Biomed & Pharmacother (1993) 47, 311-320

Dossier "Endorphins"

Physiology of β-endorphins. A close-up view and a review of the literature

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Summary – When an endogenous morphine, β-endorphin was discovered ten years ago, the fact that this morphine is present in the brain and many other tissues suggested to neurobiologists that these peptide opiates play a role which goes beyond that of a simple modulator of the perception of pain. β-endorphin is a neurohormone which is secreted by the pituitary gland and reaches all tissues present in the body by diffusion. Many laboratories have investigated variations in serum levels of β-endorphin under widely varying physiological or pathological conditions. Many references to these studies in the literature have thus demonstrated that β-endorphins play a role in certain behavioural patterns (stress, alcoholism), in obesity, diabetes and psychiatric diseases. In fact, the activity of β-endorphins would appear to have an interesting role to play and are a promising feature in the treatment of cerebral aging; in this field, β-endorphins act not only as neuroregulators of other neurotransmitting substances but also, *via* calcium channels, exert an effect on the walls of cerebral arterioles. *In situ*, the role of β-endorphins at the ionic channel level has been studied using the patch-clamp technique. In 1991, E Neher and B Sakmann received the Nobel Medicine and Physiology Prize for this work. β-endorphin, which may be the "missing link" between the neuron and the wall of the arteriole, must be considered as being a fundamental neurotransmitter in the same way as well-known substances such as noradrenaline, acetylcholine, serotonin, dopamine and the GABAergic system are also neurotransmitters.

β-endorphins / physiology / neurotransmitter / pain / ionic channel

A few points concerning our knowledge of opiate receptors and endomorphines

Brief history

In 1973, three groups of researchers demonstrated that opiate receptors able to recognise specifically morphine and its natural or synthesized derivatives were present in the central nervous system: Pert and Snyder [54], Simon *et al* [66] and Terenius [74]. The fact that these endogenic receptors are present led researchers to seek, within the central nervous system, endogenic components capable of mimicking the action of morphine by binding to opiate receptors.

In 1975, Huges and Kosterlitz [35] were the first workers to isolate and identify opiate substances present in the brain; these were two pentapeptides with morphinomimetic properties: methionone-enkephalin and leucine-enkephalin. A few months after the discovery and enkephalins, Li and Chung [44] isolated from camel pituitary glands a peptide comprising 31 amino acids and at its amino-terminal extremity the metenkephalin sequence. β-endorphin represented the 61 to 91 amino acid sequence of β-lipotropin (β-LPH), which is colocated at the anterior pituitary level with the adrenocorticotrophic hormone (ACTH). In 1977, a common precursor for these two hormones was discovered and is now known as pro-opiomelanocortin.

Discovery of opiate receptors

Many biochemical and pharmacological data pointed towards the existence of morphine receptors. In fact, it was seen that a low concentration of morphine and certain morphinomimetics was sufficient to produce an effect and this suggested that morphine exerted effects at very specific

binding sites. If binding had already occurred at these sites, physicochemical reactions then a pharmacological response would follow.

Two research pathways logically followed: identification and localisation of opiate receptors in the brain [1, 42, 74], isolation and purification of endogenous opiates.

Using membranes isolated from cerebral tissue homogenate which were incubated with a radioactive opiate, Goldstein *et al* [28] demonstrated that only 2% of radioactive opiate binding was stereospecific, the receptors being localized at the synaptic membrane level and in certain neurons. The same technique was used to study the stereospecific binding ability of agonists [66, 73] or antagonists [53]; it was shown that opiate receptors are present in the central nervous system and are highly specific.

Autoradiographic techniques have made it possible to localize elective sites of morphine receptors [2, 52].

Endomorphines

When it was demonstrated that opiate receptors are present in the central nervous system, endogenous ligands called endomorphines were discovered shortly afterwards. These substances are present in the brain and in many other tissues and act on opium alkaloid receptors. The term endogenous opiate or endomorphine designates natural peptides containing the same tyr-gly-gly-phe amino acid sequence and, as is the case in certain peptide hormones or neuromediators, these peptides are derived from the cleavage of another peptide precursor: pro-opiomelanocortin (POMC), pro-enkephalin A and pro-enkephalin B (prodynorphin). At present, two groups are being studied: the β-endorphin group and enkephalin.

