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Review

Neuropathic pain: a possible role for the melanocortin system?

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Abstract

In humans, damage to the nervous system can lead to a pain state referred to as neuropathic pain. Here, we give a short overview of the clinical picture and classification of neuropathic pain and highlight some of the currently known pathophysiological mechanisms involved, with special emphasis on neuropeptide plasticity. In this context, we discuss a specific group of neuropeptides, the melanocortins. These peptides have been demonstrated to play a role in nociception and to functionally interact with the opiate system. Recently, we demonstrated that spinal melanocortin receptors are upregulated in a rat model of neuropathic pain and that blockade of the melanocortin MC_4 receptor has anti-allodynic effects in this condition, suggesting that the melanocortin system plays a role in neuropathic pain. A natural agonist of melanocortin receptors is α-melanocyte-stimulating hormone (α-MSH), derived from the precursor molecule pro-opiomelanocortin (POMC). Cleavage of this precursor also yields β-endorphin, which is co-released with α-MSH in nociception-associated areas of the spinal cord. We hypothesise that melanocortin receptor blockade attenuates a tonic influence of α-MSH on nociception, thus allowing the analgesic effects of β-endorphin to develop, resulting in the alleviation of allodynia. In this way, treatment with melanocortin receptor antagonists might enhance opioid efficacy in neuropathic pain, which would be of great benefit in clinical practice. © 2001 Published by Elsevier Science B.V.

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1. Neuropathic pain: symptoms and classification

Probably, the best definition of pain was formulated by the International Association for the Study of Pain: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994) (for further definitions, see below).

Acute pain, elicited by the activation of nociceptors in the skin or other tissues of the body, may function as a warning of potential or ongoing tissue damage and, thus, the ability to experience pain serves to protect the organism. Typically, pain resolves as the injury heals. However, in some cases, pain can become persistent, either as a result of injury so extensive that it surpasses the healing ability of the body, or as a result of damage to the nervous system itself. The latter type of—maladaptive—pain is known as neuropathic pain and may result from injury to the peripheral (e.g. peripheral nerves, plexus, nerve roots) or central (e.g. spinal cord, brain) nervous system.

Although the causes of nervous system injury may vary (e.g. trauma, ischaemia, compression, infection, etc.), symptoms of neuropathic pain are common and include both negative and positive symptoms. Negative symptoms consist of diminished sensitivity to pain or stimulation (hypoalgesia and hypoesthesia). Positive symptoms are as follows. (1) Spontaneous sensations: stimulus-independent pain, which can be continuous (often described as burning, stabbing, cutting, prickling) or paroxysmal (described as shooting, electric-like) and spontaneous abnormal sensations, such as numbness, tingling, prickling or itching feelings (dysthesias and paresthesias). (2) Evoked sensations: increased responses to painful stimuli, such as skin heating and cooling, or strong mechanical stimuli (hyperalgesia), and pain due to normally nonpainful stimuli, such as mild warming, cooling or touch (allodynia). These symptoms are amongst the most serious and invalidating symptoms of neuropathic pain. They can occur alone or in

Abbreviations: CRPS, Complex Regional Pain Syndrome.

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combination. In clinical practice, it is very difficult to differentiate between allodynia and hyperalgesia. Also, because the stimuli are painful, the patient is often difficult to examine. All symptoms share in common that their distribution pattern is consistent with the underlying neural dysfunction, i.e. pain is experienced in the area innervated by a nerve root (radicular) or peripheral nerve (dermatome, glove and stocking area).

Because of its heterogeneity, neuropathic pain is difficult to classify. In general, neuropathic pain syndromes are classified according to the aetiology of the underlying injury. Recently, Dellemijn (1997) defined three different groups of syndromes, based on the underlying mechanisms. (1) Nociceptive nerve pain, pain due to an inflammatory process activating the 'nervi nervorum', innervating the nerve sheath, epi- and perineurium. This type of pain always originates in the peripheral nervous system. (2) Complex regional pain syndromes and dystrophies, which may be sympathetically maintained. (3) Deafferentation pain, pain due to damage to the nervous system, without an inflammatory component, stemming from either the peripheral or central nervous system. Other terms used to define central pain are "thalamic pain" or "dysesthetic pain" (see Boivie, 1999).

