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REVIEW ARTICLE

Review: 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_7 Receptors and their Role in the Modulation of Pain Response in the Central Nervous System

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Abstract: ***Background*:** The aim of this review was to identify the mechanisms by which serotonin receptors involved at the central level are able to modulate the nociceptive response. Pain is a defense mechanism of the body that entails physiological, anatomical, neurochemical, and psychological changes, and is defined as an unpleasant sensory and emotional experience with potential risk of tissue damage, comprising the leading cause of appointments with Physicians worldwide. Treatment for this symptom has generated several neuropharmacological lines of research, due to the different types of pain and the various drugs employed to treat this condition. Serotonin [5-HydroxyTryptamine (5-HT)] is a neurotransmitter with seven families (5-HT_1–5-HT_7) and approximately 15 receptor subtypes. Serotonin modulates neuronal activity; however, this neurotransmitter is related with a number of physiological processes, such as cardiovascular function, gastric motility, renal function, *etc*. On the other hand, several researches reported that serotonin modulates nociceptive response through 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors in the Central Nervous System (CNS).

***Method*:** In this review, a search was conducted on PubMed, ProQuest, EBSCO, and the Science Citation Index for studies evaluating the effects of 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors in the CNS on the modulation of different types of pain.

Conclusion We concluded that 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors in the CNS modulate the pain, but this depends on the distribution of the receptors, dose of agonists or antagonists, administration route, pain type and duration in order to inhibit, excite, or even maintain the nociceptive response.

Keywords: Pain, 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_7, central nervous system.

1. INTRODUCTION

Pain is a highly prevalent symptom in the majority of diseases and is the leading cause of visits to the doctor [1]. Although, at present and to the best of our knowledge, exact values are lacking, it is estimated that the prevalence of pain is 25–40% in communities, rising to 71-88% within cities. Pain, in itself, interferes with social, work, and professional activities, as well as mood and the periods of sleep and wakefulness of the patient, aspects that will definitely affect the quality of life of the person and their environment [2]. This represents an overload, not only for the health sector due to the burden of care obligation and the consumption of direct health resources (visits to Specialists, simple x-rays, resonances, drugs, physical therapy, *etc*.), but also for the economic and social sector because of its indirect impact on the number of casualties and work disabilities. We may be able to provide a general idea of the situation on analyzing the total work produced, but only for musculoskeletal diseases (one of the most common causes of chronic pain), which represent the third most common cause of illness in Mexico according to the World Health Organization in 2015.

The increasing use of aggressive treatment schemes based on combinations of radio- and concomitant chemotherapy, altered fractionation, and dose escalation, make pain

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a problem in daily clinical practice. However, it is important to note that in 40% of cases, adequate pain control is not achieved, indicating that the approach to a prevalent health problem is not much effective [1].

Many different neurotransmitter systems have been implicated in the transmission, processing, and control of pain [3]. Serotonin (5-HydroxyTryptamine, [5-HT]) is a widely distributed monoamine, in the periphery and in the Central Nervous System (CNS) and is involved in numerous physiological and behavioral disorders, such as major depression, anxiety, schizophrenia, mania, autism, obesity, pain, *etc*. 5-HT 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 nerve terminals during neuronal firing. Serotoninergic neurons at the CNS level are confined to the brainstem and are located in the raphe nuclei. The neurons project to the majority of the brain, including hippocampus, midbrain, prefrontal, parietal, and occipital cortical regions, cingulate cortex, thalamus, and cerebellum, whereas, 5-HT neurons in caudal raphe nuclei project to cerebellum and spinal cord [4].

It has been established that the descending 5-HT pathways exert an inhibitory (descending inhibition) or facilitatory (descending facilitation) influence on the spinal processing of nociceptive information, depending on acute or chronic pain states and the type of receptor acted upon [5-7]. Based on pharmacological, structural, and transductional characteristics, the 5-HT receptor family is divided into seven subfamilies (5-HT_1–5-HT_7), comprising 15 receptor subtypes, each of these corresponding to distinct genes. The involvement of the diverse receptor subtypes in pain neurotransmission remains largely unknown. Indeed, the use of relatively selective agonists and antagonists for these subtypes has led to inconsistent results due to poor selectivity of drugs and the diversity of experimental conditions [5, 8-10].

The peripheral pronociceptive role of 5-HT is well established to date; in contrast, its action at the spinal cord level and in supraspinal structures appears highly variable and remains a matter of debate [3]. The exact roles of 5-HT receptors involved in pain at the spinal cord are unelucidated. However, studies have revealed the presence of at least three families of 5-HT receptors in the spinal cord (5-HT_1, 5-HT_2, and 5-HT_3), with varying affinity for 5-HT, and recently the 5-HT_7 receptor has been postulated, which is also excitatory and which has been linked with, among other things, circadian rhythms, thermoregulation, and migraine [11].

Successful pain management therefore requires therapeutic strategies directed toward alleviating its affective attributes. The development of these strategies requires an understanding of the neurobiological mechanisms that modulate the affective dimension of pain. The main purpose of this review evaluated in detail the role of the 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors as modulators of pain response in the CNS.