β-endorphin. β-endorphin is an endogenous peptide opiate comprising 31 amino acids and is a derivative of pro-opiomelanocortin (POMC). POMC contains β-lipotropin (which itself contains various endorphins) and is also the precursor of several pituitary hormones: melanocyte stimulating hormone (MSH), adrenocorticotrophin (ACTH), gamma-lipotropin (LPH). The maturation of POMC in the adenohypophysis leads to ACTH and β-lipotropine production; the latter then undergoes cleavage leading to the production of β-endorphin and gamma-endorphin. At the level of the intermediary lobe of the pituitary gland, cleavage continues until shorter peptides are produced: MSH and β-endorphin (fig 1). β-endorphin and certain elements derived from POMC are then found in neurons which have cellular bodies located only in the medio-basal pituitary area and in the caudal area of the solitary tractus nucleus. The nerve fibres derived from the pituitary gland project throughout the brain.

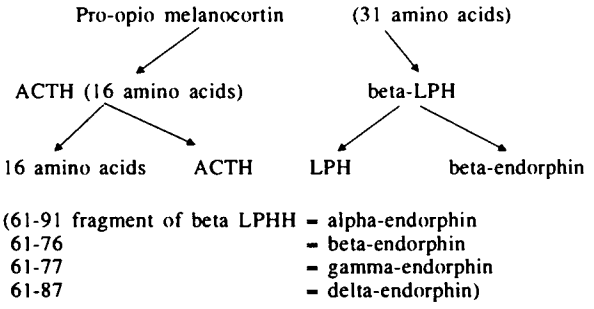

Fig 1. The β-endorphin family.

Enkephalins. Enkephalins were discovered before β-endorphin and are known to be pentapeptides which differ only at position 5 amino acid level: the pentapeptides leucine and methionine-enkephaline. Enkephalins are derived from a large molecule, pro-enkephalin, which is present in large quantities in the adrenals and to a lesser extent in the brain.

Dynorphin. Dynorphin is a peptide comprising 17 amino acids. Initially, only the 1 to 13 amino acid sequence could be identified and was called dynorphin. Later, some other peptides isolated – alpha and β-neo-endorphin – were found to have a commmon precursor: prodynorphin. Maturation of prodynorphin leads to the production of various substances according to the location within the brain [27].

Other endomorphines. Other endogenous substances with opiate activity have been isolated: humoral endorphin (detected in the brain, the blood and the cerebrospinal fluid), opionate-like pronase P, anodyn and kyortorphine dipeptide.

β-endorphin exerts many effects

The functions of endomorphines are numerous and can be attributed to the fact that they interact with hormonal systems, wherever they are local-

ized and secreted. Thus, we can cite enkephalins and ACTH localized in the adrenals and β-endorphin secreted at the same time as ACTH and MSH. β-endorphin has a two-fold action: firstly a peripheral hormone action and secondly a neuroregulating action *via* interference with other neurotransmitters (fig 2).

β-endorphin and control of pain perception

When one considers morphins' well-known properties, it appears obvious that pain control is one of endogenous morphins' properties. It should be borne in mind that at the brain stem level there is a network composed of periaqueduct grey matter from the mesencephal and adjacent reticular formation and that this network is capable of specifically inhibiting pain; these structures project onto the spinal cord and β-endorphin acts as a mediator. This pathway is serotoninergic and inhibits spinal neurons which are normally stimulated by noxious stimuli. A pain-modulating pathway which is noradrenergic does exist at the dorsal-lateral bridge area of the spinal cord.

