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COMMENTARY

# What would 5-HT do? Regional diversity of 5-HT$_1$ receptor modulation of primary afferent neurotransmission

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5-HT (serotonin) is a significant modulator of sensory input to the CNS, but the only analgesics that selectively target G-protein-coupled 5-HT receptors are highly specific for treatment of headache. Two recent papers in *BJP* shed light on this puzzling situation by showing that primary afferent neurotransmission to the superficial layers of the spinal and trigeminal dorsal is inhibited by different subtypes of the 5-HT$_1$ receptor – 5-HT$_{1B(and\ 1D)}$ in the trigeminal dorsal horn and 5-HT$_{1A}$ in the spinal dorsal horn. The inputs being studied probably include nociceptive afferents, and the similarities of the methods employed in the two studies minimize the possibility that the different findings are an experimental artefact. Rather, the findings raise interesting questions about the possible anatomical or functional basis for the apparent regional selectivity of 5-HT$_1$ receptor actions, and whether these differences could be exploited for therapy. The results also emphasize the relative lack of information we have about the molecular details of the pro- or anti-nociceptive actions of 5-HT itself on primary afferent neurotransmission.

## LINKED ARTICLE

This article is a commentary on Choi *et al.*, pp. 356–367 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2012.01964.x

5-HT (serotonin) is a significant modulator of sensory input to the CNS, with neurons in the raphe nuclei providing dense 5-hydroxytryptaminergic projections to all laminae of the spinal cord and trigeminal dorsal horn (reviewed in Millan, 2002). Drugs that mimic the actions of 5-HT at a subset of 5-HT receptors relieve migraine headache in many people (Ferrari *et al.*, 2001), but they are not effective inhibitors of non-headache-related pain, and there is little evidence that agents that selectively target other 5-HT receptors or modulate endogenous 5-HT levels are effective analgesics in people. 5-HT can act on many types of neuron involved in sensory processing in the spinal cord via multiple receptor types located on the intrinsic spinal cord neurons and their inputs (Millan, 2002). Two recent studies in *BJP* demonstrate distinct differences between the types of 5-HT$_1$ receptor (Alexander *et al.*, 2011) potentially mediating inhibitory actions of 5-HT on spinal and trigeminal primary afferent neurotransmission in rat (Choi *et al.*, 2012; Jeong *et al.*, 2012). Their results highlight that even within contiguous regions of the CNS with the same function, the distinct functional profile of closely related receptors provides a tantalizing opportunity for selective pharmacological targeting of different pain states.

In this issue of the journal, Choi and colleagues report that activation of 5-HT$_{1B}$ (and 5-HT$_{1D}$) receptors inhibit primary afferent-evoked synaptic inputs to the trigeminal dorsal horn, while Jeong *et al.* (2012) showed that 5-HT$_{1A}$ but not 5-HT$_{1B,}$ 5-HT$_{1D}$ or 5-HT$_{1F}$ receptor activation inhibited primary afferent transmission in the lumbar dorsal horn. Both studies used whole cell patch clamp techniques to record glutamatergic excitatory postsynaptic currents (EPSCs) from dorsal horn lamina II neurons in rats of a similar age and the same strain. Lamina II neurons receive significant input from nociceptive C- and Aδ fibre primary afferents and inhibition of EPSCs in these cells is reasonably considered a proxy for potential anti-nociceptive effects. The findings in the trigeminal dorsal horn are consistent with a large body of data in several species showing that 5-HT$_{1B}$, 5-HT$_{1D}$ and/or 5HT$_{1F}$ receptors inhibit activation of the second order neurons in the trigeminal dorsal horn by nociceptive inputs *in vivo*, but there is little

correlative behavioural data from awake animals, presumably because of the difficulty of applying drugs to the brainstem in these conditions. In contrast, Jeong *et al*. (2012) showed that intrathecal administration of 5-$HT_1$ receptor agonists inhibited thermal and mechanical nociception in a manner entirely consistent with their *in vitro* findings – that is, only 5-$HT_{1A}$ receptor activation was effective.