2. ACTIVITY OF SEROTONINERGIC RECEPTORS IN THE MODULATION OF PAIN 5-HT_1

Serotonin is a neurotransmitter thought to be involved in multiple functions and that includes the modulation of the sensory, autonomic, motor systems, arterial pressure, sexual behavior, *etc*. 5-HT modulates spinal nociceptive transmission in a complex manner: it employs the involvement of multiple 5-HT receptor subtypes and their specific localization in the CNS [12]. The 5-HT_1 Gi/-coupled receptor families are divided into A, B, C, D, E, and F subtypes [13-15]. 5-HT_1 receptors are present in the whole spinal cord and in the grey matter in all the areas examined; the major class of 5-HT receptor found in the dorsal horn is the 5-HT_1 family [16, 17]. Many subtypes of 5-HT_1 receptors potentially contributing to medullospinal pain regulation; the rostroventral medial medulla provides the major 5-HT descending pathway to the spinal superficial dorsal horn, the initial relay point for nociceptive inputs into the CNS [3]. The 5HT_{1A} receptor has been most studied as a modulator of pain, and it appears to play a modulatory role in nociception, it has a large distribution in the CNS rendering it possible for the actions of selective agonists or antagonist for this receptor to influence various spinal and supraspinal mechanisms that modulate pain processes. 5-HT_{1A} receptor RNA messenger (mRNA) labeling was most pronounced in the olfactory bulb, anterior hippocampal rudiment, septum, hippocampus, entorhinal cortex, interpeduncular nucleus, thalamus, and in the medullary raphe nuclei, and is widely distributed in the spinal dorsal horn [18, 19]. 5-HT1A receptor appears to be present in primary afferent nociceptive fibres, , in the rostroventromedial medulla as well as in the dorsal horn of spinal cord, with 5-HT1A receptor highest density in lamina I and II [14, 20, 21]. Administration of 5-HT_{1A} receptor agonists in the spinal cord has produced both pro- and antiallodynic effects [3]. The widespread presence of 5-HT_{1A} receptors in the spinal cord and in dorsal and median raphe nuclei, as well as in cortical and limbic areas, suggests a possible involvement of these receptors in emotional states, cognition, and pain modulation [22]. Studies in nonhuman primates [23] and humans indicate that many areas involved in the mediation or modulation of pain, such as the raphe nucleus, amygdala, cingulate cortex, insula, and prefrontal cortex, possess a high density of 5-HT_{1A} receptors [24-27]. In raphe nuclei, the 5-HT_{1A} receptors are located in serotoninergic cell bodies and dendrites and function as somatodendritic autoreceptors [28]. Among the many types of serotonin receptors, the 5-HT_{1A} receptor appears to be that which plays a significant role mediating regulatory effects of pain [29, 30]. EI Yassir *et al.* [31] and Zemlan *et al.* [32] showed that both 5-HT_{1A} and 5-HT_{1B} receptors were implicated in nociception at the dorsal-horn level. Indeed, 5-HT_{1A} receptors appear to mimic the non-selective antinociceptive effects of serotonin, while 5-HT_{1B} receptors mimic the selective effect.

Eide *et al.* [33] examined whether injection of 5-HT_{1A} and 5-HT_{1B} receptor agonists in mice had the ability to alter the tail-flick reflex, and whether effects on the reflex latency involve changes in tail skin temperature. These authors found that in mouse, both 5-HT_{1A} and 5-HT_{1B} receptor agonists inhibit the nociceptive tail-flick reflex when administered into the spinal subarachnoid space, and the effect does not depend on changes in tail skin temperature. Ali *et al.* [34] adopted a single route intrathecal (i.t.), microinjection in anesthetized rats, while recordings were carried out from dorsal horn neurons on drug application in both behavioral and electrophysiological studies; the authors showed that 5-

HT increased nociceptive responses and it is suggested that this effect is associated with the activation of 5-HT_{1A} receptors. Activity at 5-HT_{1B} receptors has the effect of suppressing or reducing responsiveness. The increased responsiveness of dorsal-horn neurons to noxious stimulation associated with activity at 5-HT_{1A} receptors may be associated either with increases in receptive field size, the promotion of spinal nocifensive reflexes, or facilitation of rostral transmission to specific brainstem sites. Moreover, the modulatory effects of 5-HT_{1B} receptor activation on wide-dynamic-range neurons in the spinal cord were studied by Gjerstad *et al.,* [35]; their results demonstrated that stimulation of the 5-HT_{1B} receptors may exert both pro- and antinociceptive effects on wide-dynamic-range neurons in the dorsal horn after repeated electrical stimulation. Likewise, Zhang *et al.* [19] reported that the excitability of dorsal-horn neurons and the sensitivity of the neurons to i.t. 5-HT_{1A} and 5-HT_{1B} receptor agonists might increase on following the inflammation model. These authors employed an intraplantar (i.p.) injection of carrageenan, which is characterized by both rapid onset and resolution of the inflammation that causes restricted distribution of hyperalgesia.

Liu *et al.* [36] conducted a study to confirm which type of 5-HT receptor was involved in the descending pathway of antinociception from the brainstem to dorsal horn of the spinal cord in rats. They reported that the 5-HT_{1A} receptor, not the 5-HT_2 nor the 5-HT_3 receptor, plays an important role in the descending pathway of antinociception from brainstem to spinal cord in intact rats, in rats with nerve injury, and in rats with inflammation. Hains *et al.* [37] performed a study to characterize the excitability of dorsal-horn neurons to 5-HT and to 5-HT_{1A} and 5-HT_3 receptor antagonists and agonists; high densities of 5-HT_3 receptors are found in the substantia gelatinosa, at all levels of the spinal cord and electrophysiologic evidence demonstrates the plasticity of 5-HT systems after spinal cord injury. In addition, they indicate the importance of 5-HT modulation in the attenuation of ensuing chronic central pain.

Bonnefont *et al.* [38] made a study to investigate, according to the nature of the noxious stimulus, the manner in which the blockade of spinal 5-HT_{1A} receptors could influence the antinociceptive actions of exogenous 5-HT, as well as of two analgesics involving endogenous 5-HT: Paracetamol and Venlafaxine. Their results showed that stimulation of the spinal 5-HT_{1A} receptors could mediate a dual influence on the integration of nociceptive mechanisms and the stimulation of 5-HT_{1A} receptors utilizing exogenous 5-HT or endogenous 5-HT mobilized by Paracetamol or Venlafaxine, which can elicit antinociception in the formalin test.

The role of medullary and spinal 5-HT_{1A} receptors in the endogenous regulation of neuropathic hypersensitivity was studied by Wei *et al.* [39]; they concluded that administration of a selective 5-HT_{1A} receptor antagonist, WAY-100635, into the rostroventromedial medulla or systemically produces selective attenuation of mechanical hypersensitivity in animals with experimental neuropathy and disinhibited descending pathways, this leading to the attenuation of hypersensitivity. Jeong *et al.* [12] examined the spinal actions of a range of 5-HT_1 agonists, including Sumatriptan, on acute pain, plus their effect on afferent-evoked synaptic transmission into superficial dorsal-horn neurons. These authors concluded that at the cellular level, 5-HT_{1A}, but not 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F}, receptor activation presynaptically inhibits primary afferent-evoked synaptic transmission in a subpopulation of lamina II superficial dorsal-horn neurons.

