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Review

Multiple roles of serotonin in pain control mechanisms —Implications of 5-HT_7 and other 5-HT receptor types

Florent Viguier [a,b,*], Benoît Michot [a,b], Michel Hamon [a,b], Sylvie Bourgoin [a,b]

[a] INSERM U894, CPN, Neuropsychopharmacology, Faculty of Medicine Pierre & Marie Curie, UPMC, Site Pitié-Salpêtrière, 75013 Paris, France
[b] University Pierre et Marie Curie (UPMC), Neuropsychopharmacology, Faculty of Medicine Pierre & Marie Curie, UPMC, Site Pitié-Salpêtrière, 75013 Paris, France

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ABSTRACT

Among monoamine neurotransmitters, serotonin (5-HT) is known to play complex modulatory roles in pain signaling mechanisms since the first reports, about forty years ago, on its essentially pro-nociceptive effects at the periphery and anti-nociceptive effects when injected directly at the spinal cord level. The discovery of multiple 5-HT receptor subtypes allowed possible explanations to this dual action at the periphery versus the central nervous system (CNS) since both excitatory and inhibitory effects can be exerted through 5-HT activation of different 5-HT receptors. However, it also appeared that activation of the same receptor subtype at CNS level might induce variable effects depending on the physiological or pathophysiological status of the animal administered with agonists. In particular, the marked neuroplastic changes induced by nerve lesion, which account for sensitization of pain signaling mechanisms, can contribute to dramatic changes in the effects of a given 5-HT receptor agonist in neuropathic rats versus intact healthy rats. This has notably been observed with 5-HT_7 receptor agonists which exert a pronociceptive action in healthy rats but alleviate hyperalgesia consecutive to nerve lesion in neuropathic animals. Analysis of cellular mechanisms underlying such dual 5-HT actions mediated by a single receptor subtype indicates that the neuronal phenotype which expresses this receptor also plays a key role in determining which modulatory action 5-HT would finally exert on pain signaling mechanisms.

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1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine widely distributed both at the periphery and in the central nervous system (CNS). Because 5-HT transport from the periphery to the CNS is prevented by the blood–brain barrier, there are actually two distinct compartments, quantitatively very unbalanced, where 5-HT can

* Correspondence to: INSERM U894—Center for Psychiatry and Neurosciences, Faculty of Medicine Pierre & Marie Curie, Site Pitié-Salpêtrière, Neuropsychopharmacology, 91, boulevard de l'Hôpital, 75634 Paris Cedex 13, France. Tel.: +33 1 4077 9709; fax: +33 1 4077 9790.
E-mail address: florentviguier@gmail.com (F. Viguier).

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exert various effects on pain signaling mechanisms. Together with other proinflammatory mediators at the periphery (prostaglandins, histamine, bradykinin, lactic acid), 5-HT is one of the active components of the "inflammatory soup" which contributes to injury (inflammation)-induced pain (Hamon and Bourgoin, 1999). Systemic (subcutaneous or intravenous) injections of 5-HT trigger excitation and sensitization of primary nociceptive afferent fibers (Aδ and C fibers) as well as nociceptive neurons from which these fibers originate in dorsal root ganglia, thereby contributing to peripheral sensitization and hyperalgesia (Sommer, 2004). Indeed, activation of any of the numerous 5-HT receptor types, namely 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_6 and 5-HT_7 receptors, present on C-fibers has been reported to mediate 5-HT-induced pronociceptive effects at the periphery (Godínez-Chaparro et al., 2011; Lin et al., 2011; Sasaki et al., 2006; Sommer, 2004).

If 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 seems highly variable and is still the matter of debate (Bardin, 2011; Bardin et al.,1997; Kayser et al., 2011; Millan, 2002). For instance, in rats subjected to the formalin test, low doses of 5-HT injected via the intrathecal route are known to exert antinociceptive effects whereas larger doses induce a pronociceptive effect, and underlying mechanisms are still not completely understood (Kayser et al., 2011; Oyama et al., 1996). Such dual actions of 5-HT, pronociceptive at the periphery and pro- and/or anti-nociceptive at the spinal level, emphasize the complexity of its implications in the neurobiological mechanisms of nociception. This complex role could be related to the existence of multiple 5-HT receptors expressed both at the periphery and in the CNS. To date, seven classes of 5-HT receptors (5-HT_1–5-HT_7) have been identified that comprise at least 15 subtypes. Except the 5-HT_3-gated cation channel, all 5-HT receptors are G protein-coupled receptors (Masson et al., 2012). Last but not least, alternative splicing of pre-mRNAs, mRNA editing and the oligomerisation of 5-HT receptor proteins with identical (homodimerisation) or different G-protein-coupled receptors (heteromerisation) further contribute to 5-HT receptor complexity (Matthys et al., 2011; Renner et al., 2012). Indeed, oligomerisation can affect markedly the functional and regulatory properties of 5-HT receptors, notably through changes in receptor internalization, downstream intracellular molecular signaling pathways and post-translational phosphorylation of specific serine and tyrosine residues (Masson et al., 2012).

