NEUROSCIENCE 2017

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Targeting pain pathways by inhibition of voltage-gated sodium channels

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Chronic and neuropathic pain is a signignificant health problem affecting millions of people worldwide each year, with 1 in 5 individuals experiencing moderate to severe chronic or persistent pain. Neuropathic pain serves no protective or healing purpose and appears to arise due to an increase in intrinsic nerve excitability. Voltage-gated Na_V channels (Na_V) are attractive targets for the treatment of these conditions due to their physiological role in action potential generation and propagation and, thus, neuronal excitability. Most of the clinically available pain therapeutics targeting Na_V channels are rather nonselective and are associated with cardiotoxic and CNS side effects.

$Na_V1.7$ is found primarily in the peripheral nervous system and is thought to play a role in nociception and pain sensing. Recently, venom isolated from different species including spider and centipede have been shown to selectively block $Na_V1.7$ and are powerful analgesics in animal models of pain. Similarly, mutations in the SCN9A gene have been shown to result in loss of function of the $Na_V1.7$ channel in patients with congenital indifference to pain (CIP).

The $Na_V1.8$ gene (originally named PN3 or SNS; gene symbol SCN10A) encodes a Na_V channel, and is selectively expressed in dorsal root ganglion (DRG) neurons. In contrast to the fast and rapidly inactivating TTX-sensitive channels, $Na_V1.8$ is TTX-resistant, with slower kinetics, and a depolarized voltagedependence of activation and inactivation.

We present data of $Na_V1.7$ and $Na_V1.8$ on a novel high throughput screening patch clamp platform. $Na_V1.7$ was expressed in CHO cells and the current voltage relationship recorded was consistent with $Na_V1.7$ obtained using other methods. Vhalf of activation was -24 mV (n = 275). Using a double step voltage protocol we were able to investigate whether compounds, such as tetracaine, exhibit state dependence. We show that tetracaine exhibited a lower IC on the second pulse, i.e. the inactivated state of the receptor, compared with the resting state. $Na_V1.8$ expressed in CHO cells started to activate at approximately -40 mV, peaking at between 10 mV and 20 mV with a Vhalf of activation of -2.7 mV (n = 380). In order to study Na_V channels involved in pain pathways in a more physiological environment, we used stem cell-derived neurons, more speci_cally with an overexpression of $Na_V1.8$. In these cells, endogenous Na_V-mediated currents were recorded with activation parameters consistent with $Na_V1.7$ (i.e. blocked by TTX in the nM range). Moreover, information about the role of Na_V channels in neuronal signalling in intact neuronal networks was gleaned using microelectrode array (MEA) technology.