The findings displayed above raise the hypothesis that the 5-HT_{1A} receptor inhibits the nociceptive transmission presynaptically, acting as an inhibitory autoreceptor, into the laminae I and II of the dorsal horn by an up-downregulation of 5-HT_{1A} receptors in the rostro ventromedial medulla. In contrast, 5-HT_{1B} receptor can act as pro and nociceptive facilitator.

2.1. 5-HT_2

In rat brains, the highest levels of 5-HT_{2A} receptors are found in the frontal cortex and other neocortical areas, claustrum, and olfactory tubercle [40] and exist in brainstem descending pain-modulation pathways, including nucleus raphe magnus, ventrolateral periaqueductal gray, and the spinal dorsal horn, reticular formation, central grey, thalamus, cerebral cortex, and limbic structures [41-42]. 5-HT_{2A} receptors in the prefrontal cortex also play an important role in cognitive functions, such as working memory, conditioned avoidance, aversive classical conditioning, and visual discrimination [43]. Contrariwise, 5-HT_{2C} receptor mRNA exhibits widespread distribution in the locus coeruleus, retrorubral area, substantia nigra pars compacta, ventral tegmental area, periaqueductal gray, basal nucleus, parabigeminal nucleus, and laterodorsal tegmental nucleus, and the 5-HT_{2C} receptor is involved in serotoninergic control of the catecholaminergic and cholinergic areas.

Abbott *et al.* [44] conducted a study whose main purpose was to identify the receptor subtype mediating synergistic interaction between 5-HT and other inflammatory mediators; they found that 5-HT_{2A} antagonists may be effective as peripherally acting analgesic agents and/or analgesic adjuncts. These analgesic actions would be expected to be specific to situations in which 5-HT release contributes to the generation of pain; similar results were obtained with the 5-HT_3 agonist. 5-HT_1 and 5-HT_{2C} receptors have attracted interest in that they play a role in the control of mood, motor behavior, nociception, and endocrine secretion, because they are colocalized in individual neurons and, in functional models, they can modify each others' actions. To help elucidate the functional role of peripheral 5-HT_{2A} receptors, Van Steenwinckel *et al.* [42] investigated their localization in lumbar dorsal root ganglia employing immunocytochemistry; these authors found that the majority of 5-HT_{2A} receptor immunoreactivity in lumbar dorsal root ganglia is localized in small- and medium-sized cell bodies, presumably nociceptive.

Millan *et al.* [45] reported that activation of 5-HT_{2C} receptors enhances 5-HT_{1A} receptor modulation in tail- flick model in rats, providing concrete support for the concept of interplay between 5-HT_{1A} and 5-HT_{2C} receptors in the expression of their functional actions. Obata *et al.* [8] examined the antiallodynic effect of i.t.-administered serotonin receptor agonists, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, and 5-

HT_3 receptor subtypes in an animal model utilizing spinal nerve ligation; they reported that administration of the 5-HT_2 receptor agonist demonstrated dose-dependent antiallodynic actions with no associated motor weakness, this suggesting that the 5-HT_2 receptor plays an essential role in spinal suppression of neuropathic pain. Activation of 5-HT_2 receptors in dorsal horn in the spinal cord possesses antiallodynic action. The results are similar according to those of Sasaki *et al.* [9]; these authors determined the subtypes of the spinal 5-HT receptors involved in modulating nociceptive transmission in the formalin test, to better understand the pharmacological mechanisms of 5-HT-induced antinociception. Their results showed that DOI, a 5-HT_2-receptor agonist (i.t.), caused a dose-dependent reduction in the number of flinches of the formalin-injected paw in both phases 1 and 2. Dorsal-horn 5-HT_2 and 5-HT_3 receptors, then, inhibit nociceptive transmission in response to chemical inflammatory stimuli.

The expression of 5-HT_{2A} receptor mRNA in the lumbar spinal dorsal horn, the nucleus of raphe magnus, ventrolateral periaqueductal gray, and the dorsal raphe nucleus following carrageenan inflammation utilizing the *in situ* hybridization technique was evaluated by Zhang *et al.* [19]; these authors reported that one hour after Carrageenan injection, the expression of 5-HT_{2A} receptor mRNA in ipsilateral dorsal horn, bilateral nucleus of raphe magnus, ventrolateral periaqueductal gray, and dorsal raphe nucleus was significantly increased. Obata *et al.* [46] investigated the possible involvement of other associated spinal receptor systems with respect to the antiallodynic effect of a 5-HT_2 receptor agonist; they reported that muscarinic receptors may be involved in this effect. Doly *et al.* [47] analyzed the distribution of 5-HT_{2A} receptor in rat spinal cord by immunocytochemistry employing an antibody directed against an N-terminal sequence of the receptor; these authors found that 5-HT_{2A} receptors were widely distributed in the whole spinal cord, with particularly high expression in motoneuron groups, in the sympathetic preganglionic cell group, and in the dorsal horn, concluding that the 5-HT_{2A} receptor localization is mainly postsynaptic.

Obata *et al.* [48] evaluated the antiallodynic effects of i.t. administration of 5-HT_{2C} receptor agonists MK212, mCPP, and TFMPP, in a rat model of neuropathic pain induced by spinal nerve ligation; they concluded that i.t. administration of each 5-HT_{2C} receptor agonist produced antiallodynic effects in a dose-dependent manner. These results suggest that stimulation of spinal 5-HT_{2C} receptors produces antiallodynic effects *via* a different mechanism from that of 5-HT_{2A} receptors. Nitada *et al.* [49] investigated the possible involvement of the 5-HT_{2A} receptor in the pathogenesis of neuropathic pain using chronic constriction injury of the sciatic nerve in rats; their results indicated that the 5-HT_{2A} receptor antagonist sarpogrelate, specifically ameliorated hyperalgesia without affecting the normal nociceptive reaction.

