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Effects of 5-HydroxyTryptamine (5-HT) on Pain Modulation: A Brief Review

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ABSTRACT

Objectives: *The objective of this article is to try to bring a discussion in light of the serotoninergic pathways and their effects on the pain modulatory circuits in order to understand the action of drugs that help in the treatment of the various pain syndromes.*

Discussion: *It is well established that monoamines have complex modulatory functions in pain signaling. Top-down processing pathways arise in the structures of the midbrain and brainstem and exert a powerful inhibitory or excitatory control over the neuronal responses of the dorsal horn; predominantly through the actions of neurotransmitters, of which serotonin [5-HydroxyTryptamine (5-HT)] stands out, which in turn acts on specific receptor subtypes. The peripheral pro-nociceptive role of 5-HT is well defined to date; in contrast, its action at the level of the spinal cord and supraspinal structures seems highly variable and remains a question under discussion.*

Conclusion: *In the presence of 5-HT 1, 5-HT 2, 5-HT 3 and 5-HT 7 receptors in different amounts and at different levels, pain inhibition has been reported for most of these studies. However, some studies mention the involvement of these receptors in hyperalgesia, or even the maintenance of the pain stimulus.*

Keywords

5-HydroxyTryptamine, Conditioned pain modulation, Pain, 5-HT receptors, QST, Phenotype.

Abbreviations

CNS: Central Nervous System; CPM: Conditioned pain modulation; DNIC: Diffuse nociceptive inhibitory control; FDA: Food and Drug Administration; IASP: International Association for the Study of Pain; MOR: Mu opioid receptor; NRI: Norepinephrine reuptake inhibitor; QST: Quantitative sensory test; RVM: Rostromedial ventral medulla; SNRI: Noradrenaline and serotonin reuptake inhibitors; SRI: Serotonin reuptake inibitors; TADs: tricyclic antidepressants; 5HT: 5 HydroxyTryptamine.

Introduction

Pain is a highly prevalent symptom in most diseases, being one of the leading causes of demand for medical care. Pain represents a huge demand for spending in the health, social and economic sectors [1]. It consists of a body defense mechanism that involves physiological, anatomical, neurochemical and psychological changes being defined, according to IASP (International Association for the Study of Pain), as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of this damage [2].

As a consequence of the most diverse pain processes, individuals may experience physical, psychic and social impairment, leading

to functional, labor, suffering and worsening quality of life [3].

The treatment for this symptom generated several lines of neuropharmacological research, due to the different types of pain and the various drugs used in the treatment of this condition. However, it is important to note that in 40% of cases adequate pain control is not achieved, indicating that the approach to this prevalent health problem seems not to be very effective [4].

It is well established that monoamines have complex modulating functions in pain signaling. Top-down processing pathways arise in the structures of the midbrain and brainstem and exert a powerful inhibitory or excitatory control over the neuronal responses of the dorsal horn; predominantly through the actions of neurotransmitters, of which serotonin [5-HydroxyTryptamine (5-HT)], which in turn acts on specific receptor subtypes [5], stands out.

The understanding of the serotoninergic pathways as well as the role of their different receptors is important to understand the action of drugs that aid in the treatment of various pain syndromes [6-14].

Discussion

Perception of pain

After a tissue injury, the release of algogenic substances that will sensitize the free endings of the nociceptors occurs, with the signal transduction and propagation of the painful stimulus [15].

In most pain syndromes, there are multiple mechanisms of pain signaling that reside in peripheral locations. Then, transmission occurs within peripheral nerves, which will be passed to the spinal cord and to the brain [16].

Specifically, the pain message is transmitted to the thalamus and cerebral cortex where the sensory components of pain are generated, allowing us to localize the pain and describe its intensity, while parallel paths transmit the message of pain to the limbic system. In this latter circuit of the brain is where the affective components of pain are produced, which is why chronic pain usually goes hand in hand with comorbidities, including depression and anxiety [17].

