The HCN channel, a novel target for the treatment of pain.

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Abstract:

One of the key initiating factors in long-lasting pain is peripheral sensitization. Peripheral sensitization results in changes to the activation threshold and thus function of primary afferent neurons. This is brought about by a variety of mechanisms but often involves the change in expression or function of individual ion channels. The Hyperpolarisation-activated cyclic nucleotide gated cation channels (HCN) are involved in mediating neuronal excitability. In this presentation evidence will be submitted for the role of these channels in peripheral sensitization.

Keywords: Pain, analgesia, orofacial, trigeminal

Full text:

Pain has a physiological role and is necessary for survival. Acute pain alerts us to the presence damaging stimuli. However, pain that persists long after tissue damage may become a clinical problem. In the sensory system the process of encoding and processing noxious stimuli is referred to as nociception.

Determining what controls neuronal excitability is one of the primary research streams in neurobiology today. In painful conditions, sensory neurons in both the peripheral and central nervous system become hyperexcitable. The underlying mechanisms of this hyperexcitability involve changes in ion channel expression and function. Currently, ion channel modulators comprise 6.5% of the top 200 prescribed drugs and are a major target for new drug development (Kaczorowski, McManus, Priest, & Garcia, 2008).

Persistent pain can result from inflammation or nerve injury. These different persistent pain states result in unique sets of neurochemical changes in sensory neurons and may explain why specific analgesics are efficacious in only certain persistent pain states (Honore et al., 2000).

Peripheral sensitisation is responsible for the initial sensitisation of nociceptors and the development of primary hyperalgesia. Peripheral sensory neurons are unique among sensory neurons because they can be sensitised, producing a decrease in activation threshold and an increase in action potential frequency, which is thought to underlie hyperalgesia or tenderness associated with tissue injury (Woolf & Ma, 2007). Agents released at the site of tissue injury sensitise sensory neurons by initiating a cascade of events (Levine, Fields, & Basbaum, 1993). The main pathways in the cascade involve protein kinase C (PKC) or protein kinase A (PKA) (Levine et al., 1993) and are likely to induce changes in ion channel expression (distribution or subcellular expression) and/or function, as has been described for primary sensory neurons innervating inflamed masseter muscle (Harriott, Dessem, & Gold, 2006) or bladder (Yoshimura & de Groat, 1999).

HCN channels:

Hyperpolarization-activated cation currents ($I_h$) have been identified in a number of excitable cells including cardiac pacemaker cells, retinal neurons and central and peripheral neurons (Craven & Zagotta, 2006). Four hyperpolarization-activated, cyclic nucleotide gated cation channels (HCN 1–4) have been cloned. HCN channels are each composed of 4 subunits and exist in both homomeric and heteromeric configurations in heterologous expression systems with HCN1 & 2 forming heteromeric complexes reported in vivo (Much et al., 2003).
As the name suggests, HCN channels are gated by both voltage and cyclic nucleotides and there is a cyclic adenosine monophosphate (cAMP) binding site on the c-terminus of the channels. Cyclic AMP (and cGMP) appears to predominantly modulate HCN2 and 4 channels and increases the amplitude of the current and shifts the activation curve to more depolarised potentials (Pape, 1996). In many neurons, HCN channels are activated at resting membrane potentials and the inward Na\(^+\) current leads to slightly depolarised membrane potentials—this includes trigeminal sensory neurons where \(I_h\) is active from -50mV (see Fig 1). Indeed, some studies suggest that HCN channels contribute around 30% to the total resting conductance (Pape, 1996), and increased HCN channel expression or function is likely to result in more depolarised resting membrane potentials, which in turn would contribute to neuronal hyperexcitability.

Expression of HCN channels in sensory neurons:
HCN channels have been described in dorsal root ganglia (DRG) and trigeminal sensory neurons (Chaplan et al., 2003; Cho, Staikopoulos, Furness, & Jennings, 2009; Cho, Staikopoulos, Ivanusic, & Jennings, 2009; Kouranova, Strassle, Ring, Bowlby, & Vasilyev, 2008; Moosmang et al., 2001; Tu et al., 2004; Wells, Rowland, & Proctor, 2007). HCN1 and HCN2 are largely confined to large, myelinated sensory neurons in both DRG and trigeminal ganglia (Chaplan et al., 2003; Cho, Staikopoulos, Furness, et al., 2009). HCN4, however, has been less well studied but has been reported to be distributed evenly in myelinated and unmyelinated populations of both DRG and trigeminal ganglia (Cho, Staikopoulos, Ivanusic, et al., 2009).

As indicated, the subunit composition of the receptor determines the functional properties of the receptor. A recent study with genetically modified animals indicates that much of the nociceptive behavior induced by peripheral inflammation is absent in animals lacking the HCN2 gene (E. C. Emery, Young, Berrocoso, Chen, & McNaughton, 2011). HCN channels have also been implicated in neuropathic pain (Edward C. Emery, Young, & McNaughton, 2012; Noh et al., 2014).

Figure 1: Schematic demonstrating the pharmacological interaction between the sensitising agent PGE\(_2\) and HCN channels in primary afferent neurons. The data supporting this schematic will be presented in the talk.
Our lab primarily focuses on factors that mediate orofacial pain, that is pain conveyed by trigeminal primary afferent nerves. In an animal model of temporomandibular joint (TMJ) inflammatory pain we have recently demonstrated that HCN channel antagonist administered at the site of inflammation block pain behaviours associated with peripheral inflammation (Hatch, Jennings, & Ivanusic, 2013). In addition, inflammation to peripheral trigeminal afferents results in increased HCN channels expression (Cho, Staikopoulos, Furness, et al., 2009; Wells et al., 2007).

These findings will be supplemented with preliminary data examining the functional role of HCN channel activation on individual trigeminal primary afferent nerves.
References:


**Biography:**
Dr. Jennings completed both his undergraduate and graduate studies at University College London, (UK) where he was awarded a PhD in 1999. He came out to Australia on a Wellcome Trust Prize Travelling Fellowship and liked it so much that he decided to stay. He has completed post-doctoral work at The University of Sydney (1999-2003) and a Heymanson Fellowship at The University of Melbourne prior to accepting an academic position at James Cook University in 2011.

Dr. Jennings heads the Ion Channel Physiology lab where the prime aim has been to better understand the mechanisms of pain, in order to improve treatment of pain conditions. In the last decade, his lab has concentrated on pain conditions that originate in the head (e.g. migraine, cluster headaches, temporomandibular disorders). The lab has taken a broad approach to studying these questions, using techniques including behaviour, protein expression assays and patch - clamp electrophysiology.

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