The role of peripheral serotonin $5HT_{2A}$ and $5HT_{1A}$ receptors on orofacial nocifensive behavioral activities evoked by the injection of formalin into the masseter muscle was evaluated in rat by Okamoto *et al.* [50]; they reported that local administration of the $5HT_{2A}$ antagonist receptor, Ketanserin, but not of the $5HT_{1A}$ antagonist receptor, Propranolol, into rat masseter muscle significantly reduced the orofacial nocifensive behavioral activity. Wei *et al.* [51] examined the effects of intraplantar (i.p.) administration of the 5-HT_{2A} receptor antagonist, Ketanserin, on hyperalgesia, inflammation, and the expression of c-fos-like immunoreactivity in spinal cord dorsal horn in the carrageenan model of inflammation; these authors showed cellular evidence indicating that peripheral 5-HT_{2A} receptors are involved in nociceptive processing in the CNS and that they are responsible for the production of neuronal activity at the level of spinal cord in an inflammatory pain model. In addition, the 5-HT_{2A} receptor and 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C}, 5-HT_3, and 5-HT_7 receptors are also expressed in primary afferent nociceptors. Sasaki *et al.* [10] in their study examined the effect of a selective 5-HT_{2A} receptor antagonist, Sarpogrelate, on the hyperalgesia and allodynia induced by thermal injury in rats. They concluded that the antagonist blocks 5-HT_{2A} receptors at primary afferent fiber terminals in the periphery to inhibit primary thermal hyperalgesia and secondary mechanical allodynia. Dorsal root ganglion neurons expressed 5-HT_{2A} receptor mRNA, and stimulation of peripheral 5-HT_{2A} receptors produced thermal hyperalgesia.

Kayser *et al.* [52] used mutant mice, which do not express 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, or 5-HT_{3A} receptors, as an indirect approach to further assess the respective roles of these receptors in the physiological control of nociceptive responses in a wide range of noxious mechanical and thermal stimuli and i.p. injection of formalin. 5-HT_{1B} and, to a lesser degree 5-HT_{1A} receptors, mediate an endogenous inhibitory control of nociception by 5-HT, whereas 5-HT_{2A} and 5-HT_3 receptors play a role in formalin-induced hyperalgesia in male mice and, compared with paired wild-type mice, 5-HT_{1A} mutants exhibited increased sensitivity in the hot-plate test. Concomitant decrease of 5-HT-mediated pronociceptive influences can also be postulated as a result of 5-HT_{2A} receptor downregulation.

5-HT_{2A} receptor antagonists might aid in alleviating various kinds of neuropathic pain. Van Steenwinckel *et al.* [42] evaluated the effect of an epidural injection of MDL 11,939 (5-HT_{2A} receptor antagonist) on the appearance of mechanical allodynia and hyperalgesia in model of peripheral neuropathy; they reported that there was significant upregulation of 5-HT_{2A} receptor immunoreactivity in the lumbar dorsal horn and peripheral nociceptive cells after peripheral neuropathy treatment. The 5-HT_{2A} receptor is involved in wide central sensitization of dorsal-horn neurons and in peripheral sensitization of nociceptive neurons. The effect of MDL 11,939 on the mechanical hypersensitivity induced by antineoplasic drug in rats was investigated by Thibault *et al.* [53], they reported that 5-HT_{2A} receptors also play a pronociceptive role in the sensitization of peripheral nociceptors and in spinal nociceptive processing. Studies to clarify the mechanism of action of some drugs have been conducted. Xie *et al.* [41] reported that Tramadol treatment alters 5-HT_{2A} receptor mRNA expression in brainstem nuclei and the spinal dorsal horn, which may partially mediate the analgesic effect of Tramadol.

Kupers *et al.* [43] investigated the role of the 5-HT_{2A} receptor system in pain processing. They found that the 5-HT_{2A} receptor plays a role in the processing of tonic heat pain, but not in the processing of short, phasic heat pain

