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Role of PKGI α -mediated Spinal Dorsal Horn Plasticity in Chronic Pain

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Chronic pain due to a variety of health conditions is the primary reason people seek medical care, yet current therapies either are inadequate or cause intolerable side effects. Understanding cellular and molecular processes that lead to the initiation and maintenance of chronic pain will give promise to the development of more effective, more specific pain therapies. Chronic pain is an expression of neuronal plasticity, which is mediated in part by increased excitability of nociceptive neurons in the dorsal horn of the spinal cord [1]. The molecular mechanisms that underlie this nociceptive plasticity are not fully understood. In the spinal cord, Nitric Oxide (NO) is known to contribute to central mechanisms that induce hyperalgesia and allodynia [2-9]. There is also convincing evidence that a downstream molecule of the NO-cyclic guanosine monophosphate (cGMP) signaling pathway, Protein Kinase G (PKG), is involved in spinal nociceptive processing [10-16]. However, PKG phosphorylation targets in the spinal cord and their role in the central sensitization of chronic pain have not been elucidated.

Previous studies have focused on understanding the role of the NO synthases (NOS), soluble guanylyl cyclase (sGC) and PKG that participate in the NO-cGMP-PKG signaling pathway in chronic pain. Each of these proteins is up regulated in chronic pain, and blockade of any of these steps results in a profound reduction in the development of chronic pain. Endogenous NO is produced by NOS, of which neuronal NOS (nNOS) is activated and up-regulated after *N*-Methyl-D-Aspartate (NMDA) receptor stimulation in the central nervous system (CNS) [17-20]. It is widely accepted that NO is an important mediator in spinal nociceptive processing and contributes to molecular mechanisms of hyperalgesia and allodynia. The NO signal is transduced through the activation of the sGC, elevated cGMP levels and activation of the cGMP-dependent PKG, which is an intracellular target for cGMP. PKG has two isoenzymes in mammals, cytosolic PKGI and membrane-bound PKGII. Furthermore, PKGI has been shown to exist in two isoforms, PKGIα and PKGIβ [21,22]. PKGII is not found in the spinal cord [16]. The NO-cGMP-PKG signaling pathway has become increasingly important as our understanding of its diverse biological actions has expanded, especially within the CNS [8,23,24]. Considerable evidence has demonstrated that the NO-cGMP-PKG signaling pathway is present in the neurons of the spinal cord and contributes to the development of hyperalgesia and allodynia in models of acute and chronic pain [8,11,12,14,16]. We have found that PKGIα is abundantly expressed in the superficial laminae at different spinal cord levels and is upregulated by intraplantar injection of complete Freund's adjuvant in the spinal cord. Noxious stimulation increases NOS expression [25-27], cGMP content [28], and PKGIα expression [12,16]in the spinal cord. Administration of inhibitors of NOS, sGC, and PKGI causes analgesic effects [3,4,9,11,12, 16,20,29-31] and enhances antinociception mediated by opioid receptors [32-34]. In addition, reduced formalin-evoked nociception and inflammatory hyperalgesia are observed in PKGI-deficient mice [14]. These studies provide strong evidence that the NO-cGMP-PKG signaling pathway plays an important role in pain modulation.

Chronic pain, consisting of tissue damage-induced inflammatory pain and nerve injury-induced neuropathic pain, is an expression of neuronal plasticity. One component of the plasticity is that the afferent input generated by injury and intense noxious stimuli triggers an increased excitability of nociceptive neurons in the spinal cord. This central sensitization is an activity-dependent functional plasticity that results from activation of different intracellular kinase cascades leading to the phosphorylation of key membrane receptors and channels, increasing synaptic efficacy [1]. The NO-cGMP-PKG signaling pathway is required for noxious stimulation-produced transcription-dependent, long-term sensitization of nociceptive sensory neurons [35]. For example, in nociceptive neurons of *Aplysia*, PKGI is located in axons, where it is activated by nerve injury. In the activated state, PKGI is transported retrogradely to the cell body and phosphorylates a Mitogen-Activated Protein Kinase (MAPK). This phosphorylation triggers MAPK translocation into the nucleus and subsequent alterations in gene expression [36].

Protein phosphorylation is a notable post-translational modulation in nociceptive neurons [1]. Pain hypersensitivity is the consequence of early post-translational changes, both in the peripheral terminals of the nociceptor and in the spinal dorsal horn neurons. This neuroplasticity is the consequence of a combination of activity-dependent changes in the neurons and specific signal molecules initiating particular signal-transduction pathways. These pathways phosphorylate membrane proteins, changing their function, and activate transcription factors, altering gene expression [37]. PKG is a serine-threonine kinase, and it functions mainly by targeting its substrates and phosphorylating the targeted molecules at serine and/or threonine residues. The phosphorylation of these molecules will result in a series of physiological responses. A few molecules have been reported to be involved in the PKG signaling pathway as its phosphorylation targets and might play important roles in spinal PKGIα-mediated central sensitization of chronic pain. For instance, the family of Transient Receptor Potential Channels (TRPCs) is the vanguard of sensory systems, responding to temperature, touch, pain, osmolarity, pheromones, taste and other stimuli [38,39]. PKG can phosphorylate TRPC3 at Thr-11 and Ser-263, causing inactivation of TRPC3 [40]. In contrast, Ca^{2+} influx triggered by the activation of TRPCs contributes to the production of NO, which subsequently stimulates the NO-cGMP-PKG signaling pathway [41].

In conclusion, PKGIα might be involved in spinal nociceptive processing by phosphorylating its target proteins and thereby mediating spinal dorsal horn plasticity in chronic pain.

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