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Kinetic properties and pharmacology of voltage-gated Na channels involved in pain pathways

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Voltage-gated Na (NaV) channels expressed in dorsal root ganglion neurons (DRG) such as NaV1.8 and NaV1.9 have been proposed to play important roles in nociception and pain signalling. NaV1.8 and NaV1.9 are exclusively expressed in dorsal root ganglion (DRG) neurons, with NaV1.9 being selectively expressed in small diameter C fibres1. The NaV1.8 channel is the predominant channel driving TTX-resistant action potentials (AP) in DRG neurons and plays a major role in shaping the AP waveform due to its slow rate of inactivation. Given its relatively depolarized voltage dependence of inactivation, NaV1.8 can contribute to action potential generation even at depolarized membrane potentials which may occur during nerve injury or pain signalling2. This property, coupled with its location in DRG neurons and the modification of expression patterns in animal models of pain and human pain states, has meant that NaV1.8 has received attention as a novel target for pain therapeutics for chronic, inflammatory and neuropathic pain. Although NaV1.9 probably does not contribute to action potential amplitude, it most likely acts as a threshold channel, contributing to resting membrane potential and lowering the threshold for action potentials thereby increasing repetitive firing3. Gain-of function mutations in human pain disorders points to a role of NaV1.9 in pain sensation and transmission in humans.

Until recently the expression of NaV1.8 or 1.9 proved problematic in heterologous expression systems. We have utilized two cell lines for NaV1.8, either in hNaV1.8 expressed in CHO cells or rNaV1.8 expressed in ND7-23 cells, and one cell line for hNaV1.9 expressed in HEK293 cells. We have used automated patch clamp to investigate the activation, inactivation and pharmacological properties of hNaV1.8, rNaV1.8 and hNaV1.9. For NaV1.8, the Vhalf of activation and inactivation was approximately -9 mV and -24 mV, respectively, in good agreement with the literature4-6. For NaV1.9, the Vhalf of activation and inactivation was approximately -40 mV and -36 mV, respectively. Concentration dependence of known blockers on NaV1.8 and NaV1.9 such as lidocaine and tetracaine will be shown. The potency of tetracaine showed state dependence with a higher affinity for the inactivated state of NaV1.8.

References:
1 Amaya, et al, 2000. Mol & Cell. Neurosci. 15:331-42
2 Clare, 2010. Expert Opin. Investig. Drugs. 19(1):45-62
3 Dib-Hajj, et al, 2015. Nat. Rev. Neurosci. 16(9): 511-519
4 Catterall et al., 2005. Pharmacol. Rev. 57:397-409
5 Leffler et al., 2007. JPET. 320:354-364
6 Cummins and Waxmann. 1997. J.Neurosci., 17(10):3503-14