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Is Diabetic Nerve Pain Caused by Dysregulated Ion Channels in Sensory Neurons?

Diabetes 2015;64:3987–3989 | DOI: 10.2337/dbi15-0006

In diabetes, a common and debilitating chronic disease, peripheral diabetic neuropathy (PDN) is the most frequent complication, occurring in about two-thirds of the patients (1,2). At least one-third of patients with diabetes experience painful symptoms including hyperalgesia and/or allodynia as well as spontaneous pain in the form of burning or tingling, despite the degeneration of peripheral nerves (3). Eventually, these painful symptoms usually subside as the disabling pain is replaced by the complete loss of sensation. Both intractable pain and loss of sensation have significant adverse effects on quality-of-life measures. Unfortunately, current treatment options are unable to reverse these symptoms.

Pain-sensing sensory neurons, or nociceptors, can be sensitized (become hyperexcitable) by various mechanisms in response to the pathological conditions or peripheral tissue injury associated with diabetes. Multiple pathogenic mechanisms, such as the formation of intracellular advanced glycation end products, inflammatory cytokines, increased aldose reductase activity, and oxidative stress, may contribute to the impaired function of sensory neurons in animals with PDN. However, multiple preclinical and clinical studies that aimed to target several of these mechanisms while simultaneously ensuring proper blood glucose control were unable to provide definite and complete pain relief (1,2). Importantly, currently available therapies are only partially effective and are often associated with serious side effects. For example, $Ca_V2.2$ channels (N-type) and their regulatory subunit α2δ are considered a major cellular target for the anticonvulsants gabapentin and pregabalin, which are commonly used to relieve diabetes-induced pain in humans and other animals. However, more than 50% of patients using gabapentin or pregabalin experience side effects, such as excessive sedation, ataxia, dizziness, euphoria, and weight gain, all of which limit its clinical use (1).

Several studies conducted in recent years have reported on the plasticity of various ion channels expressed in nociceptive sensory neurons, also known as dorsal root ganglion (DRG) neurons, which play a critical role in modulating overall cellular excitability. These findings are both important and relevant, as increased excitability of sensory neurons is believed to contribute directly to the development and maintenance of painful symptoms, including hyperalgesia, allodynia, and/or spontaneous pain. Recent studies have shown that the $Ca_V3.2$ isoform of T-type voltage-gated calcium channels is heavily expressed in the DRG cells and dorsal horn (DH) of the spinal cord and plays a distinct role in supporting pathological pain in animal models of PDN induced by both type 1 and type 2 diabetes (4–6). Additional studies have documented the upregulation of pronociceptive ion channels (such as purinergic receptors [7]; voltage-gated sodium channels, particularly the $Na_V1.7$ and $Na_V1.8$ isoforms [8,9]; and the vanilloid family of ligand-gated channels, particularly transient receptor potential cation channel, subfamily V, member 1 [TRPV1] [10]) within the sensory neurons in animal models of diabetes. In contrast, there is a decrease in the function of the main inhibitory drive in the DH neurons mediated by the γ-aminobutyric acid (GABA)ergic system, which causes disinhibition of spinal nociceptive processing in PDN (11). Figure 1 summarizes how different pronociceptive ion channels expressed in peripheral nerve terminals in skin, cell somas in DRG, and central terminals of sensory neurons may work together with spinal GABA-mediated dysfunction to increase the sensitization of pain responses under diabetic conditions.

In this issue, a study by Zhang et al. (12) sheds more light on the issue of abnormal regulation of nociceptive ion channels in sensory neurons in animal models of type 1 diabetes. Here, they investigate the role of nuclear factor-κB in the regulation of purinergic receptor P2X ligand-gated ion channel 3 (P2X3R) plasticity in DRG neurons in rats with painful PDN. First, they show that the injection of nonspecific purinergic receptor antagonists suramin and

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See accompanying article, p. 4272.