While perhaps not surprising in the context of past findings, these studies highlight some interesting questions. Perhaps foremost is how the apparent regional selectivity in 5-$HT_1$ receptor function arises. There is good anatomical evidence for the expression of each of the 5-$HT_1$ receptors in dorsal root and trigeminal ganglia (e.g. Potrebic *et al*., 2003; Classey *et al*., 2010), so why are all the receptors not active in modulating primary afferent neurotransmission? There is no easy answer. It is possible that the room temperature recording conditions in the study of Choi *et al*. (2012) preferentially limited the activity of some 5-$HT_1$ receptor subtypes, and it is not clear that this study (and previous work in the same region, Jennings *et al*., 2004) was geared to pick up the 5-$HT_{1A}$ activity of sumatriptan (in lieu of using specific 5-$HT_{1A}$ ligands). More intriguingly, it is possible that different types of 5-$HT_1$ receptor are on neurons that project to distinct laminae of the trigeminal or spinal dorsal horn. This seems unlikely for 5-$HT_{1D}$ receptors, as receptor immunoreactivity is concentrated in the superficial laminae of both trigeminal and spinal dorsal horn (Potrebic *et al*., 2003), but the situation is much less clear-cut for other 5-$HT_1$ receptors. A more complex 5-HT receptor pharmacology has been reported for dorsal horn neurons in laminae III to VI in very young rats (Garraway and Hochman, 2001), but this appeared to change even over the first 2 weeks of life, raising the possibility that plasticity of receptor expression makes comparisons between the 2- to 3-week-old animals used for electrophysiology and the young adult animals used in studies of nociception problematic.

While uncertainties may exist over the exact distribution of 5-$HT_{1A/B/F}$ receptors, there is clear evidence that 5-$HT_{1D}$ receptors are found on afferents projecting to both lamina II neurons in lumbar and trigeminal dorsal horn, yet equally compelling evidence indicates that 5-$HT_{1D}$ receptors only inhibit primary afferent neurotransmission in the trigeminal dorsal horn. In both locations, 5-$HT_{1D}$ receptors have been primarily localized to presynaptic dense core vesicles, structures whose contents are usually only mobilized to the membrane by relatively intense stimulation (Potrebic *et al*., 2003). Recent data show that 5-$HT_{1D}$ receptor activation can inhibit nociception associated with inflammation of spinally innervated structures, consistent with receptors being expressed on the surface of sensory neuron terminals undergoing strong stimulation (Nikai *et al*., 2008; Vera-Portocarrero *et al*., 2008). The proposition that inflammation induces trafficking of 5-$HT_{1D}$ receptors has not been tested using recordings of primary afferent EPSCs from dorsal horn neurons, but such experiments could provide mechanistic support for the prospect of pharmacological targeting of receptors that are only active when nociceptors are strongly activated – a very appealing idea. The activity of 5-$HT_{1D}$ agonists in the naïve trigeminal system could reflect the presence of a small population of surface localized receptors not available in spinal cord afferents, different stimulation conditions required to mobilize intracellular receptors in the two afferent populations or signal transduction pathways mediating inhibition of neurotransmitter release that are only recruited by noxious stimulation in the dorsal horn. Distinguishing between these possibilities is likely to be a worthwhile exercise.

Of course, the major unanswered physiological question in both studies is what would 5-HT do? Previous work has indicated that 5-HT can both potentiate and inhibit primary afferent neurotransmission (e.g. Hori *et al*., 1996; Garraway and Hochman, 2001), and given that most subtypes of 5-HT receptor are present in sensory ganglia, 5-HT potentially has both pro- and anti-nociceptive effects through modulation of primary afferent neurotransmission, consistent with the findings that 5-hydroxytryptaminergic neurons projecting to the spinal cord can be parts of distinct descending pathways that facilitate or inhibit noxious sensory information (Millan, 2002). The studies of Jeong *et al*. (2012) and Choi *et al*. (2012) demonstrate a clear difference in the potential mechanisms of 5-HT modulation of noxious information flow from the head and body, careful investigation of the role of other 5-HT receptors in modulating primary afferent inputs is likely to reveal more interesting and potentially therapeutically exploitable differences.

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## Conflict of Interest statement

MC currently collaborates with the authors of one the studies that are the subject of this commentary (H-Y Jeong, CW Vaughan) on unrelated work.

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