Melatonin in Antinociception: Its Therapeutic Applications
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Abstract: The intensity of pain sensation exhibits marked day and night variations. Since the intensity of pain perception is low during dark hours of the night when melatonin levels are high, this hormone has been implicated as one of the prime antinociceptive substances. A number of studies have examined the antinociceptive role of melatonin in acute, inflammatory and neuropathic pain animal models. It has been demonstrated that melatonin exerts antinociceptive actions by acting at both spinal cord and supraspinal levels. The mechanism of antinociceptive actions of melatonin involves opioid, benzodiazepine, ?1- and ?2-adrenergic, serotonergic and cholinergic receptors. Most importantly however, the involvement of MT1/MT2 melatonergic receptors in the spinal cord has been well documented as an antinociceptive mechanism in a number of animal models of pain perception. Exogenous melatonin has been used effectively in the management of pain in medical conditions such as fibromyalgia, irritable bowel syndrome and migraine and cluster headache. Melatonin has been tried during surgical operating conditions and has been shown to enhance both preoperative and post-operative analgesia. The present review discusses the available evidence indicating that melatonin, acting through MT1/MT2 melatonin receptors, plays an important role in the pathophysiological mechanism of pain.

Keywords: Pain, nociception, analgesia, melatonin, inflammatory, neuropathic, fibromyalgia, cluster headache, migraine.

1. INTRODUCTION

Pain is classically described as an unpleasant sensation. By definition “pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage” [1]. Clinical pain has been divided into two conditions, including inflammatory pain caused by inflammation and neuropathic pain caused by actual injury to the nervous system [2]. These types of pain are characterized by persistent pain hypersensitivity [2]. In addition to hyperalgesia, neuropathic pain also manifests as allodynia (pain occurring in response to normally innocuous stimuli). Multiple nociceptive mechanisms have been suggested to underlie neuropathic pain [3]. As this type of pain can persist for years, it is also associated with symptoms like anxiety, depression, and sleep-disturbances [4, 5]. On the other hand symptoms of pain can also constitute a presenting feature of major depressive disorder, suggesting pathophysiological similarities between clinical pain and certain psychiatric disorders, particularly major depression [6, 7]. The mechanism of pain perception is considered to be multifactorial involving many biochemical, humoral, neurophysiological and psychological factors [8]. Damage or inflammation of tissue releases a variety of inflammatory mediators such as prostaglandins (PGE2), leukotrienes, bradykinin, substance P and inflammatory cytokines like tumor-necrosis factor (TNF-?), ATP and adenosine. Each of these substances either directly activates nociceptors or releases local allogenic agents which sensitize nociceptors and enhance the neuronal excitability of pain transmission pathways [9]. The transmission of pain sensation involves nociceptors (the primary sensory nerve endings of A? and C fibers) that have their central processes in the dorsal horn of the spinal cord.

The dorsal horn of the spinal cord is the first site of synaptic transfer in the nociceptive pathway and it is the primary region where peripheral afferent signals are integrated and modulated. A number of neurotransmitterreceptor sites such as NMDA, AMPA, opioid (? and ?), ?2- adrenoceptors, and adenosine are located in the dorsal horn projection neurons. The dorsal horn region of the spinal cord is the region of central sensitization and this is mediated by neurotransmitters like glutamate, substance P and neurokinin which interact with the NMDA (N-methyl-D-aspartic acid) receptor system [10, 11]. In addition to this, the dorsal horn neuron is also subjected to the influences of interneurons of the dorsal horn itself and descending pathways that modulate pain perception [7, 12]. These spinal interneurons and descending neural tracts from the brain constitute endogenous pain modulatory systems that inhibit pain transmission signals. These pain modulatory systems are activated by opioid and GABAergic mechanisms located in and around the periaqueductal gray region (PAG). From the PAG, descending fibers project to the rostral ventrolateral medulla (RVM) and dorsolateral pontine structures that in turn send inhibitory projections to the spinal cord to induce antinociceptive effects. Inhibitory ?2-adrenergic, ?, ?, and ? opioid and 5-HT1A receptors are present in the post-synaptic dorsal horn neurons along with GABA-A/B receptors [7, 13]. Descending fibres synapse with primary afferent neurons, and secondary neurons or interneurons to stimulate them to release opioid peptides.

