Histamine H3 receptor inverse agonist alleviate mechanical allodynia through the activation of H1R and H2R in periaqueductal gray matter.

Yu Mei[1], Takeo Yoshikawa[1], Takuro Matsuzawa[1], Hidetoshi Tozaki-Saitoh[2], Kazuhiko Yanai[1]

[1]Dept. Pharmacol., Grad. Sch. Med., Tohoku Univ., [2]Dept. Life-Innovation., Grad. Sch. Pharm., Kyushu Univ.

The histamine H3 receptor (H3R), an inhibitory G-protein coupled receptor, is exclusively expressed at axon terminals in the brain. H3R negatively regulates histamine release as an autoreceptor and also inhibits the release of other neurotransmitters including GABA and acetylcholine as an heteroreceptor. Recent evidence indicates that H3R inverse agonists, which can induce the release of histamine and other neurotransmitter, alleviate mechanical allodynia. However, the mechanism(s) by which H3R inverse agonists attenuate allodynia remain unclear.

Here, we aimed to uncover the mechanism of action for JNJ-10181457 (JNJ1), an H3R inverse agonist, in mechanical allodynia. The intraperitoneal administration of JNJ1 to Chung-model mice significantly increased paw withdrawal threshold, confirming the therapeutic effect of H3R antagonists on allodynia. However, JNJ1 could not alleviate pain symptom in histamine-deficient mice. Pharmacological assays showed that the therapeutic action of JNJ1 were diminished by H1R antagonist and H2R antagonist. When we deleted H3R around the periaqueductal grey matter (PAG) by AAV-based gene recombination, the therapeutic action of JNJ1 was diminished.

These results indicated that histamine release around PAG by JNJ1 activated H1R and H2R and subsequently exerts an antinociceptive effect in allodynia.