Not every injury to the nervous system has the same effect, i.e. not every patient who sustains a trauma to a peripheral nerve or an infarction in the spinal cord develops neuropathic pain. Therefore, at present, there is a tendency towards a more "symptom-and-sign"-based approach (Woolf and Mannion, 1999; Nicholson, 2000) instead of the "cause-and-effect" classification based on aetiology. Similarly, the efficacy of drugs in different types of human pain syndromes generates another possible classification of neuropathic pain, based upon the response to different pharmacological agents (Sindrup and Jensen, 1999). For instance, mechanical allodynia, irrespective of its cause, may be reduced by NMDA receptor antagonists (Felsby et al., 1996), whereas lancinating pain may be best treated with anti-convulsants (Swerdlow and Cundill, 1981). Such an approach might not only improve our understanding of neuropathic pain, but might also give us a tool to establish the pharmacological treatment that best fits the individual patient's needs (Attal, 2000). However, in the search for potential new treatment strategies, it is important to understand the pathophysiological mechanisms involved in neuropathic pain.

2. Pathophysiology of neuropathic pain

It is beyond the scope of this article to give a detailed overview of the currently known mechanisms underlying neuropathic pain (for review, see Attal and Bouhassira, 1999; Woolf and Mannion, 1999; Baron, 2000). In summary, they include both peripheral and central systems, as described below.

2.1. Peripheral mechanisms

2.1.1. Primary afferent sensitisation and recruitment of silent nociceptors

In tissue injury, nociceptors may become sensitised, resulting in a decrease in the threshold for stimuli and an increased response to suprathreshold stimuli. The neurochemical basis for primary afferent sensitisation involves the release of inflammatory mediators, such as amines, prostaglandins, leukotrienes and bradykinins (see Levine and Reichling, 1999).

In addition, there are nociceptors that normally have a very high threshold for activation (so-called "silent" or "sleeping" nociceptors (Schaible and Grubb, 1993)). These receptors can become sensitised, and thus recruited, upon prolonged noxious stimulation, as is the case in tissue damage with the local release of inflammatory mediators, for which a number of receptors are found on peripheral nerve fibres (Coggeshall and Carlton, 1997).

2.1.2. Sympathetically induced discharges

An interaction between primary afferent terminals and sympathetic postganglionic efferent terminals also plays an important role. Noradrenaline released from sympathetic terminals via the activation of autoreceptors causes the production of eicosanoids, which diffuse to the sensory neuron, resulting in sensitisation (Gonzales et al., 1991). Moreover, damaged sensory neurons become sensitive to catecholamines by expressing α-adrenoceptors (Hu and Zhu, 1989). Nerve injury also induces sprouting of sympathetic axons into the dorsal root ganglion, forming baskets around the cell bodies of primary afferents (McLachlan et al., 1993). Together, this might represent a mechanism by which sympathetic activity maintains discharge in primary afferent fibres.

2.1.3. Spontaneous discharges in damaged primary afferents

Injured axons start discharging spontaneously. After axotomy, the regenerating nerve forms sprouts. In these regenerating sprouts, ectopic discharges are observed. These can be purely spontaneous (due to instability of the membrane potential) or caused by occult stimuli, such as circulating catecholamines or light mechanical stimulation (e.g. the beating of an nearby arteriole), because these sprouts also become more sensitive to mechanical, thermal, ionic or catecholamine stimulation (Kajander and Bennett, 1992). An ongoing local inflammatory process could also contribute to these ectopic discharges, because local application of eicosanoids to injured primary afferents can cause C-fibre discharge (Devor et al., 1992). These ectopic discharges are also observed in the dorsal root ganglion, where the cell bodies of the axotomised primary afferents lie (Kajander et al., 1992).

2.1.4. Collateral sprouts

Neighbouring undamaged primary afferents form new sprouts that innervate denervated areas of skin. These areas of skin are shown to become hyperalgesic and allodynic to mechanical stimuli (Kingery and Vallin, 1989; Vallin and Kingery, 1991). It is not clear whether this is a peripheral (these newly formed sprouts can exhibit some of the abnormalities seen in neuroma sprouts) or central mechanism, or a combination of both.

Taken together, these changes result in an increased afferent barrage, which, in turn, can lead to hyperexcitability of dorsal horn neurons (see below).