The management and control of pain sensation is a matter of intense study and of great clinical interest. Drugs like aspirin

and non-steroidal anti-inflammatory drugs (NSAIDS) exert their antinociceptive effects by inhibiting cyclooxygenases (COX) [14]. But the side effects of aspirin and NSAIDS including gastrointestinal bleeding and ulceration make them unsafe for long-term clinical use. Other classes of drugs like morphine or the anti-inflammatory drugs that act through the NO-cyclic GMP pathway exert their antinociceptive actions by blocking the ascending transmission of pain sensation [15]. The side effects associated with morphine including sedation, respiratory depression and dependence complicate its use in controlling nociceptive mechanisms [16, 17]. In addition there are many other painful conditions like neurodegenerative pain and varieties of neuropathic pain that are not responsive to potent analgesics including opioids. Neuropathic pain is also a frequent manifestation of neurodegenerative diseases. Although it is less appreciated in Parkinson's disease (PD), the prevalence of pain is nearly 40% in PD. Pain presentations in PD include several categories such as musculoskeletal pain, radicular or neuropathic pain, and primary central parkinsonian pain [18]. Neurodegenerative mitochondrial and cytoskeletal cellular mechanisms producing painful hyperactivity in primary afferent nociceptors have been suggested as possible causative factors contributing to hyperalgesia [19]. Tricyclic antidepressants and gabapentin are often prescribed for the treatment of neuropathic pain with variable results of response [20-22], suggesting thereby the need for the development of novel analgesic drugs that can be used for effective treatment and management of inflammatory and neuropathic pain.

2. MELATONIN AND NOCICEPTION

Diurnal variations in the perception of pain have been described both in rodents and humans [23-26]. It has been reported that patients suffer less pain during the dark phase of the photoperiod and prolonged latencies in pain thresholds have been detected in healthy human subjects during night time. These observations were recorded by Laikin and his co-workers [26] and they attributed this phenomenon to high melatonin levels occurring at night and their possible analgesic effects. Based upon this initial observation a number of investigators have evaluated the antinociceptive effects of melatonin in animals by using a variety of experimental models and designs.

3. MELATONIN BIOSYNTHESIS

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced mainly in the pineal gland of all vertebrates in a circadian fashion [27]. Tryptophan serves as the precursor for its biosynthesis and is converted into 5- hydroxytrptophan. Serotonin is then acetylated to form Nacetylserotonin by the enzyme arylalkylamine Nacetyltransferase (NAT) and then O-methylated by hydroxyindole- O-methyltransferase (HIOMT) to form melatonin (Fig. 1). Biosynthesis of melatonin in the pineal gland is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus and is synchronized to the environmental light-dark cycle [28, 29]. Special melanopsin containing ganglion cells [30] transmit this photoperiodic information to the SCN through the retino-hypothalamic tract [31]. Fibers from the SCN project to the superior cervical ganglion (SCG) through a circuitous route. Post-ganglionic fibers from SCG regulate pineal melatonin synthesis by releasing norepinephrine (NE) at pinealocyte receptor sites. NE released from the postganglionic sympathetic fibers interacts with ?-adrenergic receptors as well as ?1-adrenergic receptors of the pinealocyte membrane, activating the adenyl cyclase cyclic AMP pathway that in turn regulates the expression of NAT and other enzymes involved in melatonin biosynthesis [32]. Exposure to bright light during dark hours of the night suppresses melatonin production by degradation of NAT enzyme [33]. Once formed, melatonin is not stored in the pineal gland but diffuses into the blood [34]. But most of the melatonin from the pineal gland is also released simultaneously into the cerebrospinal fluid (CSF) in primates [35]. The concentration of melatonin in the CSF of the third ventricle is 20 to 30 times higher than that found in the blood [36].

Circulating melatonin is metabolized mainly in the liver where it is first hydroxylated in the C6 position by cytochrome P450 mono-oxygenases (isoenzymes CYP1A2, CYP1A1, and to a lesser extent CYP1B1) and thereafter conjugated with sulphate to be excreted as 6-sufatoxymelatonin (aMT6S). In the brain a substantial amount of melatonin is metabolized to kynuramine derivatives [37]. This is of interest as antioxidant and anti-inflammatory properties of melatonin are shared by some of these metabolites, N1–acetyl-N2–formyl-5-methoxy kynuramine (AFMK) and also by N2-acetyl-5-methoxykynuramine (AMK) [38].