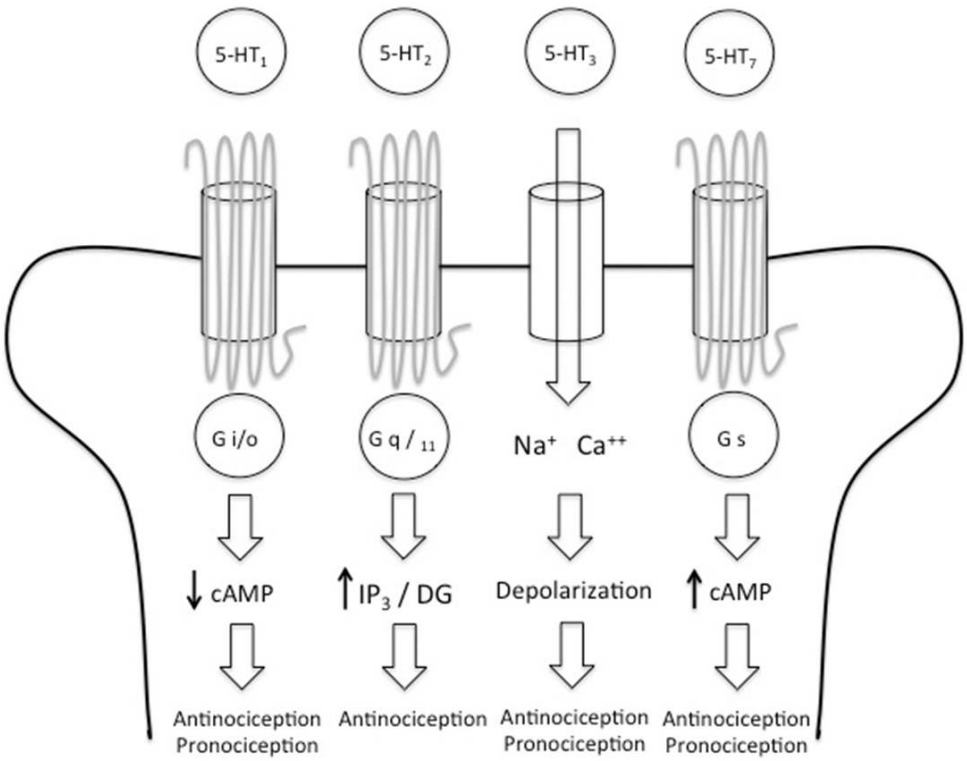

Fig. (1). The 5-HT receptors are divided into 7 families (5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5- HT7) that comprise 15 receptor subtypes. The receptors involved in the nociceptive pathway are 5-HT1, 5- HT2, 5-HT3 and 5-HT7. 5-HT1 is coupled to the G i/o protein and it reduces levels of cAMP generating anti and pronociceptive effects. 5-HT2 is coupled to the G q/11 protein and its activation leads to an increase of IP3 and DG levels, generating an antinociceptive effect. 5-HT3 is the only one that is not coupled to a G protein; instead this receptor is a ligand-gated cation channel, when activated 5-HT3 depolarizes the neuronal membrane and causes antinociception but also 5-HT3 can maintain the painful stimulus. 5.HT7 is coupled to G s protein, its activation generates an increase in the cAMP levels causing pro and antinociceptive effects.

stimuli. 5-HT_{2A} receptors in discrete brain areas are involved in the regulation of responses to tonic painful stimulation. The correlations observed in prefrontal and posterior cingulate cortices suggest a possible role with respect to cognitive evaluative appreciation and the emotional processing of pain (Fig. **1**).

2.2. 5-HT_3

Kilpatrick *et al.* [54] found 5-HT_3 binding sites in the brain for the first time, and now it is known that it participates in a wide variety of functions including, notably, pain modulation. The 5-HT_3 receptor is a ligand-gated ion channel that, when activated, gives rise to fast, depolarizing responses in neurons [55]. Depolarization of both the fibers and the cell bodies of vagal afferents occurs in response to 5-HT_3 receptor activation, activating a variety of second messenger signaling systems and, through these, indirectly regulating the function of ion channels involved in local, presynaptic control of neurotransmitter release [56, 57]. 5-HT_3 receptor-mediated enhancement of 5-HT release has been reported in brain regions, for example, hippocampus, frontal cortex, hypothalamus, and raphe nucleus [58]. On the other hand, there is 5-HT_3 receptor expression in the medial preoptic area, dorsal tegmental nucleus, trochlear nerve nucleus, and the facial nerve nucleus. The hybridization that exists within dorsal root ganglia support a role for 5-HT_3 receptors in the modulation of activity in primary sensory afferent fibers and this is consistent with the role of 5-HT_3 receptors in sensory processing [59]. Nayak *et al.* [60] reported that 5-HT_3 serotonin receptors are present in isolated terminals from the corpus striatum, hippocampus, amygdala, and cerebellum of rat brain. 5-HT_3 receptor activation produces, among other effects, postsynaptic depolarization of neurons throughout the nuclei in the striatum and, in addition, affects both spontaneous and evoked synaptic transmission [55]. A significant proportion of 5-HT_3 binding sites (40%) are associated with the terminals of unmyelinated primary afferents, while others are found in intrinsic interneurons.

Comparison of the cellular population containing 5-HT_{3A} and 5-HT_{3B} mRNA subunits demonstrated that the population of peripheral neurons expressing the 5-HT_{3A} subunit is larger than that expressing the 5-HT_{3B} subunit [61]. No functional differences between the alternatively spliced 5-HT_{3A} receptor subunits have been found to date; thus, is appears unlikely that alternative splicing of this subunit contributes to functional 5-HT_3 receptor heterogeneity [62]. Morales *et al.* [63] reported the distribution in rat CNS of 5-HT_3 receptor immunoreactivity; these authors found that it was present in the forebrain (isocortex, olfactory regions, hippocampal formation, and amygdala), brainstem (sensory and motor nuclei, and nuclei of the reticular formation), and spinal cord (dorsal and ventral horn). 5-HT_3 innervation of the striatum

modulates dopaminergic activity. Blandina *et al.* [64] indicated that at least part of this interaction occurs by means of the activation of a 5-HT_3 receptor, thus presenting, to our knowledge, the first direct evidence of a functional role of a 5-HT_3 receptor in brain.

Activation of 5-HT_3 receptors produces a variety of effects, including membrane depolarization and increase in intracellular Ca2+, modulation of neurotransmitter release, excitation of central and peripheral neurons, and release of 5-HT from enterochromaffin cells of the small intestine [65]. 5-HT_3 receptors may increase spontaneous release by producing localized depolarization of the presynaptic terminal, leading to an increased influx of Ca^{2+} through voltage-sensitive Ca^{2+} channels [55]. 5-HT_3 receptors, in particular, are most closely related with the ACh receptor, and these receptors are present in the central and peripheral nervous systems [59]. Activation of the 5-HT_3 receptor opens the cation channel of the 5-HT_3 receptor, which becomes permeable, preferentially to Na+ and K+, but also to Ca^{2+} and other cations including the organic cation guanidinium [66]. 5-HT_3 receptors are expressed in GABAergic interneurons; therefore, it is likely that 5-HT_3 receptors are localized in GABAergic nerve terminals in the basolateral amygdala, modulating synaptic GABA transmission [67]. GABA antagonists block the action of 5-HT_3. Tecott *et al.* [58] have shown that the distribution of the 5-HT_{3A} subunit closely resembles that of 5-HT_3-receptor binding sites; these authors suggest that the scattered distribution of the 5-HT_3 receptor in forebrain may reflect expression in Gamma AminoButyric Acid (GABA)ergic interneurons. 5-HT_3 receptors have been suggested to be involved in dopamine release, both in the striatum and in the nucleus accumbens [68]. In the spinal cord, 5-HT_3 immunoreactivity was concentrated in the superficial layers of the dorsal horn in lamina I/III [69], where high densities of 5-HT_3-receptor binding sites had previously been detected [56]. In addition to the postsynaptic localization of 5-HT_3 receptors in interneurons, 5-HT_3 receptors can also be found in presynaptic terminals [67].

