such as pain relief, blood pressure regulation and temperature control could be viewed as indirectly promoting or associated with pleasure in much the same way as, for example, adrenaline raises blood pressure and suppresses digestion in assisting fight and flight.

It has been proposed that the prime purpose of human behaviour is to preserve the human genome.⁹² For this it is essential to procreate; hence it is logical that the most enjoyable aspect of life (for most of us!) is heterosexual intercourse. The "drive" for this is maintained probably by the endorphinergic system in the brain. Whilst we protect ourselves from common danger by "fight and flight"—hence the adrenergic system—we seek pleasure through the endorphinergic. When we are not indulging in actual procreation, various substituted forms of pleasurable behaviour are sought on a sliding scale of pleasurable, such as, consuming opiate drugs or alcohol; eating beyond satiety; exercise. Interestingly, the higher up the "pleasure scale" the activity is, the greater are the social restrictions. Casual observation of human night-life activity in a large city will demonstrate that in leisure hours most people are seeking ways (both legal and otherwise) of elevating cerebral endorphins. It is therefore probable that other enjoyable activities involve the same endorphinergic system, for example, listening/dancing to music, smoking, religious experience, theatre, gambling and the cinema and are thus fundamental to human survival.

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