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Commentary: Serotonin Receptor 2B Mediates Mechanical Hyperalgesia by Regulating Transient Receptor Potential Vanilloid 1

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ABSTRACT

Serotonin [5-hydroxytryptamine (5-HT)] is an inflammatory mediator which contributes to inflammatory pain. We previously demonstrated that 5-HT-induced mechanical hyperalgesia is mediated by 5-HT_{2B}, but not by other 5-HT receptors. Our recent article provided further evidence how 5-HT_{2B} regulates 5-HT-induced mechanical hyperalgesia, and suggested, that 5-HT_{2B} mediates mechanical hyperalgesia through $G_{q/11}$-phospholipase Cβ (PLCβ)-protein kinase Cε (PKCε) pathway. Interestingly, transient receptor potential vanilloid 1 (TRPV1) also involves in 5-HT_{2B}-mediated hyperalgesia. It was the first evidence that 5-HT receptor regulates TRP channel to affect mechanical hyperalgesia. It is a commentary on the recent article that suggests distinct roles of peptidergic (IB_4-negative) and non-peptidergic (IB_4-positive) nociceptors in regulating 5-HT-induced mechanical hyperalgesia. In IB_4-negative neurons, 5-HT_{2B} in response to 5-HT mediates PLCβ-PKCε to regulate TRPV1 function. In IB_4-positive neurons, 5-HT_{2B} may control 5-HT_3 or other channels to regulate mechanical hyperalgesia.

Serotonin [5-hydroxytryptamine (5-HT)] is known as a neurotransmitter, which is involved in regulating transmission of nociceptive signals in central nerve system[1]. 5-HT is also an inflammatory mediator, released from immune cells, platelets and epithelial cells in the peripheral tissues. Mounting evidence has suggested that 5-HT is a pro-inflammatory and pro-nociceptive agent which can cause pain and hyperalgesia through activating various subtypes of 5-HT receptors which are present in primary afferents[2,3]. We previously demonstrated that 5-HT-induced mechanical hyperalgesia is attributed to 5-HT_{2B} activation[4]. Our recent article provided more detail mechanism that 5-HT_{2B} mediates $G_{q/11}$-phospholipase Cβ (PLCβ)-protein kinase Cε (PKCε) pathway to control mechanical hyperalgesia in both IB_4-negative and -positive neurons. Interestingly, transient receptor potential vanilloid 1 (TRPV1) and 5-HT_3 are also regulated by 5-HT_{2B} to participate in 5-HT-induced mechanical hyperalgesia.

The distinct roles of IB_4-negative and IB_4-positive neurons in 5-HT-induced mechanical hyperalgesia

Pain transduction from the periphery to central nerve system depends on Aδ and C fiber sensory neurons[5]. C-fiber sensory neurons can be divided into two classes depended on their molecular properties. The peptidergic c-fiber expresses the neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP). The non-peptidergic c-fiber binds Isolectin B_4 (IB_4) and expresses glia

cell-derived neurotrophic factor receptors (GDNF) and P2X3 receptors[6]. IB_4-negative neurons have low action potential (AP) threshold and shorter AP duration than IB_4-positive neurons[7]. IB_4-negative neurons are more important in transducing information about stimuli. Consistent with that 5-HT injection dramatically enhanced 5-HT-evoked intracellular calcium signals in IB4-negative neurons, but not in IB_4-positive neurons. Therefore, IB_4-negative neurons are the major neurons responsible for transducing 5-HT stimuli to induce mechanical hyperalgesia. Blocking $5\text{-}HT_{2B}$, PLCβ or PKCε before 5-HT injection inhibited the enhanced calcium signals in IB_4-negative neurons. It is correlated with behavioral results that blocking of $5\text{-}HT_{2B}$-PLCβ-PKCε pathway inhibited mechanical hyperalgesia.