Alhaider *et al.* [70] demonstrated that 5-HT_3 receptors in intrinsic spinal cord neurons inhibit nociceptive spinal transmission in both behavioral (in mouse) and electrophysiological (in rat) tests. Glaum *et al.* [55] reported that the antinociceptive effects of 5-HT in both the tail-flick and hot-plate tests were blocked following i.t. application of 5-HT_3 receptor antagonist ICS 205-930. 5-HT_3 receptors are associated with the sensory endings of primary afferents, and there is good evidence that ICS 205-930 have antinociceptive actions at this site [71]. 5-HT_3 receptors mediated serotonergic control of noxious transmission in the spinal cord. The responses of wide-dynamic-range (nociceptive) spinal dorsal-horn neurons to subcutaneous (s.c.) injection of formalin, and the electrically evoked responses of such neurons following intra plantar injection of carrageenan as inflammatory stimuli, was studied by Green *et al.* [72]. The authors' results revealed that, in normal animals with no inflammation, blocking the 5-HT_3 receptors exerted no significant effect on the electrically evoked responses of spinal dorsal-horn neurons. Moore and Weinreich [73] reported that 5-HT, a proinflammatory neurotransmitter, can activate 5-HT_3 receptors to depolarize vagal afferent neurons, whereas 5-HT_1 and 5-HT_2 receptor subtypes bear highest affinity for the endogenous ligand and are thought to exert an overall anti-nociceptive action, and models of persistent pain have suggested a role for 5-HT_3 receptor activation in the maintenance of pain [74]. 5-HT_3 receptor could contribute to any central plasticity that accompanies this injury state, and the hyperalgesia and allodynia manifested after tissue injury involves different peripheral and/or central mechanisms [75].

Given that 5-HT_3 receptor is a ligand gated ion channel, its pharmacology has been more studied than that of the other receptors. Camilleri and Boeckxstaens [76] reviewed a variety of studies regarding the treatment of abdominal pain in the irritable bowel syndrome (IBS) including 5-HT3 antagonists' alosetron and ramosetron, concluding that they were effective in treating this type of pain.

5-HT facilitates persistent pain-like states *via* the activation of 5-HT_3 receptors, most likely due to an increased, descending serotonergic drive from higher centers in the brain and, in particular, in the rostral ventromedial medulla [68]. At the spinal cord level, blocking 5-HT_3 receptors reversed the increase in hypersensitivity induced by amygdaloidal administration of a low dose of glutamate. This finding suggests that spinal 5-HT_3 receptors mediated the central nucleus of the amygdala (CEA)-induced increase of neuropathic hypersensitivity [77]. In summary, presynaptic 5-HT_3 receptors increase neurotransmitter release whereas postsynaptic 5-HT_3 receptors increase activity of both projection neurons and inhibitory interneurons.

2.3. 5-HT_7

5-HT_7 receptors comprise the most recently described members of the serotonin receptor family. An increasing number of studies have described the distribution of 5-HT_7 receptor in rodents by utilizing immunohistochemical techniques [78-81]. These reports showed that the protein distribution is similar to that of the mRNA, with highest abundance in the thalamus, hypothalamus, and hippocampus [4, 82]. The 5-HT_{7A} isoform predominates, followed by the 5-HT_{7B} splice variant, while 5-HT_{7C} and the 5-HT_{7D} isoforms are least frequently expressed [83], the 5-HT_{7A} receptor was the first splice variant cloned from human with a predicted length of 445 amino acids. In the spinal cord, 5-HT_7 receptors were mainly found in the superficial laminae I and II of the dorsal horn, postsynaptically in local interneurons, and presynaptically in peptidergic fibers and in astrocytes [84]. Electron microscopic examination of the dorsal horn further revealed three main localizations: postsynaptic localization in peptidergic cell bodies and in numerous dendrites; presynaptic localization in unmyelinated and thin myelinated peptidergic fibers and in astrocytes [85], the pharmacological profile of 5-HT_7 receptors is quite similar to that of the 5-HT_{1A} receptors subtype [86].

Five major properties appear to define the 5-HT_7 receptor and differentiate it from other 5-HT receptors as follows: limited sequence homology; presence and location of at least two introns; existence of an eighth hydrophobic domain; high-affinity binding of 5-HT, and positive coupling to adenylyl cyclase [87]. 5-HT_7 receptors stimulate cAMP formation by activating adenylyl cyclases *via* a stimulatory Gs-

protein, which also leads to Ras-dependent activation of the extracellular, signal-regulated kinases [88]. Activation of 5-HT_7 receptors directly stimulates extracellular signal-regulated kinase in hippocampal neurons [89], an effect that can be of importance for hippocampal function and mood regulation [4]. 5-HT_7 receptors appear to be mainly associated with limbic brain divisions receiving serotoninergic inputs (*e.g.*, the hippocampus, amygdaloid complex, or mammillary nuclei). This suggests that 5-HT_7 receptors are also involved in sleep induction and hypothermia, learning, mood, and in neuroendocrine or vegetative behaviors, and such observations were confirmed in a mouse strain with a disrupted *5-HT$_7$* gene [86, 90]. Certain behavioral stimuli can trigger the electrical activity of the dorsal raphe nucleus, leading to 5-HT release and subsequent activation of 5-HT_7 receptors in both the dorsal raphe nucleus and the medial raphe nucleus, which ultimately results in 5-HT release in the CNS [84].