It is important to emphasize that the perception of pain does not result only from the activation of these ascending pathways, but rather from a dialogue between the higher center of the brain and the spinal cord, the so-called top-down processing, through long routes that descend from the brain to the spinal cord [18].

Descending controls

The descending control pathways originate in the midbrain and brainstem regions and project to the dorsal horn of the spinal cord. They represent a mechanism through which the transmitted pain signal can be facilitated - increasing the pain we are experiencing or inhibiting it - thereby reducing it. Of the periaqueductal gray matter in the midbrain (an area that integrates the influences of the forebrain), these projections proceed to areas of the brainstem. Briefly, subsequent projections for the locus coeruleus and the rostromedial ventral medulla (RVM) are the main sources of descending controls.

A major component of the inhibitory bulb-spinal loop, for example, is mediated by fibers that run in the dorsolateral funiculi [19]. The RVM exerts inhibitory and facilitative controls on the neuronal responses of the deep dorsal horn through two opposite systems that originate from the RVM pain modulating neurons. There are three classes of cells that have clear sensitivities to mu opioid receptor agonists (MOR) and are grouped according to their different responses to noxious somatic stimulation. Whereas the "on" cells will start firing rapidly in response to noxious stimuli, and the "off cells" will stop firing, being activated by MOR agonists. Thus, RVM has neuronal substrates to enhance or inhibit pain messages.

HydroxyTryptamine (5-HT)

Serotonin is a neurotransmitter with seven families (5-HT1-5-HT7) and approximately 15 receptor subtypes. It modulates neuronal activity; however, this neurotransmitter is related to several physiological processes, such as cardiovascular function, gastric motility, renal function, among other functions. On the other hand, several studies have reported that serotonin modulates the nociceptive response through 5-HT 1, 5-HT 2, 5-HT 3 and 5-HT 7 receptors in the Central Nervous System (CNS).

5HT is synthesized from the amino acid L-tryptophan (from the diet) by sequential hydroxylation and decarboxylation. It is stored in presynaptic vesicles and released from the nerve terminals during neuronal firing. Serotonergic neurons at the CNS level are confined to the brainstem and are located in raphe nuclei. Neurons protrude into most of the brain, including the hippocampus, midbrain, pre-frontal, parietal and occipital cortical regions, cingulate cortex, thalamus, and cerebellum, while serotonergic neurons in the caudal raphe nuclei project into the cerebellum and spinal cord [20].

It has been established that 5-HT descending pathways exert an inhibitory (downward inhibitory) or facilitative (downward facilitation) influence on spinal processing of nociceptive information, depending on the states of acute or chronic pain and the type of acted receptor [9-11]. Based on pharmacological, structural and transductional characteristics, the 5-HT family of receptors is divided into seven subfamilies (5-HT1-5-HT7), comprising 15 receptor subtypes, each corresponding to distinct genes. Involvement of the various receptor subtypes in neurotransmission of pain remains largely unknown.

The peripheral pro-nociceptive role of 5-HT is well established to date; in contrast, its action at the level of the spinal cord and the supraspinal structures seems highly variable and remains a question in debate [7]. The exact roles of 5-HT receptors involved in pain in the spinal cord are not elucidated. However, studies have revealed the presence of at least three families of 5-HT receptors in the spinal cord (5-HT1, 5-HT2 and 5-HT3), with variable affinity for 5-HT and recently 5-HT7 has been postulated the receptor that

is also excitatory and has been linked, among other things, with circadian rhythms, thermoregulation and migraine [19].

HT Receptors

There are multiple 5-HT receptors in the central nervous system, and serotonin in the spinal cord pathway has been implicated in playing an important role in analgesia. The objective of this article is to analyze pain modulation by the 5-HT 1, 5-HT 2, 5-HT 3 and 5-HT 7 receptors at the central level. Several lines of evidence implicated a role for the serotonin of the spindle-cell system in the modulation of nociception [20].