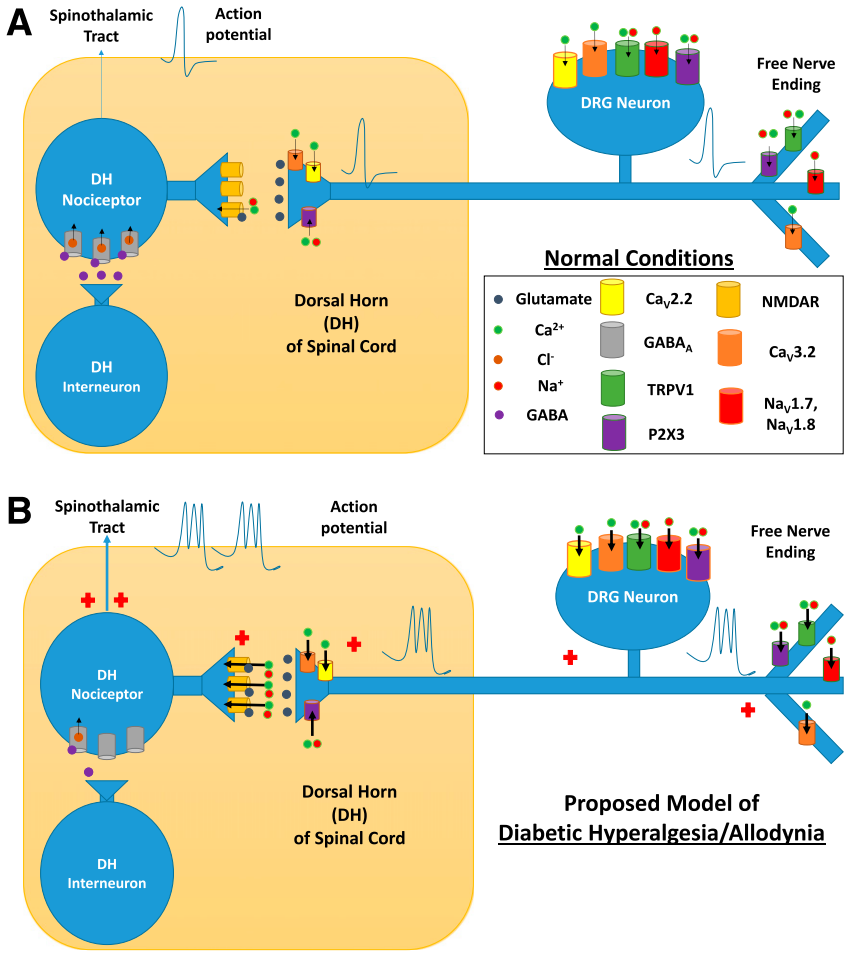

Figure 1—Proposed mechanism of diabetic hyperalgesia with dysregulated ion channels in pain pathway. *A*: Simplified model of nociception under normal conditions. Free nerve endings transduce a painful stimulus into a neural signal, which propagates to DRG centrally and eventually synapses on a nociceptive neuron within the DH of the spinal cord. The information encoded in the signal is carried via the spinothalamic tract to the processing areas of the brain. Activity of pronociceptive $Ca_V3.2$, $Ca_V2.2$, TRPV1, $Na_V1.7$, $Na_V1.8$, and P2X3 channels in sensory neurons is counterbalanced by inhibition in the DH neurons mediated by $GABA_A$ receptors. *B*: Proposed model of nociception under conditions of diabetic hyperalgesia and allodynia. A pain signal augmented by upregulated pronociceptive ion channels in sensory neurons is carried toward the DH, where it is further augmented by a hypoactive GABAergic system and subsequently diminished inhibition from an inhibitory interneuron. NMDAR, *N*-Methyl-D-aspartate receptors.

A-317491 directly into the peripheral receptive fields of sensory neurons is able to attenuate thermal and mechanical hypersensitivity in diabetic rats with minimal effect in healthy rats. The subsequent use of immunohistochemistry and patch-clamp recordings demonstrate enhanced protein expression of P2X3Rs and ATP-induced currents in DRG somas of cutaneous afferents. Finally, through the use of sophisticated molecular biology techniques, the authors elucidate an epigenetic mechanism of P2X3R dysregulation in diabetic rats. More specifically, the delivery of a lentoviral vector encoding small interfering RNA against the p65 gene (a subunit of nuclear factor-κB) and the pharmacological inhibition of p65 demonstrate that in vivo knockdown of this gene effectively reverses diabetic hyperalgesia. To ensure that the observed changes in the expression of p65 are not a result of the presumed toxicity of streptozocin itself, the authors provide additional proof by showing that a similar reversal in expression is observed once efforts are made to maintain proper blood glucose regulation in diabetic rats via insulin injections. Overall, these data indicate that p65 plays a supportive role in diabetic hyperalgesia via the epigenetic regulation of the function of P2X3Rs in peripheral sensory neurons. It is tempting to propose that similar mechanisms may exist in the central terminals of DRG neurons in the DH given that P2X3Rs are also implicated in supporting excitatory transmission in the DRG-DH synapse (13,14). However, the current study does not examine if similar pathways play a role in animal models of type 2 diabetes, which better mimic human diabetes due to the slower development of hyperglycemia.

