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.