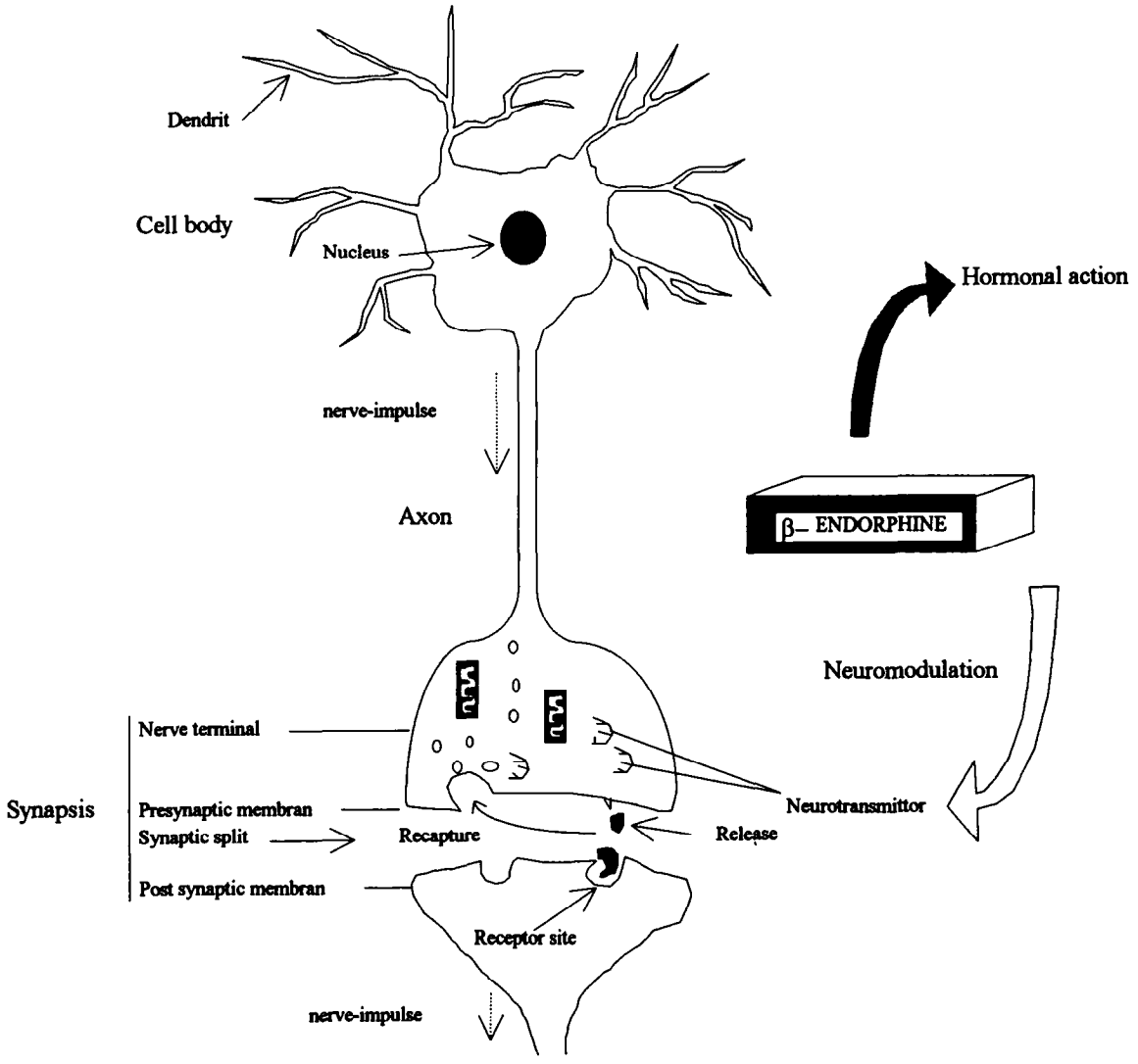

Fig 2. Physiological role of endorphins.

Moreover, in all of these areas involved in the modulation of pain, endogenous peptide opiates endowed with analgesic properties are present and reduce reactions to noxious influences. Enkephalinergic neurons act as mediators and inhibit the transmission of nerve impulses and the release of neuromediators at the neuron synapse level (the latter being pain-inducing). Enkephalinergic neurons act on presynaptic endings in order to prevent the release of substance P (pain mediator) by certain neurons in the anterior horn of the spinal cord. In this way, when pain occurs at skin level, conduction to the brain is prevented (fig 3).