2.2. Central mechanisms

2.2.1. Excitotoxicity

A high rate of discharge in damaged small afferent fibres can produce a state of central hyperexcitability. The abnormal discharge causes an excessive release of excitatory amino acids (glutamate, aspartate), resulting in high levels of activity of glutaminergic synapses (mediated by the NMDA-type receptor) (Woolf and Thompson, 1991). Subsequently, small-to-medium-sized neurons in laminae I–III, presumably inhibitory interneurons, undergo degenerative changes (and become so-called 'dark neurons'). This excitotoxicity results in a state of increased excitability, due to disinhibition (Sugimoto et al., 1990; Mao et al., 1997).

2.2.2. Wind up

Another mechanism inducing central sensitisation is the so-called "action potential wind up" or simply "wind up" in which spinal cord neurons receiving small-fibre input generate more action potentials after each successive stimulus of a pulse-volley. The key receptor in this process is the NMDA receptor (Baranauskas and Nistri, 1998).

2.2.3. Reorganisation of dorsal horn synaptic connectivity

After peripheral nerve injury, large myelinated afferents (of the Aβ type, or low-threshold mechanoreceptors) begin to sprout into lamina II of the dorsal horn, where postsynaptic targets usually receive only small afferent fibre (nociceptor) input (Woolf et al., 1992, 1995). This reorganisation may contribute to the touch-evoked pain that can follow nerve injury, because an area that normally only receives noxious information now obtains input from non-noxious tactile stimuli. The misinterpretation of this information by the nervous system as noxious input, thus, provides an anatomical basis for mechanical allodynia.

2.2.4. Spontaneous discharge and altered thresholds

Spinal neurons that connect with axotomised primary afferents (thus lacking input from the periphery) often discharge spontaneously. Cells receiving input from uninjured neighbouring axons may show abnormal responses and lowered thresholds. Similar abnormal responses and altered thresholds are also observed at higher levels, such as in spinothalamic tract neurons and in the thalamus (Guilbaud et al., 1990; Laird and Bennett, 1992, 1993; Palecek et al., 1992). It thus appears that central homeostatic mechanisms detect the failure of input and increase the excitability of central cells in an attempt to compensate for the diminished input (for review, see Wall, 1991).

2.2.5. Neuropeptide plasticity

In addition to the above-mentioned changes, the levels of several neuropeptide genes and their products are regulated in response to nerve injury. This neuropeptide plasticity can also contribute to the altered transmission of sensory information observed in neuropathic pain, because neuropeptides modulate neuronal activity in conjunction with the neurotransmitter with which they are colocalised. Thus, by acting as neuromodulators, they fine-tune the direct communication between neurons. A main event in neuropeptide plasticity is the so-called phenotypic switch of primary afferents, as reflected by an altered expression of neuropeptides, which is often accompanied by changes in their receptor levels in the dorsal horn (reviewed in Hokfelt et al., 1994).

Substance P and calcitonin-gene-related peptide (CGRP) are normally expressed by thin primary afferents conveying information from nociceptors. CGRP in sensory primary afferent neurons has an excitatory effect on postsynaptic neurons and potentiates the effect of substance P in the rat spinal dorsal horn (Miki et al., 1998). After peripheral nerve injury, the levels of these peptides are markedly decreased in primary afferents and in the dorsal horn (Nahin et al., 1994; Kajander and Xu, 1995; Honore et al., 2000). Thus, the two main excitatory peptides involved in the transmission of nociceptive information to the dorsal horn are downregulated in a neuropathic state. In adjacent intact nerves, however, CGRP is upregulated, which could contribute to the hyperexcitability of dorsal horn neurons (Fukuoka et al., 1998). Moreover, a subpopulation of dorsal root ganglion neurons associated with large myelinated fibres starts to synthesise these peptides (Miki et al., 1998; Malcangio et al., 2000).

Different response patterns have been described for a group of peptides that are normally almost nondetectable in small-diameter primary afferents. After nerve injury, there is a marked increase in the level of galanin, in both injured and spared dorsal root ganglion neurons (Villar et al., 1991; Zhang et al., 1998; Ma and Bisby, 1999). Galanin has a predominantly inhibitory effect (Wiesenfeld-Hallin and Xu, 1998) and reduces the activity of wide dynamic range neurons (Xu et al., 2000). However, galanin is also reported to be involved in the facilitation of nociceptive transmission (Kuraishi et al., 1991b) and increases the release of substance P evoked by stimulation (Kuraishi et al., 1991a).

Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) are also up-

regulated after peripheral nerve injury (Nahin et al., 1994; Dickinson and Fleetwood-Walker, 1999). Studies of nociceptive responses have revealed an excitatory role for VIP (Cridland and Henry, 1988; Wiesenfeld-Hallin, 1989), and it has been suggested that this peptide can take over the role of substance P, which is downregulated in nerve injury and, thus, maintain nociceptive transmission in the dorsal horn (Wiesenfeld-Hallin et al., 1990). PACAP, which belongs to the same peptide superfamily as VIP (Dickinson and Fleetwood-Walker, 1999), has an excitatory effect on spinal cord function as well (Narita et al., 1996; Xu and Wiesenfeld-Hallin, 1996), similar to that of the above-mentioned peptides. This list of neuropeptides that undergo upregulation or downregulation after nerve injury is far from complete, e.g. alterations in neuropeptide Y (Ma and Bisby, 1998; Marchand et al., 1999), cholecystokinin (Antunes et al., 1999; Afrah et al., 2001) and somatostatin (Noguchi et al., 1993), have been reported as well. These changes in the levels of neuropeptide messengers reflect a complex adaptive response of the organism to neuropathic conditions and might contribute to the hyperalgesia seen in patients with neuropathic pain. A group of neuropeptides not mentioned until now is the melanocortins. The melanocortin system also appears to undergo adaptations in neuropathic pain and may be a newly discovered participant in the control of this condition, as explained below.

3. The melanocortin system in pain

The melanocortins comprise a group of natural peptides all derived from the precursor molecule pro-opiomelanocortin (POMC) and various synthetically derived related peptides. In the anterior lobe of the pituitary gland, POMC is processed to form the melanocortin adrenocorticotropic hormone (ACTH), the effects of which on the adrenal gland have been long known. POMC is also expressed in the pituitary intermediate lobe, where it is processed to form the melanocortins ACTH, β-MSH and α-MSH, a peptide which plays an important role in skin pigmentation. However, aside from these effects on peripheral tissues, direct effects of melanocortins on the nervous system have been described as early as the late 1950s (Ferrari, 1958; De Wied, 1964). Demonstration of immunoreactivity for α-MSH (Jacobowitz and O'Donohue, 1978) and ACTH (Watson et al., 1978), as well as the expression of POMC in the brain (Gee et al., 1983), indicated that the nervous system has its own melanocortin system, distinct from that in the pituitary. Since then, a wide variety of effects of melanocortin has been described, including effects on inflammation, fever, nerve regeneration, grooming, social behaviour and regulation of body weight (for review, see De Wied, 1999; Adan, 2000).

An additional intriguing effect of the melanocortin system is its functional interaction with the opiate system, as suggested by several lines of evidence. Electrophysiological studies have demonstrated that melanocortins can block morphine-induced depression of evoked potentials in frog and cat nervous tissue (Zimmermann and Krivoy, 1973; Krivoy et al., 1974). Indications that melanocortins interfere with the effects of opiates also come from pharmacological studies. Intracerebroventricular (i.c.v.) or peripheral administration of melanocortins, prior to or simultaneously with morphine, attenuates the analgesia induced by morphine (Gispen et al., 1975, 1976; Wiegant et al., 1977; Smock and Fields, 1981; Contreras and Takemori, 1984). Repeated administration of morphine leads to a reduction of its analgesic potency and an apparent increase in the potency of naloxone to block the effects of morphine. The development of this opiate tolerance can be inhibited by melanocortins (Szekely et al., 1979; Contreras and Takemori, 1984). Also, melanocortins can attenuate the acquisition of heroin self-administration (Van Ree et al., 1981) and counteract opiate addiction (for review, see Alvaro et al., 1997), as demonstrated by the induction of withdrawal-like symptoms in morphine-dependent (Bertolini et al., 1981) and drug-naive (Jacquet, 1978) rats.