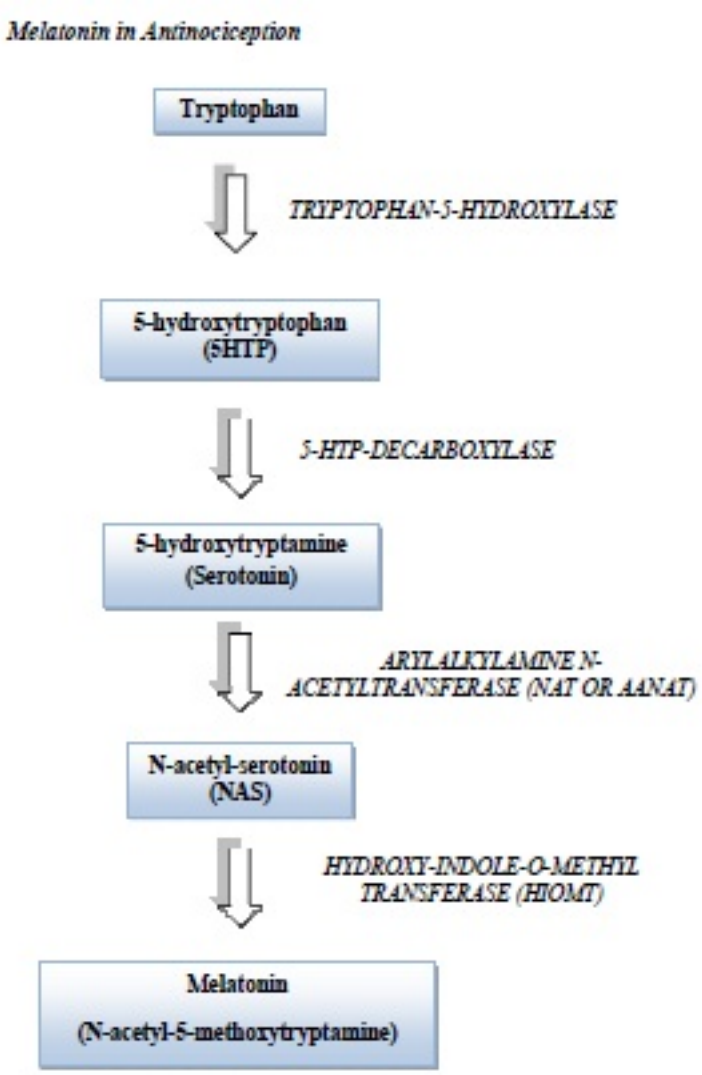

Fig. (1). Melatonin Biosynthesis.

Melatonin is also synthesized in many other regions of the body like skin [39], gastrointestinal tract, lymphocytes [40] and thymus [41]. In these regions melatonin has either a paracrine or autocrine role. Among other functions, extrapineal melatonin has a modulatory role on inflammation, reducing hyperalgesia, thus contributing to pain control [42]. Melatonin is synthesized by a number of plants. Of these, St John's Wort (Hypericum perforatum) is of medical importance and it has very high concentrations of melatonin [43, 44]. In a recent study it is reported that extracts of Hypericum perforatum (St John's Wort or SJW), Harpagophytum procumbens (HPE) and grape seed proanthocyanidins (GSPE) exerted significant antinociceptive effects in mice [45]. Nearly 60 commonly used Chinese medicinal herbs contain melatonin in concentrations ranging from 12 to 3771 ng/g [46]. It is an interesting fact that many of these melatonin containing herbs used in Chinese traditional medicine have age retarding effects and have been in use for treating diseases associated with increased generation of free radicals. Indeed the presence of melatonin in plants helps to protect them from oxidative damage and also from many environmental insults to which they have been subjected [47, 48]. Melatonin was observed to be elevated in alpine and Mediterranean plants exposed to strong UV radiation, a finding amenable to the interpretation that melatonin's antioxidant properties can antagonize damage caused by light-induced oxidants [49]. Melatonin in plants serves as a good antioxidant nutrient. The high concentration of melatonin detected in seeds also provide anti-oxidative defence even in a dormant and more or less dry system when most of the other substances and enzymes are not able to provide their full capacity as antioxidants [50].

4. MELATONIN RECEPTORS

Most of the physiological and pharmacological actions of melatonin are mediated through the activation of high affinity G-

protein coupled receptors, namely MT1 and MT2 and belong to the seven-transmembrane receptor family [51-53]. Melatonin binding to nuclear receptors has been demonstrated [54]. Some of these binding sites were identified as belonging to retinoid orphan related receptors like RZR? and RZR?, and they are present in the central and peripheral nervous systems [55]. Both MT1 and MT2 receptors have been identified in the ventral and dorsal horn of thoracic and lumbar regions of the spinal cord, specifically in lamina I-V and X of the spinal cord which are involved in the pain regulatory mechanisms [56]. Earlier studies have localized melatonin receptors in different areas of the brain like the thalamus, hypothalamus, spinal trigeminal tract and trigeminal nucleus [57, 58].

