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Glutamatergic and GABAergic signaling in peripheral nociceptive neurons: contributions to chronic pain

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Although it is well known that pro-nociceptive molecules such as AMPAR and PKG-I, and anti-nociceptive molecule such as $GABA_B$ receptors are expressed in the peripheral and central nervous system, their peripheral versus central contributions in chronic pain are still unknown. To elucidate the role of these signaling molecules expressed in peripheral nociceptive neurons towards pain modulation, we generated conditional knock-out mice lacking GluA1 or GluA2 subunit of AMPAR or $GABA_{B(1)}$ subunit of $GABA_B$ receptors or PKG-I specifically in nociceptors using Cre/lox system under the control of $Na_v1.8$ promoter. In this study, we also successfully characterized the deletion of GluA1 and GluA2 subunits of the AMPAR, PKG-I and $GABA_{B(1)}$ subunit of $GABA_B$ receptor specifically in peripheral nociceptive neurons without altering their expression elsewhere in the nervous system.

Detailed analyses in mice lacking GluA1 and GluA2 revealed that peripherally expressed GluA1, but not GluA2 of the AMPAR led to a significant reduction in endogenous agonist-induced calcium permeability and in the firing rate of peripheral nerve fibers following inflammation, without changing the basal properties of nociceptors. This clearly demonstrates that AMPAR play a vital role in regulating the activation properties of nociceptors to different algogens present in the inflammatory milieu. Moreover, these results suggest that GluA1 containing AMPAR affect both peripheral and central hyper-excitability processes by controlling the inflow of nociceptive impulses from the periphery into the central nervous system. Our analyses on SNS-PKG-I mice suggest that PKG-I expressed in nociceptor terminals is the key target of cGMP produced by NMDA-NO-sGC pathway as well as NPs-mGC pathway at the nociceptive spinal synapses, where it mediates potentiation of nociceptive transmission. Furthermore, phosphorylation of IP3R1 and MLC at presynaptic terminals is the major downstream signaling event that mediates the action of PKG-I in amplifying the nociceptive transmission, thus contributing to pathological pain hypersensitivity. Our findings in mice lacking $GABA_{B(1)}$ subunit of $GABA_B$ receptor in peripheral nociceptors clearly illustrate that $GABA_B$ receptors are not involved in the

modulation of nociceptive transmission under different pathological states accompanied with pain hypersensitivity. Besides, we also found that peripheral $GABA_B$ receptors are not involved in baclofen-induced anti-nociception.

Taken together, these findings clearly elucidate and delineate the central versus peripheral components of actions of key pro- and anti-nociceptive molecules in chronic pain. These results also support the hypothesis that peripheral mechanisms play a fundamental role in triggering central changes, which are associated with chronic pain conditions.

Finally, these results provide a basis for developing drugs that target specifically GluA1 containing AMPAR or PKG-I present in the periphery may help in improving chronic pain and offer a unique opportunity to get rid off any unwanted deleterious central side effects. Our results also suggest that peripheral $GABA_B$ receptor play a lesser important role in the modulation of nociceptive information as compared to centrally expressed $GABA_B$ receptors. Hence, therapeutic approaches targeting peripheral $GABA_B$ receptors are unlikely to be beneficial in alleviating pain.