Although IB_4-positive neurons did no increases intracellular calcium signals after 5-HT injection, the number of the neurons responding to 5-HT was increased. IB_4-positive neurons with higher density of tetrodotoxin ((TTX)-resistant Na+ channel and longer AP could lead more efficient calcium influx into the presynaptic terminal, resulting in more transmitter release[8]. IB_4-positive neurons mediating more reliable synaptic connection could participate maintenance of hyperalgesia. As expected, blocking $5\text{-}HT_{2B}$, PLCβ or PKCε before 5-HT injection also inhibited the calcium signals in IB_4-positive neurons.

In IB_4-negative neurons, 5-HT-induced calcium signals were inhibited by removal of extracellular calcium; while only some of IB_4-positive neurons were sensitive to calcium-free condition. It indicated that channels allow calcium influx may participate in 5-HT-induced calcium signals. TRPV1 and $5\text{-}HT_3$ are identified to participate in the downstream of $5\text{-}HT_{2B}$-mediated signaling pathway in IB_4-positive and IB_4-negative neurons, respectively.

Participation of TRPV1 in 5-HT signaling transduction in IB_4-negative neurons: contribution to induction of mechanical hyperalgesia

TRPV1 is known as a heat and capsaicin receptor, which is widely expressed in sensory neurons, especially in c-fiber nociceptors. TRPV1 is expressed both in peptidergic and non-peptidergic c-fiber in rat but predominantly in peptidergic c-fiber in mouse by immunohistochemical analysis[9,10]. Although capsaicin-induced calcium signals were greater in IB_4-positive neurons than in IB_4-negative neurons before 5-HT injection, capsaicin-evoked calcium signals were significantly enhanced in IB_4-negative neurons after 5-HT injection. Therefore, capsaicin-sensitive IB_4-negative neurons may play a role in 5-HT-induced mechanical hyperalgesia under regulation of $5\text{-}HT_{2B}$-PKCε.

As confirmed in animal behavioral studies, administration of a TRPV1 antagonist before 5-HT injection in mice inhibited 5-HT-induced mechanical hyperalgesia. Mice lacking TRPV1 genes also showed the absence of mechanical hyperalgesia after 5-HT injection. Even though TRPV1 participates in thermal hyperalgesia, several lines of evidence have also suggested that the involvement of TRPV1 in capsaicin, acid or CFA-induced mechanical hyperalgesia which indicated the involvement of TRPV1 in mechanical hyperalgesia[11,12]. In those studies, TRPV1 is activated either by acid or by capsaicin. Despite that TRPV1 function is enhanced by 5-HT through PKA and PKC phosphorylation[13,14]. However, no evidence demonstrated that TRPV1 can be activated by 5-HT. How $5\text{-}HT_{2B}$ regulates TRPV1 function remains unclear. In addition to being activated by allyl-isothiocyanate, capsaicin, acid, noxious heat and the pungent compound in mustard and wasabi, TRPV1 can be activated by some endogenous ligands. Anandamide (AEA), an endogenous fatty acid neurotransmitter derived from arachidonic acid (AA), can bind to and activate cannabinoid CB1 and CB2 receptors[15]. The AEA is generated from N-acylphosphotidylethanolamides (NAPE) through phospholipase C-mediated hydrolysis[16] and is reported to activate TRPV1[17]. The data give one possible way that activation of $5\text{-}HT_2$ receptor may mediate PLC leading AEA formation to activate TRPV1. Arachidonic acid (AA) is the precursor that can be metabolized by various enzymes. The products of lipoxygenase include 12- and 15-HEPETE, and 5-HETE that are also TRPV1 agonists[18]. $5\text{-}HT_{2B}$ receptor activation activate phospholipase A2, leading the neuronal secretion of AA[19]. Therefore, peripheral $5\text{-}HT_{2B}$ activation by 5-HT may relieve phosphatidylinositol 4,5-bisphosphate-dependent channel inhibition and generates endogenous ligands AEA or AA to activate and regulate peripheral TRPV1 function, resulting in mechanical hyperalgesia.