5. MELATONIN'S ANTINOCICEPTIVE ACTION: EVIDENCES FROM ANIMAL MODELS

Melatonin's antinociceptive effects have been demonstrated in animals like mice and rats by using a number of experimental models of nociception and this has been brought out extensively in an earlier review [59]. A brief analysis of this is presented in this paper with the aim of understanding the clinical significance of the antinociceptive and beneficial effects of melatonin. Using the hotplate procedure, it was shown that a melatonin injection (20-40 mg/kg, i.p) exerted its maximal analgesic effect when given in the late afternoon. This analgesic effect was blunted by the administration of either the opiate antagonist naloxone or the central benzodiazepine antagonist flumazenil, showing thereby the involvement of central opioid or benzodiazepine (BZD) receptors [60]. Soon after, it was showed that ?- endorphin, through ?-opioid receptors, is involved in melatonin-induced modulation of brain BZD receptors [61]. Dose-dependent antinociceptive effects of melatonin were evaluated by means of the hot-water tail flick test in a group of rats in which melatonin, injected (i.p) at three different doses (30, 60, 120 mg/kg), produced dosedependent antinociception [62]. The antinociceptive effect began within 15 minutes after injection and reached a peak in 30 minutes, and with 60-120 mg/day doses, lasted for 100 minutes. Melatonin's antinociceptive effect with 60 to 120 mg/kg (i.p) was antagonized by an i.c.v injection of naloxone within 10 minutes after injection and lasted for 45 minutes. As the i.c.v injection of naloxone blocked melatonin's antinociceptive effect it was concluded that the CNS is the primary site for melatonin's antinociceptive effect. In another study, it was found that melatonin potentiated the antinociceptive effects of deltorphin-1 a, ?-opioid agonist but not of the ?-opioid agonist endomorphin-1. In this study melatonin was injected either i.p (1, 5, 25 mg/kg) or i.c.v (0.25, 0.5, 1 mg/kg), which produced significant tail withdrawal latencies, thereby confirming antinociceptive effects of melatonin [63]. A summary of the antinociceptive effects of melatonin in a variety of animal models is presented in Table 1.

Table 1. Melatonin's Antinociceptive Actions - Experimental Animal Studies

Animal Model Used	Melatonin or Its Agonist Dose & Route	Effect of Melatonin	Blocked by	Typ Inv
Hot-plate	30 mg/kg i.p (melatonin)	Antinociception	Naloxone	Opi
Hot-plate	20-40 mg/kg i.p (melatonin)	Antinociception	Naloxone & flumazenil	Opi
Carrageenan-induced paw inflammation	5 & 10 mg i.p (melatonin)	Reduction of paw inflammation & antinociception	-	-
LPS model	5 & 10 mg i.p (melatonin)	Antinociception	-	-
Hot-water tail flick test	30, 60 or 120 mg/kg i.p (melatonin)	Antinociception	Naloxone	Opi
Electrical stimulation of tail	0.5 & 1.0 mg i.p (melatonin)	Antinociception	-	-
Carrageenan-induced paw inflammation	5 & 10 mg i.p 0.25, 0.5, 1.0 mg i.c.v (melatonin)	Reduction of inflammation & antinociception	-	-
Paw-withdrawal threshold	70 mg/kg i.v cumulative dose (210 mg/kg) (melatonin)	Antinociception	Naloxone or luzindole	Opi mel
Tail-clamping response	38 mg/kg (35-41 mg/kg) (bromomelatonin)	Antinociception	-	-
Capsaicin-induced hyperalgesia	Melatonin, 6-chloromelatonin	Antinociception	4-P-PDOT	MT_2
Ligation of sciatic nerve (neuropathic pain)	120 mg/kg i.v 0.1 nmol i.c.v (melatonin)	Antinociception	Naloxone	Opi L-A
Ligation of spinal nerves (neuropathic pain)	37.5-300 mg oral 3-100 µg intrathecal (melatonin)	Antinociception	Luzindole both oral and intrathecal & 4-P-PDOT	MT_2
Formalin injection model	150 mg/kg oral (melatonin)	Antinociception	4-P-PDOT	MT_2
Hot-plate latency test	4 mg/kg s.c (melatonin) and 5.16, 5.13, 6.88 & 5.40 mg/kg s.c (melatonin analog, compounds 3, 5, 9a, & 12)	Antinociception	-	-
Inflammatory pain model	150-600 µg/paw (melatonin)	Antinociception		
Post-inflammatory visceral hyperalgesia to colorectal	60 mg/kg (melatonin)	Antinociception	Naltrexone or luzindole	Opi