Location, Location, Location?

Is the Pain of Diabetic Neuropathy Generated by Hyperactive Sensory Neurons?

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Pain is a useful sensation. Nociceptive pain provides warning of impending or actual tissue damage and prompts aversive or attentive actions that protect the body from harm. People who do not feel pain, due to mutation of certain ion channels (1), suffer a lifetime of otherwise avoidable injuries. The consequences of losing the ability to feel pain also are highlighted by the symptoms and clinical outcomes of diabetic neuropathy. Sensory neuropathy, in conjunction with vascular disease and impaired wound healing, leads to unattended lesions and ulcers, infection, and amputation (2). However, despite having a predominant neuropathy phenotype of degeneration and sensory loss, a proportion of people with diabetes also report spontaneous tingling, pricking, and pain sensations (3). This neuropathic pain is an enigmatic and disruptive symptom that adds psychological insult to the physical injury of progressive nerve degeneration. The prevalence of neuropathic pain is frequently underestimated, but a recent community-based study found that pain was reported by a third of all participants (4). There are currently only three FDA-approved treatments for painful diabetic neuropathy: the anticonvulsant pregabalin, the serotonin–norepinephrine reuptake inhibitor (SNRI) duloxetine, and the opioid/SNRI tapentadol. All are used to treat diverse pain conditions, are likely to suppress pain perception rather than intervene in pathogenic mechanisms of painful diabetic neuropathy, and have undesirable side effects. None are effective in more than an unpredictable subset of diabetic patients and they do not dramatically outperform the historical off-label use of tricyclic antidepressants (5). Treating painful diabetic neuropathy therefore remains a march through a list of potential treatments in search of an acceptable balance between pain relief and side effects (6).

Data emerging from animal models of painful diabetic neuropathy advances three broad mechanisms of pain generation: inappropriate or exaggerated activity of peripheral sensory neurons, distortion of sensory processing within the spinal cord, and spontaneous activity in the central nervous system that is perceived as pain deriving from the periphery (Fig. 1). Of these, the first reflects the reasonable assumption that pain is generated at the site where it is perceived to emanate from. The last is perhaps most controversial, as it implies a form of phantom pain (7). The recent study by Orestes et al. (8) adds support to the hypothesis that peripheral sensory neurons are hyperexcitable during diabetes. Previous studies have identified changes in expression of assorted ion channels that are involved with action potential generation or sculpting in diabetic rodents and the idea that altered membrane depolarization properties could generate allodynia, hyperalgesia, or spontaneous pain is not new. Fewer have addressed the mechanisms by which diabetes might promote such changes. A particular appeal of the present work lies in the evidence that inappropriate glycosylation of an ion channel, in this case the $Ca_V3.2$ isoform of the T-type calcium channel, produces a posttranslation modification that enhances function, thereby offering a simple pathogenic mechanism that is directly related to poor glycemic control.

The argument presented by Orestes et al. is grounded in studies that manipulate glycosylation of $Ca_V3.2$, when expressed in human embryonic kidney cells, to establish that $Ca_V3.2$ function can be modulated by glycosylation status, as reported for other ion channels (9). Pertinence to sensory neurons is then demonstrated, as enhanced T-type calcium currents found in sensory neurons obtained from the *ob/ob* mouse model of type 2 diabetes are ablated by the deglycosylation agent neuraminidase. Finally, relevance of these in vitro studies to abnormal pain perception is suggested by showing that injection of neuraminidase to the paws of *ob/ob* mice rapidly ameliorates mechanical and thermal hyperalgesia. These assays measure behavioral indices of stimulus-evoked nociceptive pain (10), not the spontaneous pain experienced by many diabetic patients, but there are clinical parallels in disorders identified during quantitative sensory testing (11). The progression from idealized cell biology to animal model of disease makes this study a substantive addition to the literature. Together with the recent identification of the glucose derivative methylglyoxal as another molecule that posttranslationally modifies ions channels (12), these data implicate hyperglycemia-initiated peripheral sensory drive as a primary pathogenic mechanism of painful diabetic neuropathy.

A notable absence from the work of Orestes et al. is direct demonstration that $Ca_V3.2$ undergoes abnormal glycosylation in diabetic animals, and it remains plausible that alleviation of hyperalgesia is mediated by other actions of neuraminidase in vivo. The extent to which sensory neuron hyperexcitability drives hyperalgesia or spontaneous pain in diabetes also deserves consideration. While it is known that gain of function modifications to ion channels can lead to pain-associated behaviors in animals that