Apart from their interactions with the opiate system, melanocortins are also known to have direct effects on nociception. I.c.v. administration of 0.1–10 μg α-MSH in rats induced hyperalgesia in the tail-flick test, an effect lasting for 20 (0.1–1 μg) to 80 (10 μg) min (Sandman and Kastin, 1981). Similar results were obtained with 20–50 μg, i.c.v.-administered ACTH, which induced hyperalgesia in the hot plate and tail-shock tests in the rat, an effect which lasted for 80 min (Bertolini et al., 1979). In the hedgehog, high doses of peripherally administered ACTH also produced hyperalgesia (Sollertinskaya, 1997). Much lower doses of ACTH (0.5 and 1.0 μg) also caused hyperalgesia, as indicated by decreases in ear withdrawal latency from heat in the rabbit (Williams et al., 1986), although a similar dose (1.0 μg) had no effect on tail-flick latency in the rat (Smock and Fields, 1981). Also, i.c.v. α-MSH (0.25–2.0 μg) had no effect on ear withdrawal latency in the rabbit (Williams et al., 1986). A few reports claimed that melanocortins can also produce hypoalgesia. Ohkubo et al. (1985) showed that i.c.v. administration of 0.1–10 μg α-MSH in mice induced analgesia in the hot-plate test, an effect lasting 20 min. Microinjection of α-MSH in the periaqueductal grey matter also significantly reduced responsiveness to pain (Walker et al., 1980).

In spite of the growing list of the biological actions of melanocortins, the molecular mechanisms underlying these effects were largely unknown. Only since the 1980s have brain-binding sites for the melanocortins been demonstrated (Tatro and Reichlin, 1987; Tatro, 1990). Soon thereafter, the first melanocortin receptors were cloned (Chhajlani and Wikberg, 1992; Mountjoy et al., 1992), which started a new era in the field of melanocortin research. So far, five melanocortin receptor subtypes have been identified, all members of the G-protein-coupled

receptor superfamily (for review, see Cone et al., 1996; Tatro, 1996). Of these five subtypes, the melanocortin MC_3 and melanocortin MC_4 receptors are expressed in the nervous system. The melanocortin MC_3 receptor has a limited distribution in the brain and is found mainly in the hypothalamus, thalamus, brainstem and cortex. Compared to the melanocortin MC_3 receptor, the melanocortin MC_4 receptor has a much more widespread distribution in virtually every region of the brain (Gantz et al., 1993; Roselli et al., 1993; Mountjoy et al., 1994; for review, see Adan and Gispen, 1997; Wikberg, 1999). Moreover, it is the only subtype to be expressed in the spinal cord (Mountjoy et al., 1994). Binding of a radioactively labelled α-MSH analogue to rat spinal cord demonstrated that melanocortin MC_4 receptors are expressed most abundantly in the superficial dorsal horn (lamina I and II) and in the grey matter surrounding the central canal (lamina X), areas that are important in nociceptive transmission (Van der Kraan et al., 1999). In addition, mRNA encoding for POMC has been demonstrated in spinal cord (Plantinga et al., 1992; Van der Kraan et al., 1999), and the nucleus tractus solitarius has been suggested as a possible source of POMC projections to the spinal cord (Tsou et al., 1986). Interestingly, electrical stimulation of the nucleus tractus solitarius has been shown to produce pronounced analgesia (Lewis et al., 1987), suggesting that the POMC system may play a role in modulating nociceptive transmission.

Immunoreactivity for the POMC-derived peptides ACTH and α-MSH has been detected in the dorsal horn and lamina X (Tsou et al., 1986; Plantinga et al., 1992). Together, the presence of melanocortin MC_4 receptors, mRNA and cleavage products of POMC strongly suggest the presence of a functional melanocortin system in the rat spinal cord. The expression of the melanocortin MC_4 receptor in nociception-associated areas in the spinal cord suggests that this spinal melanocortin system might play a role in pain and that the melanocortin MC_4 receptor might be a potential target in the ongoing search for new analgesics.

None of the natural melanocortin peptides show distinct selectivity for one of the melanocortin receptors, although γ-MSH is relatively more selective for the melanocortin MC_3 than the melanocortin MC_4 receptor (Schiöth et al., 1996). The synthetic peptide [Nle^4,D-Phe^7]α-MSH is a very powerful agonist for all melanocortin-receptor subtypes and can be used as a radioligand when labelled with iodine. Another strong synthetic melanocortin receptor agonist is cyclo-[Nle^4,Asp^5,D-Phe^7,Lys^{10}]α-MSH (melanotan II). A ligand with a significant higher affinity and potency at the melanocortin MC_4 receptor than at the melanocortin MC_3 receptor is cyclo-[Nle^4,Asp^5,D-Tyr^7,Lys^{10}]α-MSH (D-Tyr-melanotan II). In contrast, Ac-[Nle^3]γ_2-MSH (Nle-γ-MSH) is a ligand with higher selectivity for the melanocortin MC_3 receptor (Adan et al., 1999).

