Involvement of kinase modulation of T-type calcium channels in inflammatory pain

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T-type Ca^{2+} channels (T-channels) play a crucial role in central and peripheral pain processing. A series of our studies have shown the involvement of the $Ca_v3.2$ isoform of T-channels in neuropathic and visceral pain. Interestingly, all isoforms of T-channels, $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$, are sensitized by protein kinase A (PKA). Therefore, it is likely that prostaglandin E_2 (PGE_2), a mediator of inflammatory pain, known to enhance intracellular cyclic AMP (cAMP) levels via EP2 or EP4 receptors, might sensitize T-channels. Using undifferentiated NG108-15 cells that abundantly express $Ca_v3.2$, we demonstrated that PGE_2 or dibutyryl cAMP (db-cAMP) increased T-channel-dependent currents, an effect blocked by NNC 55-0396, a selective T-channel inhibitor. The sensitization of T-channels by PGE_2 or db-cAMP was suppressed by A-kinase-anchoring protein (AKAP) St-Ht31 inhibitor peptide (AKAPI), an inhibitor of AKAP as a scaffolding protein for PKA. The PGE_2-induced increase in T-currents was blocked by RQ-00015986-00 (RQ), an EP4 antagonist. Using the immunoprecipitation technique, we detected formation of a protein complex of $Ca_v3.2$ and AKAP150, and demonstrated that activation of the cAMP/PKA pathway enhanced phosphorylation of $Ca_v3.2$. In rats, intraplantar administration of PGE_2 or db-cAMP caused mechanical hyperalgesia, an effect suppressed by AKAPI, NNC 55-0396 and $ZnCl_2$, known to inhibit $Ca_v3.2$, but not $Ca_v3.1$ or $Ca_v3.3$. The PGE_2-induced hyperalgesia was also blocked by RQ. These results suggest that the PGE_2/EP4/cAMP/PKA pathway causes phosphorylation and subsequent sensitization of $Ca_v3.2$ in an AKAP-dependent manner, contributing to the development of mechanical hyperalgesia during inflammation.