Rocha-González *et al.* [91] conducted a study in which the main purpose was to determine the possible participation of local peripheral and spinal 5-HT_7 receptors in formalin-induced nociception, employing electrophysiological, immunohistochemical, and behavioral data, the authors suggest a pronociceptive role for the 5-HT_7 receptor in the dorsal horn of the spinal cord. Microinjection of formalin was preceded by either local or spinal administration of SB-269970 and/or 5-HT, both known for their antinociceptive activity, which significantly reduced formalin-induced flinching, while local 5-HT or 5-CT dose-dependently augmented the formalin-induced nociceptive behavior. On the other hand, the role of spinal 5-HT_7 receptors in the antinociceptive effects of systemic morphine was elucidated in a study conducted by Drogul and Seyrek [92], these authors reported that systemically administered morphine activates the descending serotonergic pathways and that 5-HT_7 receptors in the spinal cord play an important role in systemic morphine antinociception. Brenchat *et al.* [93] evaluated the potential role of the 5-HT_7 receptor in nociception associated with a sensitizing stimulus in mice; intrinsic efficacy as an activator of human 5-HT_7 receptors and the selectivity of 5-HT_7 receptor agonists used were also investigated. Their results showed that 5-HT_7 receptors participate in antinociceptive mechanisms and 5-HT_7 receptor blockade by i.t. administration of SB-269970, inhibiting the antinociceptive effect of systemic morphine in the tail-flick test. The following year, Brenchat *et al.* [94] examined whether 5-HT_7 receptors participates in some modulatory control of nerve injury-evoked mechanical hypersensitivity and thermal hyperalgesia in mice. These authors found a significant increase of 5-HT_7 immunoreactivity in laminae I–II and III–V of the dorsal horn on the ipsilateral side of the spinal cord 11 days after nerve injury. In the case of 5-HT_7 receptors, a recent study found that systemic administration of 5-HT_7 receptor agonists reduced mechanical hypersensitivity in nerve-injured mice, suggesting that 5-HT_7 receptors play an antinociceptive role. Studies suggest that spinal 5-HT_7 receptors may play a pronociceptive, rather than an antinociceptive, role [82]. Likewise, systemic and spinal administration of the selective 5-HT_7 receptor antagonist SB-269970 reduces the tactile allodynia induced by L5/L6 spinal nerve ligation, and 5-HT_7 receptors possess a pronociceptive role in this type of pain spinal nerve ligation, which leads to a reduction in the level of 5-HT_7 receptors [95].

The analgesic effect of morphine co-administered with the selective 5-HT_7 receptor agonist E-55888, the antagonist SB-258719, or both, was evaluated by Brenchat *et al.* [96]. They reported on 5-HT_7 receptors in opioid analgesia and pointed out a potential use of 5-HT_7 receptor agonists as adjuvants of opioid analgesia; systemic administration of a selective 5-HT_7 receptor agonist per se is not sufficient to reproduce the antinociception exerted by opioids in acute thermal nociceptive models. The respective roles of peripheral and spinal 5-HT_7 receptors in the modulation of mechanical hypersensitivity were investigated under two different experimental pain conditions by Brenchat *et al.* [97]; they demonstrated that activation of 5-HT_7 receptors exerts antinociceptive effects at the spinal cord level and pronociceptive effects at the periphery. A previous study at the light microscope level revealed that 5-HT_7 receptors co-localize with GABA in neurons of the spinal-cord dorsal horn [93], and it has been reported that spinal GABAergic interneurons are involved in 5-HT_7 receptor-mediated antinociception. Dogrul *et al.* [98] investigated the role of descending serotonergic pathways and spinal 5-HT_7 receptors compared with 5-HT_3 and 5-HT_{2A} receptors in terms of the antinociceptive and antihyperalgesic effects of Paracetamol; they reported that activation of descending serotonergic pathways and spinal 5-HT_7 receptors following systemic administration of Paracetamol produces antinociceptive and antihyperalgesic effects, and that the 5-HT_7 receptor antagonist blocks the antinociceptive and antihyperalgesic effects of systemic Paracetamol, indicating a novel role of spinal 5-HT_7 receptors in the mechanism of action of Paracetamol. The role of spinal 5-HT and 5-$HT_{4/6/7}$ receptors in the long-term secondary mechanical allodynia and hyperalgesia induced by formalin in rat comprised a study conducted by Godínez-Chaparro *et al.* [99]; these authors showed that formalin activates a descending serotonergic system, which releases 5-HT at the spinal cord and contributes to the development and maintenance of secondary allodynia and hyperalgesia. Viguier *et al.* [100] investigated how 5-HT_7 receptors contribute to neuropathic pain modulation by using potent 5-HT_7 receptors antagonist (SB-269970) and/or agonists (MSD-5a, AS-19, E-55888) in rats with unilateral ligations of the sciatic nerve or the infraorbital nerve, reporting that 5-HT_7 receptors mediated inhibitory control of the neuropathic pain underlying the excitation of GABAergic interneurons within the dorsal horn. Yang *et al.* [101] compared the role of 5-HT_7 receptors and the influence of descending serotonergic modulation between formalin- and carrageenan-induced inflammatory pain; they concluded that activation of 5-HT_7 receptors exerted a significant antinociceptive effect on formalin- induced pain, but no effect on carrageenan-induced pain, indicating differences in the involvement of 5-HT_7 receptors according to the pain modality, (Fig. **2**).

3. DISCUSSION

Multiple 5-HT receptors exist in the central nervous system, and the serotonin in the raphe-spinal pathway has been implicated in playing an important role in analgesia. The main purpose of this review was to analyze the modulation

