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Commentary

Ion channels and pain: Important steps towards validating a new therapeutic target for neuropathic pain

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Introduction

Acute pain is caused by noxious stimuli, and by stimuli that threaten to or cause tissue damage. Pain serves a crucial physiological function as a rapid warning system that can help prevent injury or limit the extent of damage. However, chronic pain, which is pain that persists after the initial noxious stimulus, tissue damage, and subsequent healing periods have passed, and is elicited by stimulus types or levels that do not normally elicit pain, is a major clinical challenge. Most chronic pain patients complain of a lack of complete relief from currently available drugs, and many of these drugs have adverse side effects. As such, there are intensive basic research and drug discovery efforts focused on developing better treatments for chronic pain (http://www.ninds.nih.gov/disorders/chronic_pain/chronic_pain.htm). One major form of chronic pain is neuropathic, in that it is based in the neurons involved in perception of pain, and the transduction, or processing of the resultant pain signals to the brain. Peripheral neuropathic pain is due to altered function and sensitization of neurons within the peripheral nociceptive system (i.e., nociceptive neurons), the sensory system responsible for the perception of pain and the transduction of pain signals to the spinal cord (http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions). A recent paper published in Experimental Neurology (Tsantoulas et al., 2014) identifies a novel contributor to peripheral neuropathic pain that may represent an attractive target for future drug discovery efforts aimed at ameliorating this form of chronic pain.

Sensory ganglia such as trigeminal ganglia, and dorsal root ganglia (DRG), contain a variety of primary sensory neurons, with distinct morphologies and functions. Sensory neurons with medium and large diameter cell bodies have myelinated axons or A fibers that transduce signals from a variety of sensory modalities, and while those with small diameter cell bodies give rise to unmyelinated C fibers that transduce painful stimuli [reviewed in Lawson, 2002]. Within these major classes of neurons are those with a diversity of morphologies and functions, allowing for the selective discrimination of a wide variety of painful and non-painful stimuli. Within these neurons are the ion channels that underlie the fundamental steps of sensory transduction, namely the initiation of a propagating electrical signal at the sensory nerve endings in tissues, its conduction along the axon, and its transmission from the central terminals to neurons in the spinal cord [reviewed in Gold and Gebhart, 2010]. There are also a number of regulatory ion channels that shape diverse aspects of each of these events. When dysregulated, these ion channels that underlie the normal function of nociceptive neurons can contribute to the pathological states of neuropathic pain [reviewed in Gold and Gebhart, 2010]. The recent paper by Tsantoulas et al. (2014) focuses on the role of a specific family of ion channels that serves as a critical component of the sensory transduction machinery in DRG neurons. The expression of these channels is reduced in an animal model of peripheral neuropathic pain. The authors were able to link this downregulation to a crucial aspect of peripheral neuropathic pain, the hyperexcitability of the nociceptive neurons that leads to ectopic transduction of pain signals to the spinal cord in the absence of a painful stimulus. This study not only identifies an important role for this particular class of ion channels, but also suggests that enhancing the activity of these channels represents an attractive approach for future drug discovery efforts targeting neuropathic pain.

Ion channels and nociceptor excitability

A wealth of information has been obtained as to the functional contribution of specific classes of ion channels with particular biophysical and pharmacological properties to normal nociceptive signaling, and how they are altered in response to conditions resulting in hyperexcitability of nociceptive neurons and peripheral neuropathic pain [reviewed in Gold and Gebhart, 2010]. Among these, voltage-sensitive Na^+ or Nav channels mediate the initiation and rising or depolarizing phase of the action potential, and voltage-gated K^+ or Kv channels mediate the falling or repolarizing phase, and also contribute in diverse ways to determine whether action potentials are initiated, and if so their duration, amplitude and frequency (Hille, 2001). Nav channels are excitatory, such that Nav channel inhibitors are effective at decreasing or eliminating electrical excitability, and are in common use in neurology as anti-epileptic drugs, and as local anesthetics [reviewed in

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Savio-Galimberti et al., 2012)]. In general, Kv channels are inhibitory, such that drugs that enhance Kv channel function should in principle have effects similar to Nav channel blockers. Consistent with this paradigm, retigabine, a Kv channel opener, has been recently approved as a first in class anti-epileptic drug [reviewed in Gunthorpe et al., 2012].

