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Downregulation of neuroligin1 ameliorates postoperative pain through inhibiting neuroligin1/postsynaptic density (PSD) 95-mediated synaptic targeting of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor *GluR1* subunits in rat dorsal horns

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Statement of the Problem: Neuroligin1 is an important synaptic cell adhesion molecule that modulates the function of synapses through protein-protein interactions. Yet, it remains unclear whether the regulation of synaptic transmission in the spinal cord by neruoligin1 contributes to the development of postoperative pain.

Methodology: In a rat model of postoperative pain induced by plantar incision, we conducted Western blot study to examine changes in the expression of postsynaptic membrane of neuroligin1, postsynaptic density (PSD)-95, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor *GluR1* and *GluA2* subunits in the spinal cord dorsal horn after injury. The interaction between neuroligin1 and *PSD-95* was further determined by using co-immunoprecipitation.

Findings: Protein levels of neuroligin1 and *GluR1*, but not *GluA2* and *PSD-95*, were significantly increased in the postsynaptic membrane of the ipsilateral dorsal horn at 3 h and one day after incision, as compared to that in control group (naïve). A greater amount of *PSD-95* was co-immunoprecipitated with neuroligin1 at 3 h after incision than that in the control group. Intrathecal administration of small interfering RNAs (siRNAs) targeting neuroligin1 suppressed the expression of neuroligin1 in the spinal cord. Importantly, pretreatment with intrathecal neuroligin1 siRNA2497, but not scrambled siRNA or vehicle, prevented the upregulation of *GluR1* expression at 3 h after incision, inhibited the enhanced neuroligin1/PSD-95 interaction, and attenuated postoperative pain.

Conclusion & Significance: Current findings suggest that downregulation of spinal neuroligin1 expression may ameliorate postoperative pain through inhibiting neuroligin1/PSD-95 interaction and synaptic targeting of *GluR1* subunit. Accordingly, spinal neuroligin1 may be a potential new target for postoperative pain treatment.

Recent Publications

1. Kim J A, Kim D, Won S Y, Han K A, Park D, et al. (2017) Structural insights into modulation of neurexin-neuroligin trans-synaptic adhesion by MDGA1/Neuroligin-2 complex. Neuron 94(6): 121–1131.
2. Wang Q, Li D, Bubula N, Campioni M R, McGehee D S, et al. (2017) Sensitizing exposure to amphetamine increases AMPA receptor phosphorylation without increasing cell surface expression in the rat nucleus accumbens. Neuropharmacology
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4. Zhang B, Sudhof T C (2016) Neuroligins are selectively essential for NMDAR signaling in cerebellar stellate interneurons. J Neurosci. 36(35): 9070–83.
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Biography

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