Silent myocardial ischaemia

Many studies have sought to evaluate the role of opiate derivatives in asymptomatic myocardial ischaemia compared with the symptomatic painful form [65]. The high level of β-endorphin measured where silent myocardial ischaemia is present has been put forward as the physiopathological basis for this particular syndrome [70]. β-endorphin levels have been measured before and after effort tests in three groups of patients (one group suffering from angina, one group of asymptomatic patients and one group of healthy volunteers). In patients with symptoms, β-endorphin levels are lower than in the other two groups and this was true both before and after exercise; in these patients with symptoms, where pain peaked, β-endorphin concentrations were lower than those present between episodes of pain. No significant difference in β-endorphin levels was observed in the two groups of asymptomatic patients. This study suggests that low β-endorphin levels are related to angina and hypersensitivity to pain in patients suffering from angina. There is a positive correlation between plasma β-endorphin levels and the onset of pain [31, 35].

Other pain

β-endorphin in circulating blood produces pain sedation through inhibition of electric responses of sensitive motor fibres. Whereas increased β-endorphin during surgical stress positively correlates with better pain tolerance, it has been demonstrated that the administration of an exogenous opiate such as Fentanyl reduces plasma concentrations of β-endorphin by competition processes. This reduction in β-endorphin concentrations may play a role in trigeminal neuralgia, migraine and rheumatoid arthritis [32, 33].

In situ injection of exogenous β-endorphin relieves artificially-induced inflammation in rats.

β-endorphin and behavioural status

General stress. In stress-inducing situations, firstly the adrenals and the enkephalins react by

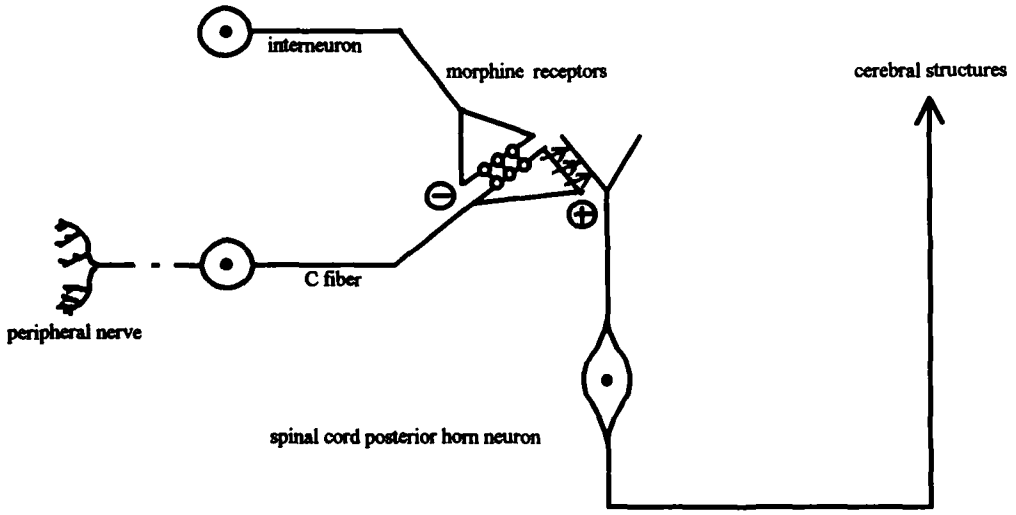

Fig 3. Enkephalinergic (ENK) neurons inhibit pain transmission by preventing substance P (SP) release.

releasing adrenaline, then the adrenal cortex reacts under the effects of ACTH, releasing corticosteroids. β-endorphin is released at the same time as ACTH. There is thus a link between stress-induced situations and endogenous morphines and this link has been extensively studied.

Surgical stress. In patients undergoing abdominal surgery, the concentration of β-endorphin rises significantly and correlates perfectly with a simultaneous rise in plasma cortisol levels. These results appear to indicate that endorphins are involved where acute stress is present and demonstrate the relationship between plasma β-endorphin and the hypothalamus-pituitary-adrenal axis [17, 22].

