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REVIEW

Neuropathic pain: targeting the melatonin MT_2 receptor

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Abstract

Neuropathic pain affects a large proportion of the population and reduces a person's ability to perform optimally. In South Africa, there are a host of factors that hinder the correct diagnosis and treatment of neuropathic pain. Patients suffering from neuropathic pain are treated suboptimally with NSAIDS and opioids as first-line therapy. In 2012, a South African guideline on neuropathic pain was released, which stated that opioid therapy should be reserved for last-line treatment only. More recently, melatonin, commonly known as the neurohormone that regulates the circadian rhythm, has come to light as a therapeutic treatment option in the neuropathic pain setting. Early clinical trials showed a link between melatonin and chronic pain, which includes neuropathic pain. The MT_2 receptor has also been specifically linked to the control of neuropathic pain and inflammation.

Keywords: melatonin, neuropathic pain, MT_2 receptor, opioids, NSAIDs

Introduction

What is neuropathic pain?

Neuropathic pain is considered to be a major health problem and affects a significant number of patients, thus leading to a rise in healthcare costs and reduced productivity.[1] Neuropathic pain can occur from injury to any point along a neuronal pathway, from the terminal of the peripheral nociceptors, to the cortical neurons in the brain.[2] In 2011 the International Association for the Study of Pain published the following definition of neuropathic pain: "pain caused by a lesion or disease of the somatosensory system".[3] The somatosensory system forms part of the sensory system and is associated with feelings like pain, touch, any movement, any change in temperature and position. The somatosensory system may respond to stimuli that originate from within the skin, muscles and joints.[4]

Due to the absence of effective treatment, there is a high prevalence of neuropathic pain. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids is highly effective in the treatment of nociceptive pain, but only has a modest effect in a minority of patients that suffer from neuropathic pain. The main reason for this is because the underlying mechanism of neuropathic pain is not clearly understood.[5] Melatonin has demonstrated to possess a good safety and efficacy profile during the treatment of both nociceptive and neuropathic pain in several studies.[6]

Local challenges

In South Africa there are a number of challenges which affect the diagnosis and treatment of neuropathic pain, including a lack of education amongst doctors about neuropathic pain. This, in turn, leads to suboptimal diagnosis and treatment of neuropathic pain. Inappropriate use of opioids and NSAIDs as first-line therapy, as well as inappropriate back surgery is common. Therefore, many patients do not respond satisfactorily to current therapies.[7]

Classification of neuropathic pain

Pain may be categorised into two main types, namely nociceptive pain and neuropathic pain. The distinction is important as it reflects the cause of pain and thus guides the treatment thereof.[5]

Neuropathic pain is further classified as being either central (originating from injury to the brain or spinal cord) or peripheral (originating from injury to the peripheral nerve, plexus, dorsal root ganglion, or root). Neuropathic pain is also classified on the basis of the aetiology of the insult to the nervous system.[2] In addition, it may be characterised by intermittent or continuous, spontaneous pain, by provoked pain, by paraesthesias, dysesthesias and other positive symptoms, and by negative symptoms that reflect neural damage.[2] Refer to Table I.

Signs and symptoms of neuropathic pain

Neuropathic pain is known to be chronic and does not respond to drug treatment. Hyperalgesic (increased sensitivity to stimuli) and allodynic (pain due to a stimulus that does not normally activate the nociceptive system) are two symptoms commonly found in neuropathic pain.[8] Other common features associated with neuropathic pain include paraesthesia (abnormal sensations), dysesthesia (unpleasant sensations), hypoesthesia (decreased sensitivity to stimulation), hypoalgesia (diminished response to a normally painful stimulus) and hyperalgesia (exaggerated response to a normally painful stimulus).[2,9]

Table I: Classification of neuropathic and nociceptive pain [5]

	Neuropathic pain	Nociceptive pain
Aetiology	• Injury to the nervous system, often accompanied by maladaptive changes in the nervous system	• Can cause damamge to tissues
Description	• Lancinating, shooting, electric-like, stabbing pain	• Pressure-like pain that can be accompanied by throbbing and aching.
Sensory deficits	• Common symptoms like numbness, tingling, pricking	• Uncommon, if present they have a non-dermatomal or non-nerve distribution
Motor deficits	• If a motor nerve is affected then neurological weakness may be present. Central and peripheral nervous system lesions will result in dystonia and spasticity	• Can cause pain-induced weakness
Hypersensitivity	• Pain often caused by a usually non-painful stimulus (allodynia) or by an exaggerated response to a usually painful stimulus	• Hypersensitivity usually occurs in the immediate area surrounding an acute injury but is otherwise uncommon
Character	• Distal radiation common	• Distal radiation less common; proximal radiation more common
Paroxysms	• Exacerbations common and unpredictable	• Exacerbations less common and often associated with activity
Autonomic signs	• In almost half the patients sudomotor (sweating) occurs; this could be accompanied by a change in temperature, swelling and colour changes	• Uncommon

