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MEETING ABSTRACT

A2.8

Mechanisms underlying the excitation of rat sensory neurons via metabotropic 5-HT receptors

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Background: Serotonin (5-HT) is an inflammatory mediator and involved in pain sensation. Ionotropic 5-HT_3 receptors of dorsal root ganglion (DRG) neurons are thought to mediate this effect. However, the role of metabotropic 5-HT receptors is still unknown. Here, the contribution of metabotropic 5-HT receptors and their functional interactions with K_V7, TRPV1 and Ca^{2+}-activated Cl^- channels (CaCCs) were investigated.

Methods: Using the perforated patch-clamp technique in voltage- and current-clamp mode on primary cultures of rat DRG neurons, effects of 5-HT receptor ligands on membrane potential and currents through K_V7, TRPV1 and Ca^{2+}-activated Cl^- channels were investigated.

Results: 5-HT increased the excitability of DRG neurons and caused depolarizations. This effect was not altered by the 5-HT_3 receptor antagonist tropisetron, but reduced by the 5-HT_2 receptor antagonist ritanserin. Moreover, this excitation of DRG neurons by 5-HT was inhibited by the TRPV1 antagonist iodoresiniferatoxin (I-RTX) and the CaCC (TMEM16) blocker $CaCC_{inh}$-A01, but not by the TMEM16A-specific blocker $T16A_{inh}$-A01. Furthermore, this 5-HT-induced excitation was inhibited by the 5-HT_{2A} receptor-specific antagonist 4F 4PP oxalate rather than by the 5-HT_{2C} receptor-specific antagonist RS-102221 hydrochloride. Currents through K_V7 channels of DRG neurons were not inhibited by 5-HT. By contrast, 5-HT enhanced currents through TRPV1 channels in DRG neurons. This increase of the TRPV1 current was inhibited by the 5-HT_2 receptor antagonists ritanserin and ketanserin. Moreover, the enhancement was also inhibited by blocking both 5-HT_{2A} and 5-HT_{2C} receptors. As expected, this enhancement of currents through TRPV1 channels by 5-HT was inhibited by the PLC-blocker U73122, the PKC blocker GF109203X, the Ca^{2+}-ATPase blocker thapsigargin and the Ca^{2+} chelator BAPTA-AM, respectively. Additionally, 5-HT also enhanced currents through CaCCs. The involvements of 5-HT_2 receptors in the potentiation of CaCC currents via 5-HT and related signaling mechanisms will be investigated further.

Discussion: These results indicate that the 5-HT_2 receptor-induced increase in excitability is not mediated by K_V7 channel inhibition, but rather by sensitization of TRPV1 channels and activation of CaCCs. Additionally, this effect involves activation of both PLC and PKC.

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