Stress and the oestrous cycle. Stress can lead to decreased serotonin levels which can in turn produce disturbances in the oestrous cycle which could be attributed to increased β-endorphin levels already observed where stress is present. Furthermore, β-endorphin stops cortisol secretion and reduces the harmful effects of the latter [16].

Behaviour with respect to food and alcohol. In patients with anorexia, neuropeptide Y, CRH and β-endorphin dysfunction have been demonstrated at the cerebrospinal fluid level and this could at least partially explain the symptoms present in anorexia. Thus, disturbed CRH leads to raised cortisol levels while abnormalities in the NPY system can lead to the occurrence of amenorrhoea [77].

In patients with Wernicke-Korsakov syndrome, excessive alcohol consumption leads to raised β-endorphin concentrations in the mammillary bodies that are seen on autopsy [59, 71].

Maternal behaviour. In the mother, maternal behaviour which commences at the moment of birth, is attributed to a series of neuroendocrine and neurochemical reactions at the cerebral level and in particular ocytokinergic and β-endorphin peptide systems acting on specific cerebral areas, controlling maternal behaviour, are thought to be involved [41].

Other studies have confirmed that ocytocin and β-endorphins do determine maternal behaviour; these studies emphasise the importance of a decrease in high cerebral β-endorphin concentrations at the time of birth. This decrease is vital in inducing maternal behaviour. It has also been shown that morphine blocks this onset of maternal behaviour [58].

β-endorphin and cerebral aging

Symptoms of cerebral aging (ideomotor slowing, vigilance disorders, mood fluctuations, disorders of balance) constitute a handicap which can present a major drawback in daily life. One explanation for these disorders is that of decreased β-endorphin secretion where cerebral aging is present [11]. In elderly subjects with chronic dementia, reduced β-endorphin secretion has been observed following a brief stimulus (cold test). This drop in β-endorphin secretion is not present in the non-demented elderly or in young subjects. Although basal β-endorphin levels do not differ with age, circadian rhythm is less marked and the acrophase occurs 3 hours earlier in young compared with elderly subjects [10]. This has been confirmed in a study concerning hyperdypsia in the elderly and in another study involving patients with chronic cerebrovascular insufficiency [68].

In elderly patients, the lowered β-endorphin levels encountered at the pituitary level are attributed to a loss in neuronal immunoreactive β-endorphins. In the mouse, this neuronal loss, due to the normal aging process is about 35%. In mice with a pituitary tumour, no additional neuronal loss is present. This decrease in endorphinergic neurons is thus part of the normal aging process but does not vary if other disease is present [49].

β-endorphin and memory

Within the endomorphine system, β-endorphin plays a fundamental physiological role in the construction of memories (enkephalins are not released during the learning process and dynorphin does not affect memory). The synthesis of β-endorphin in the brain takes several hours whereas depletion, caused by an exercise involving the memory, takes less than six min. Following an exercise, the synthesis of β-endorphin takes place at the same time as the synthesis of proteins in the brain. Naloxone blocks the effects of β-endorphin on memory through competitition [36]. Where stress is present or where memorizing capacity is altered, β-endorphin, which reduces stress, increases mnemonic capacity to retain. The administration of β-endorphin could also be of value in re-establishing memories in the amnesia syndrome in man [36].

ACTH and adrenalines' amnesia-inducing effects could be modulated by the release of β-endorphin [35, 57]. The mechanisms which explain the role of endorphins in man have yet to be totally elucidated, but it is certainly likely that endogenous opiates, ACTH and vasopressin all

play important roles in memory and learning processes [80].

Many studies have been performed in healthy subjects, using variable doses of naloxone administered intravenously and compared with a placebo. In the low dose range (10 to 20 mg and 0.8 to 1.6 mg range) [18, 76], auditory and visual short-term memorizing and concentration remained unchanged. However, when high doses of naloxone (0.3 to 4 mg/kg) were administered, a significant dose-related effect was observed in behaviour and at hormonal and physiological levels [13]. Other studies concerning behaviour with respect to food have shown that activation of β-endorphin release raises food consumption. Thus, it is likely that the serotinergic system interacts with and exerts an inhibiting effect on β-endorphinic neurons [56].