Diagnosis of neuropathic pain

It is critical to appropriately investigate and characterise the underlying pathology of neuropathic pain and to intervene early. Neuropathic pain can be difficult to diagnose due to the fact that there are no standard diagnostic procedures to follow. A comprehensive evaluation will need to be done, which includes taking a thorough patient history and evaluating the patient's neurological and physical symptoms. Clinicians may also diagnose neuropathic pain if a nerve lesion is found.[9] The patient's sensory abilities (touch, temperature, vibrations and pinprick) should be assessed along with the patient's mood (anxiety). The presence of a Babinsky reflex, accelerated tendon reflexes and spasticity should be determined. [10] Improved awareness about neuropathic pain amongst both healthcare professionals and patients will improve the ultimate management of neuropathic pain.[2,11] Refer to Figure 1.

Pathway of melatonin in pain modulation

The precise mechanism of pain modulation is not completely understood; however, evidence suggests that many systems, including the opioid system and nitric oxide pathways, play a role in melatonin pain modulation. Melatonin has a high degree of lipid solubility and a wide distribution of binding sites throughout the central nervous system (CNS). It is therefore able to cross the blood-brain barrier, which suggests central nociceptive regulation of melatonin.[8]

The MT_2 receptor

What is the M_2 receptor?

The MT_1 and MT_2 receptors are the two membrane-bound G-protein coupled receptors of melatonin. The MT_3 receptor has been found in other areas of the body including the kidney, liver and ovaries.[12,13]

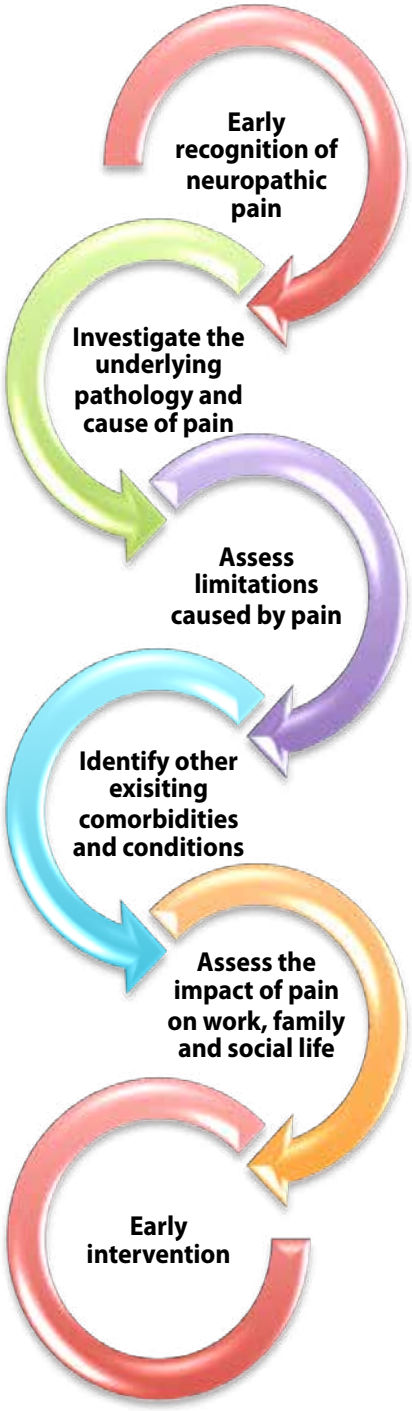

Figure 1: Diagnosis of neuropathic pain[9]

A large number of experiments suggest that the MT_1 and MT_2 receptors play an important role in pain modulation. This is because these receptors influence a number of systems, including the opioid system, adrenergic system and secondary messenger system.[8] Zurowski et al[14] confirm that exogenous melatonin has antinociceptive effects and it influences the pain threshold via modulation of the opioid system. Melatonin also exerts its antinociceptive effects by activating the MT_1/MT_2 receptor pathway and thus proves that a MT_1/MT_2 receptor agonist could become a therapeutic option in the treatment of pain.[14]

Localisation of the M_2 receptor

The MT_2 receptor has been implicated in non-rapid eye movement sleep (NREM) in humans and other mammals such as rats.[12,13]

