GlyR3: An essential target for spinal PGE2-mediated inflammatory pain sensitization

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Glycine receptors (GlyRs) are involved in the control of spinal motor and sensory pathways, but little is known about the biological roles of different GlyR subtypes. We show that GlyR 3 subunits are distinctly expressed in superficial laminae of the dorsal spinal cord, the first site of synaptic integration in the pain pathway. At this site, glycinergic neurotransmission is inhibited by prostaglandin E2 (PGE2), a pivotal mediator of inflammatory pain sensitization. An exaggerated sensation of pain, induced by inflammation, can result from either increased excitability of primary afferent nociceptive nerve fibers (peripheral sensitization) or changes in the central processing of sensory stimuli, (central sensitization). Here, we demonstrate that inhibition of a specific glycine receptor subtype (GlyR3) by PGE2-induced receptor phosphorylation underlies central inflammatory pain sensitization. We show that mice deficient in GlyR3 not only lack the inhibition of glycinergic neurotransmission by PGE2 seen in wild-type mice, but also show a reduction in pain sensitization induced by spinal PGE2 injection or peripheral inflammation. These results identify a new molecular pathway involving GlyR3 subunits as a primary substrate responsible for spinal inflammatory pain sensitization. Thus, GlyR3 may provide a novel molecular target in pain therapy.

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