A derivative of melanotan II, cyclo-[Nle^4,Asp^5,D-Nal(2)^7,Lys^{10}]α-MSH (SHU9119), has been shown to be a potent competitive melanocortin receptor antagonist (Hruby et al., 1995). The relative potency of these compounds are summarised in Table 1.

With the availability of these ligands, it became possible to study the potential of the melanocortin MC_4 receptor as a new drug target in the control of neuropathic pain. Recently, we have demonstrated that changes in the spinal cord melanocortin system occur after chronic constriction injury of the sciatic nerve, a widely accepted and reproducible animal model of chronic neuropathic pain that causes a syndrome similar to human neuropathic pain (Bennett and Xie, 1988). An increase in in situ binding of ^{125}I-[Nle^4,D-Phe^7]α-MSH in the spinal cord suggests an increase in spinal melanocortin receptors in neuropathic pain (Vrinten et al., submitted for publication). Intrathecal administration of the melanocortin receptor antagonist SHU9119 to rats with a chronic constriction injury induced a decreased sensitivity to cold and mechanical stimulation, whereas the strong melanocortin receptor agonist melanotan II or the more selective melanocortin MC_4 receptor agonist D-Tyr melanotan II had the opposite effect. These effects were observed in both acute and chronic administration paradigms (Vrinten et al., submitted for publication). Drugs were administered directly into the cerebrospinal fluid surrounding the spinal cord through a cannula placed in the cisterna magna (Lankhorst et al., 1999). Since the doses used in these studies were high enough to affect grooming behaviour (Adan et al., 1999) and body weight (Grill et al., 1998; Kask et al., 1998) when administered i.c.v. and no such effects were observed upon administration into the cisterna magna, these effects on nociception are most likely mediated at the spinal level.

In contrast with melanotan II and D-Tyr melanotan II, the selective melanocortin MC_3 receptor agonist Nle-γ-MSH had no effect on nociception. Taken together, these data suggest that the effects of melanocortins in neuropathic pain are exerted through the spinal melanocortin MC_4 receptor.

Table 1
Affinity of melanocortin receptor ligands for the rat melanocortin MC_4 and MC_4 receptor

Ligand	K_i for rat MC_3	K_i for rat MC_4
[Nle^4,D-Phe^7]α-MSH	1.19 ± 0.51	3.14 ± 1.18
Melanotan II	4.77 ± 2.13	1.74 ± 0.77
D-Tyr-Melanotan II	204 ± 87.2	3.84 ± 0.84
Nle-γ-MSH	1.44 ± 0.26	77.5 ± 37.7
SHU9119	0.879 ± 0.170	0.238 ± 0.060

Affinities (K_i, in nM) were determined on a hamster-embryonic kidney cell line expressing either the rat melanocortin MC_3 or melanocortin MC_4 receptor, using ^{125}I-[Nle^4,D-Phe^7]α-MSH as radioligand. Data are expressed as means ± 95% confidence interval (adapted from Adan et al., 1999).

Abbreviations used: MSH, melanocyte-stimulating hormone; Melanotan II, cyclo-[Nle^4,Asp^5,D-Phe^7,Lys^{10}]α-MSH; D-Tyr-Melanotan II, cyclo-[Nle^4,Asp^5,D-Tyr^7,Lys^{10}]α-MSH; Nle-γ-MSH, Ac-[Nle^3]γ_2-MSH; SHU9119, cyclo-[Nle^4,Asp^5,D-Nal(2)^7,Lys^{10}]α-MSH.

The endogenous melanocortin receptor agonist α-MSH, which is released in the dorsal horn (Tsou et al., 1986), may exert a tonic influence on nociception. Consistent with this view is the aforementioned induction of hyperalgesia upon central administration of melanocortins (Bertolini et al., 1979; Sandman and Kastin, 1981; Williams et al., 1986) and the upregulation of spinal melanocortin receptors in chronic neuropathic pain (Vrinten et al., submitted for publication), which could contribute to the increased sensitivity. The anti-allodynic effects of the melanocortin receptor antagonist SHU9119 may be caused by a blockade of an endogenous α-MSH-induced tone.