Danilov and Kurganova[6] (2016) also confirm the localisation of the MT_2 receptors in various regions of the brain, such as the pars tuberalis of the pituitary gland, the hypothalamus, the cerebellum, the frontal cortex, the nucleus accumbens, the amygdala and the hippocampus, thus suggesting that the MT_2 receptor has a distinct function in the neurophysiological and neuropathological systems. The MT_2 receptor was also found to play a direct and indirect role in the secretion of vasopressin and oxytocin, supporting a role of melatonin in the control of uterine contractions, because of its localisation in the paraventricular nucleus and the magnocellular preoptic and supraoptic nuclei.[6]

Abnormal expression of the MT_2 receptor has been linked to neurodegenerative diseases. It has been documented that abnormal expression of the MT_2 receptors in the hippocampus and the cortex have been linked to Alzheimer's disease. Furthermore, post-mortem examinations have indicated that there is a decrease in the expression of MT_2 receptors in the substantia nigra in patients with Parkinson's disease.[6,12]

Furthermore, it has been suggested that the MT_2 receptor is involved in the motor effects of systemic administration of melatonin in the substantia nigra pars reticulata, red nucleus, the oculomotor, pararubral nuclei and the colliculi.[15]

Recently the role of the MT_2 receptors and melatonin has been documented in the control of neuropathic pain and inflammation. Because of the MT_2 receptor localisation in the descending nociceptive pathways, the pharmacological and physiological properties of melatonin have been proved.[6]

Management of neuropathic pain

In 2012, Chetty et al[7] published a guideline for the management of neuropathic pain in South Africa. After accurately diagnosing neuropathic pain, it is recommended that pregabalin, gabapentin, low-dose tricyclic antidepressants (e.g. amitriptyline) and dual serotonin-noradrenaline reuptake inhibitors (venlafaxine and duloxetine) be used as first-line treatment options in the management of neuropathic pain.

If there is no response, or the response is limited to the selected first-line treatment option after two to four weeks, it is recommended to switch to a different class or to combine classes of agents. Opioid therapy should be reserved for when combination therapy fails. For central neuropathic pain it is recommended that amitriptyline or pregabalin be used as first-line therapy.[7]

Melatonin

Melatonin is known as an exceptional neurohormone, synthesised from serotonin and secreted by the pineal gland. Melatonin secretion follows a distinct circadian rhythm,[8,12] and the gland is located deep in the centre of the brain.[16] The route by which melatonin is supplied to the brain follows its direct release into the cerebrospinal fluid (CSF) of the third ventricle.[17]

Melatonin is known to be a versatile molecule and has a wide distribution throughout the body. Thus, the molecule plays a role in a number of physiological functions, which include sleep modulation, circadian rhythm, reproduction and vasomotor responses.[6, 8,13]

According to Anwar et al,[13] melatonin has additional physiological effects, other than the regulation of the circadian rhythm. Melatonin is reported to act as a hypnotic, antiepileptic, immune modulator and antidepressant, and also plays a role in cardiovascular and bone disease.[13] Melatonin is also known as an antioxidant and anti-apoptotic agent, because of its ability to reduce the formation of reactive oxygen and nitrogen species.[13] During tissue damage and inflammation a variety of inflammatory mediators, including reactive oxygen species, are released. Evidence indicates that reactive oxygen species are involved in chronic pain, which includes neuropathic pain. [18] Clinical trials that were mainly conducted on chronic pain, such as migraines and fibromyalgia, have proven that melatonin eases pain, and improves sleep and depression.[1,6, 8]

Early clinical trials suggested that there is a connection between the action of melatonin and nociceptive pain. Patients who suffered from chronic pain had significantly lowered levels of melatonin in their blood and urine. Patients with fibromyalgia also had lowered concentrations of the melatonin precursors, L-tryptophan and serotonin.[14]

The physiological effects of melatonin are manifested due to the activation of the MT_1 and MT_2 receptors that are located in the brain.[1]

Clinical trials have shown that melatonin has analgesic properties in chronic pain. A number of animal studies have demonstrated that melatonin has anti-inflammatory and antinociceptive effects in chronic neuropathic pain, which are mediated by the MT_2 receptor.[1] Experiments have supported the analgesic and antihyperalgesic effect of melatonin in neuropathic pain.[8] It has been discovered that the maximum analgesic effect of melatonin occurs at night due to its circadian rhythm concentration in the blood, and that surgically removing the pituitary gland will inhibit this effect.[14]

Conclusion

The nature of neuropathic pain poses significant healthcare challenges, especially in terms of the effective alleviation of the symptoms thereof. This may be exacerbated by potential delays in correctly diagnosing patients suffering from this form of chronic pain. Recent advances include moving away from the more traditional pain management approach, of utilising staggered and combined treatment options belonging to the opioid and NSAID group of pharmacotherapeutic agents, to alternative treatment options that include pregabalin, gabapentin, low-dose tricyclic antidepressants and dual serotonin-noradrenaline reuptake inhibitors, as well as melatonin.

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