This review deals with the multiple roles played by the various 5-HT receptors present at strategic sites along pain signaling circuits, with a particular attention to 5-HT_7 receptors, for which recent data support the idea that they might be a promising target for innovative strategies aimed at alleviating neuropathic pain (Brenchat et al., 2009, 2010, 2011, 2012a, 2012b; Viguier et al., 2012a, 2012b).

2. The role of bulbospinal serotoninergic system in pain control mechanisms

From the nucleus raphe magnus, the nucleus paragigantocellularis and the ventral portion of the nucleus gigantocellularis in the rostroventral medulla, serotoninergic neurons project specifically into the superficial laminae of the dorsal horn of the spinal cord where primary afferent fibers convey nociceptive signals to second order (mainly spino-thalamic) neurons (Kwiat and Basbaum, 1992). In both rodents and cats, 5-HT terminals at the spinal level have an exclusive supraspinal origin because transection of the thoracic spinal cord leads to an extensive depletion of 5-HT and the disappearance of 5-HT immunoreactivity in the lumbar segments (Oliveras et al., 1977; Ruda et al., 1986). Direct electrical stimulation of the rostroventral medulla induces both the release of 5-HT at the spinal level and concomitant anti-nociceptive effects (Bourgoin et al., 1980; Cui et al., 1999; Hentall et al., 2006; Rivot et al., 1982). In contrast, selective lesions of 5-HT-containing neurons by focal neurotoxin infusion into the rostroventral medulla (Wei et al., 1999) or the lack of these neurons caused by conditional knock out of the transcription factor Lmx1b (Zhao et al., 2007) markedly enhanced inflammation-evoked pain, suggesting that 5-HT neurons within the rostroventral medulla normally mediate a 5-HT-dependent inhibitory control of (persistent) pain. But, after more than 30 years of extensive research, numerous questions regarding the exact role of 5-HT are still pending.

Indeed, in addition to 5-HT, several neuropeptides (substance P, somatostatin, enkephalins, thyrotropin releasing hormone) as well as inhibitory (GABA) and excitatory (glutamate) amino acid neurotransmitters are colocalized in different subpopulations of bulbar serotoninergic neurons projecting into the spinal cord (Finnegan et al., 2004; Kaneko et al., 1990; Minson et al., 1991; Nakamura et al., 2004; Nicholas et al., 1990; Stornetta and Guyenet, 1999). Thus, co-release of a given neuropeptide or of another neuroactive molecule might result in some modulation of the effect of 5-HT and contribute to either enhancement or reduction of its anti-nociceptive action. As a matter of fact, a major breakthrough toward elucidation of the actual implication of 5-HT in pain control mechanisms at spinal cord level has been achieved recently by experiments that consist of the selective suppression of the expression of tryptophan hydroxylase 2 (Tph2), the rate limiting enzyme for 5-HT synthesis, using a sh-RNA (Tph-2-shRNA) approach (Wei et al., 2010). In contrast to previous investigations which involved the loss of serotoninergic neurons, and therefore the elimination of not only 5-HT but also of other neuroactive molecules produced in and released from these neurons, the local administration of Tph-2-shRNA caused the selective depletion of endogenous 5-HT within both neuronal somas of the rostroventral medulla and their projection terminals into the spinal cord without causing any cell loss. Thanks to this innovative approach, Wei et al. (2010) could conclude that the descending spinal serotoninergic pathway originating in the rostroventral medulla exerts a facilitatory influence on pain signaling in animals exhibiting peripheral and/or central sensitization of nociceptive pathways. In line with this inference, inactivation of 5-HT neurotransmission by Tph2-shRNA significantly attenuated hyperalgesia associated with spinal nerve ligation-induced neuronal sensitization in rats (Wei et al., 2010). Accordingly, the net effect of 5-HT not only depends on the receptor subtype mediating its action but also on the physiological/pathophysiological status of the animal. In healthy animals, spinal 5-HT apparently exerts mainly an inhibitory influence of pain signaling mechanisms whereas in animals sensitized by lesion of the peripheral and/or the central nervous system, the bulbo-spinal 5-HT system may exacerbate pain (see also Kayser et al., 2011).

However, also using the spinal nerve ligation model of neuropathic pain for which Wei et al. (2010) found an *up-regulation* of the Tph-2 protein in the rostroventral medulla, Liu et al. (2010) reported a *decrease* in the release of 5-HT within the dorsal spinal cord. Yet, such an apparent decrease in spinal 5-HT tone has been found in other models of neuropathic pain (Goettl et al., 2002; Hains et al., 2002). Accordingly, instead of a neuropathic pain-associated increased activity of a descending 5-HT facilitatory system, it could be postulated that a loss or a decreased activity of a descending inhibitory 5-HT system might contribute to the development of central sensitization. In line with this inference, 5-HT itself and agonists at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-HT_3 and 5-HT_4 receptors administered via the intrathecal route produce an inhibition of the response of dorsal horn wide dynamic range neurons to C-fiber inputs in both normal healthy rats and neuropathic rats, although their efficiency was lower (by about 10-fold) in the latter animals. Furthermore, Hains et al. (2003) found that intrathecal transplantation of serotoninergic neural precursors corrected nearest to control level neuronal hyperexcitability induced by spinal cord injury.