It is believed that the major nucleus of raphe is the main source of descending serotonin that contains fibers that terminate in the spinal cord [21]. The physiological functions of the spinal cord and the impact of 5-HT on them are distributed in the following four areas: the first is the dorsal horn, which corresponds to the primary "relay" of nociceptive inputs; the second corresponds to the cells of the intermediolateral column, from which the sympathetic preganglionic neurons originate; the third is the central canal, which may be involved in the exchange with cerebrospinal fluid, and the last area is the anterior horn, which is involved in motor functions [22]. It is known that serotonin-containing axons descending from the brainstem terminate in the anterior horn and the intermediate-lateral spine, as well as in the dorsal horn [23].

At the cellular level, 5-HT produces pre and post-synaptic inhibition and excitation within the dorsal superficial spinal horn and the trigeminal [24-29].

Different techniques, drugs and pain models have been employed to determine the distribution and action of the receptors [19].

All serotonin receptors are coupled to G proteins, except 5-HT3, characterized as an ionotropic channel [19]. Serotonergic receptors can modulate the nociceptive response mediated by the descending system in the spinal cord [30].

Previous studies on 5-HT 1, 5-HT 2 and 5-HT 3 receptors have shown controversial results, in which both inhibition and pain facilitation have been reported.

Behavioral studies of neuropathic pain in animal models by Nakai, Nakae, Oba, Mashimo and Ueda [31], Obata, Saito, Sakurazawa, Sasaki, Usui and Goto [32] and Pichon, Wattiez, Becamel, Ehrlich, Bockaert, Eschalier, Marin and Courteix [33] found attenuation of nociception through the 5-HT 1A / 1B, 5-HT 1B / D, 5-HT 2A, 5-HT2C and 5HT3.

Contradictory results reported increased pain behavior after activation of these 5-HT receptors. Aira, Buesa, Salgueiro, Bilbao, Aguilera, Zimmermann and Azkue [34] studied the effect on 5 HT2A and 5-HT2B receptors, which showed the facilitation of pain in rats with neuropathic pain, as well as in 5-HT3 by Chen, Oatway and Weaver [35].

In the presence of 5-HT 1, 5-HT 2, 5-HT 3 and 5-HT 7 receptors in different amounts and at different levels, pain inhibition has been reported for most of these studies. However, some studies mention the involvement of these receptors in hyperalgesia, or even the maintenance of the pain stimulus.

It is important to note that the tests conducted on animal models of neuropathic pain and other factors involved may also result in such contradictory reports as the different pain models that attempted to explain the involvement of serotonergic receptors in the nociceptive response (the (acute pain, inflammatory pain, neuropathic pain or chronic pain) determines which and how the serotonergic receptors participate [36].

Investigation of administration with agonists or antagonists towards 5-HT receptors has shown that the anti-or hyperalgic effect depends on the dose of the drug at all receptors and may participate in conjunction to inhibit, excite or maintain the painful stimulus [21].

In summary, there are important points to be considered in understanding how pain is modulated by serotonergic receptors in the central nervous system: (i) the distribution of the different serotonergic receptors in the spinal cord; (ii) the dose of agonists or antagonists in terms of 5-HT receptors; (iii) the route of administration of agonists or antagonists to 5-HT receptors; (iv) the type of pain and (v) the duration of the pain.

It is necessary to be involved in new lines of investigation to clarify the involvement of 5-HT receptors in the modulation of pain, considering the points. The knowledge generated with future research can be used to generate new drugs and therapies in order to reduce pain and improve patients' quality of life.

Pharmacological and functional implications

The analgesic effects of many drugs depend on the activity in the descending circuits. The Food and Drug Administration (FDA) approves drugs targeting the downstream facilitator and inhibitor systems for use in patients with chronic pain [37].

In studies with rats submitted to spinal nerve damage, the activation of 5HT5A and 5HT1A / 1B / 1D receptors has been shown to reduce pain processing, emphasizing the importance of these receptors in the descending pain inhibitory circuit [38].

