Discovery of a new MrgprA3 agonist and evaluation of its effect for itch sensation

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The G-protein-coupled receptor MrgprA3 (MAS-related GPR family member A3) is expressed specifically in a subpopulation of dorsal root ganglion (DRG) sensory neurons. Recently, MrgprA3^{+} DRG neurons are identified as itch-selective neurons. While MrgprA3 responds to the anti-malaria drug chloroquine and causes strong itch, chloroquine requires high concentrations to activate MrgprA3 and also displays non-selective effects. Therefore, it is necessary to accurately evaluate the ability of MrgprA3 to cause itch sensation. In this study, we screened a series of small molecule compounds to search for agonists that activate MrgprA3 by high-throughput Ca^{2+} imaging. We identified papaverine, an opium alkaloid, that specifically evoked Ca^{2+} responses in cells expressing MrgprA3. Papaverine also increased Ca^{2+} level in primary cultured DRG neurons that were responded to chloroquine. Furthermore, we found that intradermal injection of papaverine to the cheek produced scratching behavior but not wiping behavior in mice. Papaverine-evoked scratching was resistant to the histamine H1 receptor antagonist chlorpheniramine. We further found that intradermal papaverine caused phosphorylation of extracellular signal-regulated kinases (ERK) in the superficial dorsal horn. Finally, we showed that mice lacking gastrin-releasing peptide receptors (GRPR) that are required for itch transmission in the spinal cord exhibited reduction of the papaverine-evoked scratching compared with wild-type mice. In this study, we found that papaverine potently activates MrgprA3 and may cause itch sensation via activation of MrgprA3.