Aberrant regulation of nociceptive ion channels in sensory neurons and ensuing hyperexcitability may be contributing factors to the painful symptoms of PDN. For example, it was shown that posttranslational modification

via glycosylation of specific extracellular asparagine residues of $Ca_V3.2$ T-channels in sensory neurons under conditions of hyperglycemia led to increased channel activity and membrane expression (15). Furthermore, posttranslational modification of the $Na_V1.8$ and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) via methylglyoxal—a metabolite of glucose—has been demonstrated in DRG neurons (9,16). In addition, upregulation of high voltage–activated calcium currents in sensory neurons in diabetic rats via G-proteins may underlie their diminished responsiveness to opioids (17,18).

It is likely that multiple signaling pathways targeting nociceptive ion channels may work in concert to promote hyperexcitability of sensory neurons and contribute to hyperalgesia, allodynia, and spontaneous pain in patients with PDN. It is hoped that future efforts in targeting these pathways may lead to novel and safer pain therapies in patients with diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther 2008;120:1–34

2. Gooch C, Podwall D. The diabetic neuropathies. Neurologist 2004;10:311–322

3. Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34:2220–2224

4. Latham JR, Pathirathna S, Jagodic MM, et al. Selective T-type calcium channel blockade alleviates hyperalgesia in ob/ob mice. Diabetes 2009;58:2656–2665

5. Jacus MO, Uebele VN, Renger JJ, Todorovic SM. Presynaptic $Ca_v3.2$ channels regulate excitatory neurotransmission in nociceptive dorsal horn neurons. J Neurosci 2012;32:9374–9382

6. Jagodic MM, Pathirathna S, Nelson MT, et al. Cell-specific alterations of T-type calcium current in painful diabetic neuropathy enhance excitability of sensory neurons. J Neurosci 2007;27: 3305–3316

7. Xu G-Y, Li G, Liu N, Huang L-YM. Mechanisms underlying purinergic P2X3 receptor-mediated mechanical allodynia induced in diabetic rats. Mol Pain 2011; 7:60

8. Hoeijmakers JG, Faber CG, Merkies IS, Waxman SG. Channelopathies, painful neuropathy, and diabetes: which way does the causal arrow point? Trends Mol Med 2014;20:544–550

9. Bierhaus A, Fleming T, Stoyanov S, et al. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy [published correction in Nat Med 2012;18:1445]. Nat Med 2012;18: 926–933

10. Brederson JD, Kym PR, Szallasi A. Targeting TRP channels for pain relief. Eur J Pharmacol 2013;716:61–76

11. Lee-Kubli CA, Calcutt NA. Altered rate-dependent depression of the spinal H-reflex as an indicator of spinal disinhibition in models of neuropathic pain. Pain 2014;155:250–260

12. Zhang H-H, Hu J, Zhou Y-L, et al. Promoted interaction of nuclear factor-κB with demethylated purinergic P2X3 receptor gene contributes to neuropathic pain in rats with diabetes. Diabetes 2015;64:4272–4284

13. Chen M, Gu JGA. A P2X receptor-mediated nociceptive afferent pathway to lamina I of the spinal cord. Mol Pain 2005;1:4

14. Saeed AW, Ribeiro-da-Silva A. Non-peptidergic primary afferents are presynaptic to neurokinin-1 receptor immunoreactive lamina I projection neurons in rat spinal cord. Mol Pain 2012;8:64

15. Orestes P, Osuru HP, McIntire WE, et al. Reversal of neuropathic pain in diabetes by targeting glycosylation of $Ca_v3.2$ T-type calcium channels. Diabetes 2013;62:3828–3838

16. Eberhardt MJ, Filipovic MR, Leffler A, et al. Methylglyoxal activates nociceptors through transient receptor potential channel A1 (TRPA1): a possible mechanism of metabolic neuropathies. J Biol Chem 2012;287:28291–28306

17. Hall KE, Sima AA, Wiley JW. Opiate-mediated inhibition of calcium signaling is decreased in dorsal root ganglion neurons from the diabetic BB/W rat. J Clin Invest 1996;97:1165–1172 Nat Med. 2012 Sep;18(9):1445

18. Hall KE, Liu J, Sima AA, Wiley JW. Impaired inhibitory G-protein function contributes to increased calcium currents in rats with diabetic neuropathy. J Neurophysiol 2001;86:760–770