Contribution of DNMT3a to neuropathic pain genesis by downregulating Kcna2 in primary afferent neurons

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Neuropathic pain is hard to treat in part due to a vague understanding of nerve injury-induced changes in gene transcription in dorsal root ganglion (DRG) neurons. DNA methylation gates gene expression. Here, we report that nerve injury increases the *de novo* methyltransferase DNMT3a expression via the activation of the transcription factor octamer transcription factor 1 in the injured DRG neurons. Blocking this increase inhibits nerve injury-induced elevation in the methylation of the voltage-dependent potassium (Kv) channel *Kcna2* promoter region and rescues its expression in the injured DRG and impairs neuropathic pain, whereas mimicking this increase reduces the *Kcna2* promoter activity, its expression and Kv current and increases excitability in the DRG neurons and leads to spinal cord central sensitization and neuropathic pain symptoms. DNMT3a co-localizes with Kcna2 in DRG neurons. DNMT3a likely acts as an endogenous instigator of neuropathic pain by epigenetically attenuating DRG Kcna2 expression.