Parkinson's disease

In Parkinson's disease, neurotransmitters other than dopamine may play an important role in physiopathology and therapy. A post-mortem study performed on cerebral tissue has suggested that the anomaly in the enkephalin system present in this disease could be attributable to damage at the striatum nuclei level [6]. It would also appear that the dependence of Parkinsonian patients on dopamine is a secondary effect of this lack of enkephalins. Given the importance of endomorphines in motor function, behaviour and memory, it can easily be understood that where dysfunction of this system occurs, symptoms become more marked [67].

β-endorphin and psychiatric disorders

Panic reactions. In patients with panic disorder, the administration of serotonin produces effects which suggest that these patients are hypersensitive at serotonin receptor levels. In all subjects, the administration of serotonin raises cortisol and β-endorphin plasma levels [14].

Depression – melancholia. In depressed patients, there is no β-endorphin response when a perfusion of CRH is administered. This suggests that abnormal feedback is present at the cerebral level (more than at the pituitary level) [79]. β-endorphin plasma levels and free cortisol urinary levels measured following a dexamethasone test suggest that highly specific, highly sensitive tests should be used to diagnose severe depression in melancholia. The fact that no "braking" of secretion of these two hormones is present following dexamethasone administration is the best way of confirming that the hypothalamic-adrenal-pituitary axis is no longer in control where melancholia is present [45, 46].

Suicide. It has been demonstrated that asymmetrical distribution of β-endorphin occurs in the brain of those people who attempt suicide: β-endorphin levels are lower in both the left temporal and frontal lobes in these subjects [61].

Schizophrenia. The concentrations of alpha and gamma-endorphins in the hypothalamus are significantly higher in schizophrenics (72.9 and 50.5% respectively) while β-endorphin levels are comparable. As β-endorphin is a precursor for alpha and gamma-endorphins, these results tend to indicate that a β-endorphin metabolic anomaly is present at the cerebral level in this disorder [78].

Self-mutilation – stereotypy. Many studies have investigated the role played by disturbances in the endorphinic system in the onset of psychotic behaviour patterns such as self-mutilation and stereotypy. From a therapeutic point of view, it would seem that the administration of exogenous β-endorphins could be of value where usual treatment has failed [60].

Other effects exerted by β-endorphins

β-endorphin and physical exercice. β-endorphin's beneficial effects during endurance sports have been described and include improved mood and reduction in pain [26, 62]. A significant rise in β-endorphin, β litropin and cortisol plasma concentrations have been measured after a race and the highest increase was observed following a long-distance race [55].

Opiate drug addiction. Different β-endorphin levels are present in the hypothalamus and pituitary gland of foetuses of drug-addicted mothers; at birth, no such difference is present. This would suggest that there is a spontaneous return to normal basal levels as soon as the newborn infant is no longer exposed to chronic maternal opiate consumption [20].

β-endorphin and the oestrous cycle. High levels of β-endorphin are considered to be related to certain types of amenorrhoea in which stress is present and low levels are considered to be related

to ovarian polycysts when a premenstrual syndrome or menopause is present.

β-endorphin and immunity. Melanotonin is well known for its biological clock regulating effects and is involved in the onset of immune functions in man – in this process β-endorphin acts on lymphomorphines. Other studies have suggested that interleukine-1s interact in the central nervous system and that there is also an interaction with peripheral production of lymphokine [9].

Substances which interfere with the secretion of β-endorphins

Glucose and obesity. The fact that endorphins play a role in food intake has given rise to the possibility that β-endorphins may play a role in the pathogenesis of obesity in man. This theory is based on the fact that opiate antagonists (naloxone and naltrexone) are capable of reducing the quantity of food consumed and that raised β-endorphin levels are observed in obese children and adults [23]. Where obesity is present, hyperproduction of endomorphines stimulates insulin secretion following food ingestion [75]. This hypersecretion of insulin is accompanied by increased C-peptide and moderately lowered glucose levels [25, 75]. The influence of synthetic β-endorphin on insulin and glucagon responses to a glucose perfusion has demonstrated that, *via* cAMP (the second messager in glucose's chemical reactions), β-endorphins produce hyperglycaemia by stimulating glucagon secretion and inhibiting insulin release (whether basal insulin or insulin response to hyperglycaemia is considered) [24, 48].