Participation of $5\text{-}HT_3$ in 5-HT-induced calcium signal in IB_4-positive neurons: contribution to maintenance of mechanical hyperalgesia

The calcium signals in IB_4-negative neurons were completely dependent on $5\text{-}HT_{2B}$- PLCβ- PKCε signaling and TRPV1 activation as described above. 5-HT-induced calcium signals in IB_4-positive neurons were partially sensitive to removal of extracellular calcium, suggesting that the calcium signals may be from channels in both the plasma membrane and the endothelium reticulum (ER). $5\text{-}HT_3$ receptor antagonist (Granisetron) specifically inhibited 5-HT-induced calcium signals in a small set of IB_4-positive population, explaining sensitivity of these neurons to removal of extracellular calcium. Thus, there are at least two distinct pathways in IB_4-positive neurons in response to 5-HT stimulation. One is $5\text{-}HT_{2B}$- PLCβ- PKCε pathway and the other is $5\text{-}HT_{2B}$- PLCβ- PKCε/$5\text{-}HT_3$ pathway.

$5\text{-}HT_3$ was found in pain-related regions and is involved in pain processing[20,21]. In our previous study, mice with pre-injection of $5\text{-}HT_3$ antagonist did not inhibit mechanical hyperalgesia but shortened the duration of pain after 5-HT

injection[4]. Data from the recent article are consistent with the previous study by Lin et al., that 5-HT_3 is not involved in 5-HT-induced mechanical hyperalgesia[1]. However, the shortening of mechanical hyperalgesia suggests that 5-HT_3 may have an influence on modulating the maintenance of hyperalgesia. Stucky and Lewin[7] suggested that IB_4-positive neurons have a higher action potential (AP) threshold and longer AP duration than IB_4-negative neurons. Also, there are some reports showing that IB_4-positive neurons can exhibit sustained responses, but not transient or mixed responses to low pH[22]. Therefore, the responses in IB_4-positve neurons that are sensitive to granisetron are thought to be responsible for extending the duration of 5-HT-induced mechanical hyperalgesia.

The GPCR-TRP channel axis in 5-HT-induced pain and itch-like sensation

In previous studies, 5-HT can induce pain and itch sensations in mice and humans[23]. A subset of 5-HT-sensitive neurons is also sensitive to histamine and chloroquine, suggesting that these neurons are involved in itch perception[24]. A distinct subgroup of c-fibers that were preferentially excited by pruritic compounds has been reported[25]. 5-HT_2 receptors were reported to respond for 5-HT-induced itch through activating Gq/11-PLC pathway, which leads to mitogen-activate protein kinase (MAPK) and PKC activation[26]. GPCR-TRP channel pathways are the major pathways to itch responses. Similarly, 5-HT-induced mechanical hyperalgesia is also mediated by 5-HT_{2B}-TRPV1 pathway. Our recent article also provides more detailed mechanisms about transduction and maintenance of pain signals. Transduction of noxious stimulation could be located at IB_4-positive nociceptors and mediated by 5-HT_{2B}-5-HT_3 channel axis and 5-HT_{2B}-second messenger pathways. The similarity of GPCR-TRP channel axis between pain and itch sensation suggests that mechanisms used in pain sensation are possibly involved in itch sensation.

Conclusions

The recent article demonstrated that peptidergic and non-peptidergic nociceptors mediate 5-HT signaling through distinct mechanisms to induce mechanical hyperalgesia. The axis of 5-HT_{2B}-Gq-PLCβ-PKCε-TRPV1 used in peptidergic neurons contributes to induction of hyperalgesia, while the axis of 5-HT_{2B}-Gq-PLCβ-PKCε-5-HT_3 in non-peptidergic neurons participates in maintenance of hyperalgesia. The GPCR-TRP channel axis used in pain sensation could be also involved in itch sensation.

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