The number of Nav channel voltage-sensing and pore-forming principal or α subunits encoded in the human genome is relatively small, in that there are ten different SCNA genes, and there are relatively modest structural and functional differences between the different Nav channel subtypes [reviewed in Catterall, 2012]. This limited diversity could be considered a drawback for drug discovery, making the development of subtype-selective inhibitors problematic. Moreover, the limited size of the Nav channel gene family means that any individual Nav channel subtype might have a broad cellular and/or tissue expression, confounding development of drugs that exhibit precise cell- or tissue-specific targeting. However, Nav channel inhibitors are used successfully in the clinic for a variety of indications [reviewed in Savio-Galimberti et al., 2012]. Numerous drug discovery programs are focused on the specific Nav channel subtypes expressed in nociceptive neurons as targets for novel therapeutics for chronic pain [reviewed in Dib-Hajj et al., 2010; Liu and Wood, 2011].

Compared to Nav channels, there exists a huge complexity of Kv channels that differ widely in their structural and functional characteristics [reviewed in Jan and Jan, 2012]. The human Kv channel superfamily contains 30 genes encoding canonical Kv channel α subunits (Yu et al., 2005). Moreover, unlike Nav channels that are formed by a single α subunit, Kv channels arise from the combinatorial assembly of four α subunits, yielding a huge repertoire of homomeric and heteromeric channel complexes with distinct properties [reviewed in Jan and Jan, 2012]. As different Kv channel α subunits differ in their temporal and spatial patterns of expression [reviewed in Vacher et al., 2008], any given α subunit can participate in a variety of distinct channel types depending on the extent and nature of its coexpression and resultant coassembly with other α subunits. Certain Kv channels contain electrically silent modulatory α-like subunits (of which 10 are encoded in the human genome), which do not form functional Kv channels themselves but that when incorporated into complexes with functional Kv channel α subunits alter the properties of the resultant channels (Bocksteins and Snyders, 2012). Both Nav and Kv channel complexes also contain auxiliary subunits, which for Kv channels are more numerous and diverse, and also more variable in their inclusion in Kv channel complexes, than are those for Nav channels [reviewed in Brueggemann et al., 2013]. The overall α, α-like, and auxiliary subunit composition of a particular Kv channel complex dictates not only its functional characteristics, including its pharmacology, but also the subcellular localization, and modulation by various signaling pathways [reviewed in Vacher and Trimmer, 2011]. The structural diversity of Kv channels offers a broad potential for drug discovery, as it may be possible to develop modulators that preferentially act on Kv channel complexes of a specific subunit composition [reviewed in Castle, 2010; Maljevic and Lerche, 2013]. Moreover, given the huge number of possible Kv channel complexes that can be assembled from the available α, α-like, and auxiliary subunits, a Kv channel with a particular subunit composition and stoichiometry may be present in only small subset of cell types within a tissue, or tissues within the body,offering the potential that specific modulators of that particular Kv channel would have highly selective action. However, it remains a challenge to link the native Kv currents present in specific cell types, and in particular nociceptive neurons, with molecularly defined complexes comprising specific Kv channel subunits. The recent paper by Tsantoulas et al. (2014), is an important step in this process, as it combines classical biophysical and pharmacological characterization of native nociceptor Kv currents, with targeted molecular level expression and pharmacological inhibition studies that define the two members (Kv2.1, Kv2.2) of the of the Kv2 subfamily of α subunits as the basis for a native Kv delayed rectifier current important in the normal function and pathological plasticity of nociceptive neurons.