Cleavage of POMC yields not only the melanocortin receptor agonists α-MSH and ACTH, but the opioid peptide β-endorphin as well, which has also been immunocytochemically localised in the dorsal horn and lamina X (Tsou et al., 1986). Furthermore, the μ- and δ-opioid receptor subtypes, for which β-endorphin displays a high affinity, have also been demonstrated in these areas by immunocytochemistry (Zerari et al., 1994; Cheng et al., 1996, 1997). Recently, it was demonstrated that morphine treatment induces downregulation of melanocortin MC_4 receptor expression in brain regions associated with the behavioural responses to opiates (Alvaro et al., 1996). This anatomical linkage between the melanocortin and opiate systems may form a substrate for their functional antagonism. In cells derived from the locus coeruleus, which express different melanocortin receptor subtypes and the δ-opioid receptor, α-MSH and β-endorphin increase and decrease the level of the second messenger cAMP, respectively, via adenylate cyclase (René et al., 1998). Thus, in neurons receiving input through opioid and melanocortin receptors, adenylate cyclase might function as an integrator of these signals, thereby regulating the output of the cell in vivo. We hypothesise that the observed anti-allodynic effects of SHU9119 are caused by blockade of the tonic endogenous α-MSH-induced activation of adenylate cyclase, mediated via the MC_4 receptors in the spinal cord. This would tip the balance in favour of the inhibitory actions of β-endorphin, which is co-released with α-MSH in the same POMC projection areas, thereby producing analgesia (see Adan and Gispen, 2000).

Neuropathic pain remains one of the most difficult forms of pain to treat. The wide variety of drugs currently used in its treatment, including tricyclic antidepressants, anticonvulsants, systemic administration of local anaesthetics and NMDA receptor antagonists, often do not provide adequate pain relief (reviewed in Fields et al., 1999). Moreover, the use of a major class of analgesics, the opioids, is controversial, given their limited efficacy in this pain state as compared to other pain states (Arner and Meyerson, 1988; McQuay, 1997). The generally accepted view nowadays is that the opioid insensitivity of neuropathic pain is relative (dose–response curve shifted to the right), so that adequate pain relief can be achieved by using higher doses (Portenoy et al., 1990; Jadad et al., 1992; Dellemijn and Vanneste, 1997). This, however, increases the incidence and severity of unwanted side effects, such as respiratory depression, nausea, pruritus and constipation (see MacPherson, 2000). From a clinical point of view, an interaction between of the melanocortin and opioid systems is interesting because administration of melanocortin receptor antagonists might increase the sensitivity for opioids, thus improving the efficacy to adverse effects ratio of opioids in neuropathic pain control. Future research is needed to further elucidate the mechanisms underlying these effects of melanocortin and to see whether the melanocortin MC_4 receptor can indeed be a target in the challenge to alleviate neuropathic pain.

4. Definitions of terms used in the description of neuropathic pain syndromes

The following definitions of terms for the description of neuropathic pain syndromes are used, according to the task force on taxonomy of the International Association for the Study of Pain (IASP) (Merskey and Bogduk, 1994).

Allodynia Pain due to a stimulus that does not normally provoke pain

CRPS type I A syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of pain, or allodynia or hyperalgesia (= reflex sympathetic dystrophy).

CRPS type II Burning pain, allodynia and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its major branches (= causalgia)

Deafferentation pain Pain initiated or caused by a primary lesion of the peripheral or central nervous system

Dystesthesia An unpleasant abnormal sensation, whether spontaneous or provoked

Hyperalgesia An increased response to a stimulus that is normally painful

Hyperesthesia Increased sensitivity to stimulation, excluding the special senses

Hyperpathia A painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold

Hypoalgesia Diminished pain in response to a normally painful stimulus

Hypoesthesia Decreased sensitivity to stimulation, excluding the special senses

Neuropathic pain Pain initiated by a primary lesion or dysfunction in the nervous system

Nociceptor A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged

Noxious stimulus A stimulus that is damaging to normal tissues

Paresthesia An abnormal sensation, whether spontaneous or evoked

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