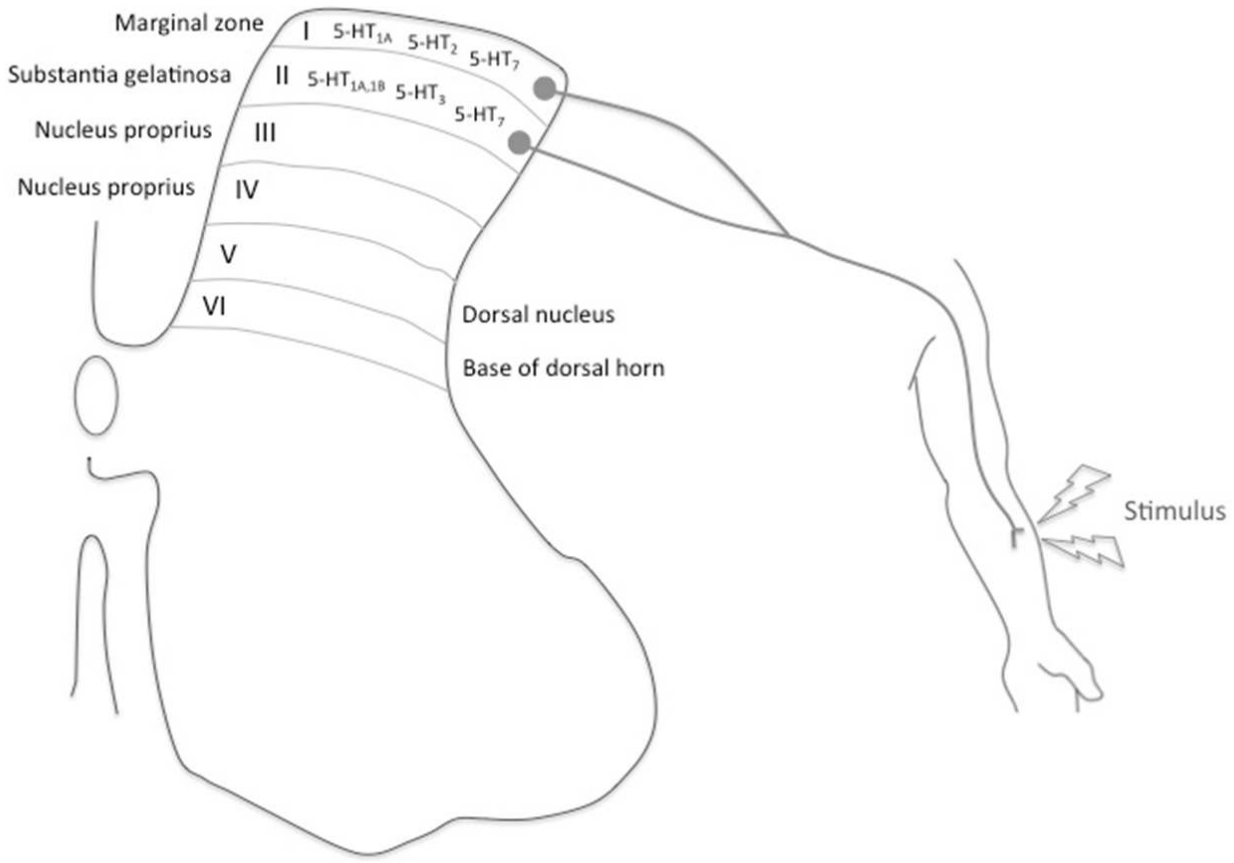

Fig. (2). The dorsal horn is the area that receives the painful stimuli; it is divided into five Rexed laminae. The 5-HT1, 5-HT2, 5-HT3 and 5-HT7 receptors are mainly located in the lamina I and II. The receptor involved in antinociception (5-HT1A, 5-HT2 and 5-HT7) receptors are mainly expressed in the lamina I, also known as marginal zone. This lamina is mostly innervated by A-δ fibers. In the lamina II, substantia gelatinosa, the receptors involved in pronociception (5-HT1B, 5-HT3 and 5-HT7) are expressed. This lamina is innervated by C fibers.

of pain by 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors at the central level. A total of 70 studies from different authors were evaluated, and we found certain differences and commonalties among these studies.

Several lines of evidence have implicated a role for the serotonin-containing component of the raphe-spinal system in modulating nociception. Medullary nucleus raphe magnus is thought to be a major source of the descending serotonin that contains fibers terminating in the spinal cord [102]. The physiological functions of the spinal cord and the impact of 5-HT on these are distributed in the following four areas: the first is the dorsal horn, which corresponds to primary relay of nociceptive inputs; the intermediolateral cell column from which originate the sympathetic preganglionic neurons is the second area, the third area is the central canal that might be involved in exchanges with the cerebrospinal fluid, and the last area is the ventral horn, which is implicated in motor functions [37]. Serotonin-containing axons descending from the brainstem are known to terminate in the ventral horn and in the intermediolateral column, as well as in the dorsal horn [103]. At the cellular level, 5-HT produces both pre- and postsynaptic inhibition and excitation within the spinal and trigeminal superficial dorsal horn [12, 104-108].

Different techniques, drugs, and pain models have been employed to determine the distribution of the different serotonergic receptors that are able to modulate the nociceptive response mediated by the descending system at the spinal cord and the presence of 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors in different amounts and at different levels was reported with the majority of these studies implicating these receptors in pain inhibition. However, these studies mention the involvement of these receptors in hyperalgesia, or even in maintaining the painful stimulus. Furthermore, there have been different pain models that have attempted to explain the involvement of serotonergic receptors in the nociceptive response (the tail-flick test, the hot-plate test, the formalin test, the carrageenan test, *etc*.); these studies reported that the type of pain (acute pain, inflammatory pain, neuropathic pain, tonic pain, or chronic pain) determine which and how the serotoninergic receptors participate. Investigation with administration agonists or antagonists regarding 5-HT receptors showed that the anti- or hyperalgesic effect depends on the drug dose in all of the receptors. Finally, several authors have reported that the participation of serotonergic receptors depends on pain duration, and different serotonergic receptors may even participate in conjunction to inhibit, excite, or maintain the painful stimulus. In summary, there are important points to consider in order to understand how pain is modulated by serotonergic receptors in the central nervous system as follows: (i) the distribution of the different serotonergic receptors in the raphe-spinal pathway; (ii) the dose

of agonists or antagonists on terms of the 5-HT receptors; (iii) the route of administration of agonists or antagonists with respect to the 5-HT receptors; (iv) the type of pain, and (v) pain duration. We think it necessary to engage in novel lines of investigation to clarify the involvement of 5-HT receptors in the modulation of pain considering the abovementioned points. The knowledge generated with future research could be used for generating new drugs and therapies to reduce pain and to improve the quality of life of patients.

CONCLUSION

We concluded that 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_7 receptors in the CNS intervene in the modulation of pain, but this modulation depends on the distribution of the receptors, the dose of agonists or antagonists, the route of administration, and the type and duration of pain required to inhibit, excite, or even maintain the nociceptive response.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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