Kv2 channels in brain neurons

Kv2.1 and Kv2.2 have widespread expression in brain neurons by in situ hybridization (Drewe et al., 1992; Hwang et al., 1992) and by immunohistochemistry (Kihira et al., 2010; Trimmer, 1991). There appears to be distinct spatiotemporal patterns of their expression in mammalian brain neurons (Hermanstyne et al., 2010; Kihira et al., 2010), suggesting that although these Kv2 family members share a high degree of amino acid sequence similarity, and have very similar functional properties, they may have distinct physiological functions. Kv2.1 is unusual in being highly posttranslationally modified by phosphorylation, with 34 in vivo phosphorylation sites identified to date from an array of mass spectrometry based proteomics analyses of Kv2.1 from rat and mouse brain [reviewed in Trimmer and Misonou, 2014]. Kv2.1 is also modified by SUMOylation (Plant et al., 2011). These modifications have profound effects on Kv2.1 expression, localization and function [reviewed in Cerda and Trimmer, 2010; Mandikian et al., 2011]. Less is known of the role of posttranslational modification and modulation of Kv2.2, although many fewer phosphorylation sites have been identified on Kv2.2 (11) than on Kv2.1, suggesting that these two highly-related Kv2 family members may have distinct sensitivities to modulation [reviewed in Trimmer and Misonou, 2014].

Neurons also express a family of Kv8 and Kv9 electrically silent Kv channel α-like subunits that specifically associate with and modulate the function of Kv2 channel α subunits [reviewed in Bocksteins and Snyders, 2012]. Although resembling Kv channel α subunits overall, Kv8 and Kv9 α-like subunits have the property of true modulatory subunits, in that when expressed alone in heterologous cells do not generate functional channels [reviewed in Bocksteins and Snyders, 2012]. However, when coexpressed with functional Kv2 channel α subunits, these modulatory subunits form heteromeric channels with functional properties distinct from channels formed from Kv2 α subunits alone (Ottschytsch et al., 2002; Salinas et al., 1997). Recently, an additional Kv2 interacting protein, AMIGO-1, was identified as an auxiliary subunit of brain Kv2 channels (Peltola et al., 2011). There exist three highly related AMIGO family members, although the association of AMIGO-2 and AMIGO-3 with Kv2 channel complexes has not been studied. Thus, native Kv2 channel complexes may exist as diverse assemblies of functional Kv2.1 and Kv2.2 α subunits, modulatory electrically silent Kv8 and Kv9 α-like subunits, and auxiliary AMIGO subunits. Kv2 channels formed from distinct combinations of these subunits would exhibit a wide array of biophysical and pharmacological properties, and sensitivity to modulation. This structural and functional complexity presents a challenge for those interested in defining the contributions of specific Kv channels, in this case Kv2 channels, to the function of specific types of neurons, including nociceptors. However, this same daunting complexity also enhances the potential of these channels as targets for neuropathic pain.

Kv2 channels and nociceptive neurons

Previous studies have demonstrated the expression of Kv2 channel subunit mRNA and/or polypeptides in rodent DRG neurons, in both cell culture (Ishikawa et al., 1999) and in intact DRG (Kim et al., 2002). Expression of Kv2 subunits is decreased in models of neuropathic pain, in DRG neurons cultured from animals subjected to sciatic nerve axotomy (Ishikawa et al., 1999), and in DRGs from animals subjected to chronic constriction injury (Kim et al., 2002). Bocksteins et al. (2009) showed that Kv2 family-associated electrically silent subunits are also expressed in DRG neurons, which contain a delayed rectifier Kv current inhibited by stromatoxin, an inhibitor of Kv channels containing Kv2 and Kv4 family α subunits (Escoubas et al., 2002), but whose action here is presumably on Kv2 family members as Kv4 α subunits form transient A-type channels [reviewed in Gutman et al., 2005]. This study also showed that the biophysical properties of the delayed