Contributory mechanisms in neuropathic pain include aberrant ectopic activity in the nociceptive nerves, as well as central sensitization and impaired inhibitory modulation. Top-line treatments include tricyclic antidepressants (TADs), noradrenaline and serotonin reuptake inhibitors (SNRIs), as well as anticonvulsants, such as pregabalin and gabapentin, although it is recognized that individualized and multidisciplinary approaches to rehabilitation are important for outcome ideal in the treatment of the patient [39].

Monoamines and their concentrations in the spinal cord also play a

key role in terms of the analgesic efficacy of the SNRIs and TADs. Increased noradrenaline / 5-HT in the spinal cord after the use of reuptake inhibitors is considered the main mechanism of action of the therapeutic benefit of antidepressants in neuropathic pain. This increase is considered relevant for the anti-hyperalgic efficacy of duloxetine - an inhibitor of the norepinephrine and serotonin reuptake.

TADs and SNRIs are more effective than serotonin reuptake inhibitors (SRIs) in neuropathic pain, and this is at least partially explained by the additional inhibitory role of noradrenaline. A recent study looked at the effect of a norepinephrine reuptake inhibitor (NRI) versus an SRI on the antinociceptive action of morphine in mice under conditions of painful disorders. NRI treatment, but not with SRI, improved the antinociceptive action of morphine, suggesting that under conditions of chronic stress morphine actions would be improved by the activation of the noradrenergic system, but not serotonergic [40].

Endogenous pain modulation is a broad term that describes the succession of events that the central nervous system can use to reduce, and in some cases increase, pain sensitivity. A known form of pain modulation is the phenomenon of inhibition by a previous painful stimulus. The term diffuse nociceptive inhibitory control (DNIC) was used by Le Bars and colleagues to describe the event where an intense painful stimulus in one part of the body inhibits pain in remote parts by activating the pain inhibitory pathways. The term, conditioned pain modulation (CPM) was used to describe this phenomenon in humans [41].

The interindividual variation in pain perception is substantial [42-43]. Threshold and tolerance in response to a variety of painful stimuli have a normal distribution in the population. This variability in pain sensitivity as well as analgesic response can be explained, at least in large part, by genetic alterations.

It is possible to better evaluate this variation by administering a standardized nociceptive stimulus and quantifying the response to pain under laboratory-controlled conditions by means of a quantitative sensory test (QST). The QST is the method used to evaluate the nerve fibers of small calipers, Delta and C, which transmit the thermal and painful sensations. It consists of applying, through calibrated equipment and without risk of causing injury to the patient, different stimuli (thermal and mechanical) with different intensities in a predetermined area [44-45].

Recent works show a relationship between a less efficient CPM and chronic pain. This relationship has already been demonstrated in patients with fibromyalgia, irritable bowel syndrome, tension headache, osteoarthritis and musculoskeletal pain [46].

In a recent study, patients with diabetic neuropathy who presented with impairment of CPM and, consequently, of pain inhibitory descending pathways, responded well to the use of duloxetine, a serotonin and noradrenaline reuptake inhibitor, whereas patients with normal CPM did not present good response therapy [47].

It is still frustrating that only a minority of patients with neuropathic pain have an adequate response to drug therapy; the improved understanding of these modulatory circuits as well as modifications in neuropharmacology clinical trials could help reduce therapeutic failures [48]. Thus, it is possible to monitor a form of downward inhibition in patients which could theoretically help predict response to treatment by characterizing certain phenotypic pain profiles by proposing individualized therapies [49].

Conclusion

It is concluded that the serotonergic receptors in the CNS represent a very complex theme, since the true role at the level of the spinal cord and the supraspinal structures seems to be highly variable. It was found that the effects of these receptors, in fact, affect the modulation of pain, whose outcomes are influenced by a series of factors, such as: the distribution of the receptors; the dose of agonists or antagonists; the route of administration, as well as the neurofunctional state of these circuits in each individual, both of which may occur in antinociception in different situations.

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