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Novel Regulatory Mechanisms Mediated by a K^+ Channel Interacting Protein NCS-1 (an Intracellular Ca^{2+} Sensor)

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Summary

[Purpose] The number of patients with neuropathic pain is more than hundreds of thousands in Japan. However, conventional analgesics is not effective enough, thus, a new therapeutic strategy is required. Many ion channels such as voltage-gated Na^+ channels and TRP channels are involved in the mechanism of pain reception and transmission. Among them, the generation of action potentials due to depolarization and the increase in intracellular Ca^{2+} concentration induce pain. On the other hand, there is a system that suppresses pain in the living body. The voltage dependent A-type K^+ current (ISA) suppresses the firing of action potentials by hyperpolarization and suppresses neural excitability. In fact, it has been suggested that the Kv4 channel, known as the molecular component of ISA, may be a target for pain relief. On the other hand, we have previously identified the Ca^{2+} sensor NCS-1 as a regulator of the Kv4 channel. NCS-1 physically interacts with the Kv4 channel in mouse brain and increases the Kv4 channel current amplitude. However, the relationship between NCS-1 and pain relief is completely unknown. The purpose of the present study is to clarify whether the Ca^{2+} sensor NCS-1 can be a novel therapeutic target for neuropathic pain, including its molecular mechanism.

[Methods and results] We first confirmed that both Kv4.3 and NCS-1 proteins are highly expressed in mouse dorsal root ganglion (DRG) by immunofluorescence. In addition, when NCS-1 deficient (KO) mice were compared with wild-type (WT) mice, it was found that KO mice were more sensitive to mechanical stimuli in both males and females. On the other hand, no difference was detected regarding the sensitivity to thermal stimulation between WT and KO mice.

[Discussion] The above results suggest that NCS-1 may specifically contribute to the pain relief pathway by mechanical stimulation rather than thermal stimulation. It is necessary to consider whether NCS-1 physically binds to Kv4 channels in DRG, whether the expression/activity of Kv4 channels is reduced, and whether membrane excitability and intracellular Ca^{2+} dynamics are changed in KO mice. If new pain relief pathways mediated by NCS-1 are elucidated, they can be specific targets for the development of new analgesics for neuropathic pain.