1. No.

   2021G022

2. Title

   Novel Regulatory Systems of Pain and Itch by α4β2 Nicotinic Acetylcholine Receptor-Expressing Neurons

3. Period

   2021-2025

4. Summary

Given that the economic burden of chronic pain and itch has been estimated to be substantial, the establishment of effective therapeutic strategies for these conditions is an urgent priority. This study aimed to elucidate the mechanisms underlying the regulation of pain and itch mediated by α4β2 nicotinic acetylcholine receptor–expressing ($nAChR^+$) neurons in the spinal dorsal horn (SDH).

Among individual nAChR α and β subunits, α4 (*Chrna4*) and β2 (*Chrnb2*) subunits exhibited the highest mRNA expression levels in the mouse SDH. Using *Chrna4*-enhanced green fluorescent protein (EGFP) mice, in which the α4 subunit is fluorescently labeled, we found that the EGFP was abundantly expressed in lamina II of the SDH. The majority of $EGFP^+$ cells were $NeuN^+$, and those were localized to both excitatory ($EBF2^+$) and inhibitory ($Pax2^+$) populations. Moreover, a subset of these EGFP+ neurons were partially responded to acute pain or itch stimuli.

Systemic administration of TC-2559, an α4β2 nAChR agonist, suppressed capsaicin-induced acute pain and chloroquine-induced non-histaminergic itch in mice; however, intrathecal (i.t.) administration suppressed acute pain but had no effect on itch. In contrast, systemic administration of another α4β2 nAChR agonist, sazetidine A, suppressed both chloroquine- or compound 48/80-induced acute itch and diphenylcyclopropenone-induced chronic itch, and i.t. administration also produced antipruritic effects comparable to those observed with systemic administration. By contrast, the inhibitory effects of sazetidine A on acute pain were limited.

These findings suggest that α4β2 nAChR signaling in the superficial SDH may play a key role in the regulation of pain and itch processing via diverse populations of interneurons. Future studies aimed at further functional characterization of α4β2 $nAChR^+$ neurons will help elucidate the molecular basis of pain and itch and may contribute to the development of novel therapeutic strategies.