Nicotine. In heavy smokers, high levels of β-endorphin and cortisol are present in the plasma, but in moderate smokers this is not the case. Nicotine-induced uneasiness where the nitocine level is above 2.4 mg and also raised cortisol and β-endorphin levels have been reported. Administration of 1 mg of nicotine to non-smokers does not induce these effects [21]. Elevated β-endorphin concentrations are observed in heavy smokers only.

Other substances. Several drugs used in various therapeutic fields stimulated β-endorphin secretion: calcitonin [12, 51, 72], fublomedil [5, 7, 19] and clonidine [19].

This property means that radioimmunological blood assays are required in patients taking these drugs in order to evaluate the circulating fraction equivalent to β-endorphin's neurohormonal activity.

The clinical repercussions can be superimposed onto β-endorphin's numerous effects and cover actions ranging from central analgesia to certain neuropsychological effects. The analgesic effect attributed to calcitonin is thus likely to be serotonin-mediated.

Given β-endorphin's considerable therapeutic potential, many research teams all over the world are at present studying the pharmacoclinical value of molecules affecting β-endorphin secretion.

Endomorphines and ion currents [7, 29]

In 1991, Erwin Neher and Bert Sakmann [50] received the Nobel Medicine and Physiology Prize for their work involving the development of the patch-clamp technique. By individualizing a fragment of cell membrane using a micropipette, these authors were able to isolate and study membrane ion currents (fig 4).

β-endorphin inhibits calcium currents

Both humoral and nervous control of cerebral circulation depend on variations in the arteriole diameter which in turn regulate cerebral blood perfusion. The smooth muscle fibre of the arteriole wall contracts at the cerebral parenchyma level only if the intracellular concentration of free Ca++ is raised, that is, if Ca++ enter the cell in massive quantities. Intracellular calcium activates coupled actine-myosine which enables smooth muscle fibres to contract. β-endomorphine acts on both cerebral vasomotor function (vasodilating ef-

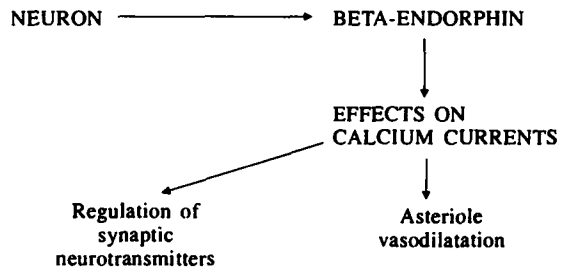

Fig 4. The effects of endorphins on ionic channels.

fect) by preventing calcium from entering the cell, and also acts as a neuroregulator by affecting synaptic calcium channels which are activated when neurotransmitters are released. This mechanism of action could explain the beneficial effects of β-endorphin on memory and cerebral aging in behavioural problems.

β-endorphin stimulates potassium currents

β-endorphin binds to mu opiate receptors which stimulated potassium currents, thus promoting potassium input at the hypothalamic neuron level. Opoid peptides can also modulate their own secretion *via* an ultra short retro-control loop [40]. Mu receptors probably also exert an inhibiting effect on calcium currents [64].

Conclusion

The field of action of endomorphines appears to be enormous and highly varied. Endomorphines are involved where pain, cerebral aging, behaviour with respect to feelings, food and emotions and psychiatric disorders are concerned. These endomorphines are found in many areas of the brain and can behave as modulators or hormones or mediators – this explains their wide range of activity. These molecules were discovered relatively recently and already occupy an important place in neurobiology. Much promising research on endomorphines is taking place at the moment, particularly in the field of cerebral activity: brain vascularisation (action on calcium currents), memory, learning processes and behaviour.

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