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Mechanism of calcium channel $\alpha_2\delta$-1 subunit mediated neuropathic pain

Z.D. Luo[1], D. Kim[1], A. Boroujerdi[2], k. Li[1], P. Deng[3], X. Zhang[1], M. Corpe[1], F. Zaucke[4], Z. Xu[3]

[1]Anesthesiology & Perioperative Care, University of California, Irvine, Orange, CA, [2]Pharmacology, University of California, Irvine, Irvine, CA, [3]Anatomy & Cell Biology, Indiana University, Indianapolis, IN, [4]Center for Biochemistry, University of Cologne, Cologne, Germany

Peripheral nerve injury induces upregulation of spinal voltage-gated calcium channel $\alpha_2\delta$-1 subunit that causes neuropathic pain through an unknown mechanism. Since $\alpha_2\delta$-1 is the neuronal receptor for thrombospondin (TSP), astrocyte-secreted, synaptogenic proteins that are also upregulated in spinal cord post injury, we hypothesized that $\alpha_2\delta$-1 might interact with TSP4 in abnormal synaptogenesis, leading to spinal neuron hyperexcitability and behavioral hypersensitivity. To test this hypothesis, we examined the role of spinal $\alpha_2\delta$-1 or TSP4 in dorsal horn neuron hyperexcitability and behavioral hypersensitivity; and their potential interactions in mediating abnormal sensations. Our data indicated that increased spinal $\alpha_2\delta$-1 or TSP4 enhanced frequency of dorsal horn neuron mEPSC and behavioral hypersensitivity, both of which could be blocked by gabapentin, a drug binds to $\alpha_2\delta$-1 proteins. In addition, allodynia induced by overexpressing $\alpha_2\delta$-1 in transgenic mice could be blocked by intrathecal TSP4 antibodies, which did not alter behavioral sensitivity in age- and sex-matched wild-type littermates. TSP4 immunoprecipitates from rat spinal cord contained the calcium channel α_{1B}, $\alpha_2\delta$-1 and β3 subunits. Nerve injury induced up-regulation of $\alpha_2\delta$-1/TSP4, enhanced co-localization of these proteins, co-localization of TSP4 with pre-synaptic marker SV2, but not post-synaptic marker PSD95 in spinal dorsal horn of injury side when injured animals displayed allodynia. Together, our findings support a mechanism of $\alpha_2\delta$-1-induced neuropathic pain in which spinal $\alpha_2\delta$-1 interacts with TSP4 that leads to enhanced neurotransmitter release and dorsal horn neuron hyperexcitability, presumably through increased pre-synaptic excitatory synapse formation.

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