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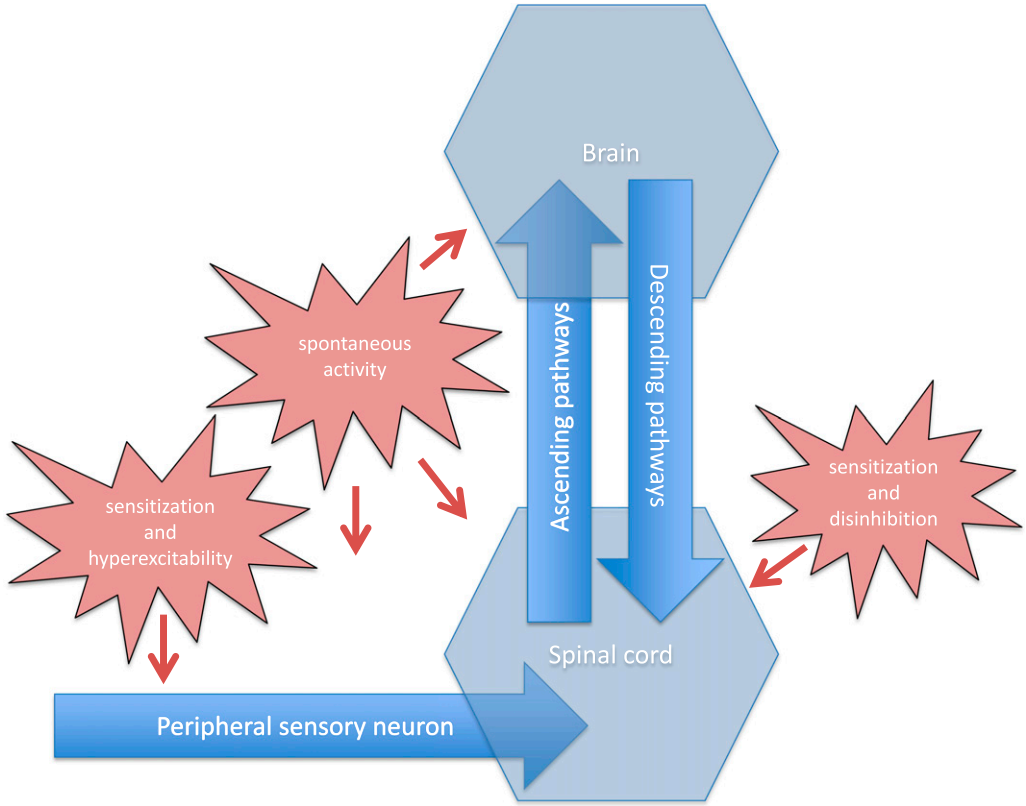

FIG. 1. The location of potential generator and amplifier sites for neuropathic pain in diabetes includes peripheral sensory neurons, the spinal cord, and the brain.

have direct human equivalents (13), diabetes-induced pain frequently coexists with the degenerative neuropathy phenotype of reduced production, transport, and stimulus-evoked spinal release of neurotransmitters (14). A hyperexcitable peripheral sensory neuron with no voice will likely remain silent—although perhaps causing higher order neurons to adjust their listening mechanisms. The identification of ion channel glycosylation as a driving force for pain must also be reconciled with preclinical evidence that impaired insulin signaling rather than hyperglycemia promotes hyperalgesia (15) and the efficacy of interventions that prevent onset of hyperalgesia without altering hyperglycemia (16). Clinical studies emphasize that acute hyperglycemia does not alter perception of sensory stimuli or pain (17,18) whereas, paradoxically, restoring normoglycemia in diabetic patients can initiate the pain state commonly called insulin neuritis (19).

Peripheral hyperexcitability is an appealing mechanism that may contribute to pain in some diabetic patients and offers a therapeutic approach targeting glycosylated ion channels that may quickly alleviate pain, with improving glycemic control presumably being the preferred long-term goal. However, the diverse manifestations of painful diabetic neuropathy and variable responses to current drug interventions imply that a number of mechanisms can contribute, with each patient having a specific pathogenic profile. New clinical tests or biomarkers to identify the location of pain generation or amplification sites and specific pathogenic mechanisms would be valuable tools in guiding choice of therapy. The complexity of painful diabetic neuropathy may not be solved for all by a single intervention, making this condition a plausible archetype that could benefit from the emerging promise of personalized medicine.

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REFERENCES

1. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature 2006;444:894–898
2. Boulton AJ. Diabetic neuropathy: is pain God's greatest gift to mankind? Semin Vasc Surg 2012;25:61–65
3. Koroschetz J, Rehm SE, Gockel U, et al. Fibromyalgia and neuropathic pain—differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. BMC Neurol 2011;11:55
4. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34:2220–2224
5. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931–1937
6. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in Neurology 2011;77:603]. Neurology 2011;76:1758–1765
7. Rajbhandari SM, Jarratt JA, Griffiths PD, Ward JD. Diabetic neuropathic pain in a leg amputated 44 years previously. Pain 1999;83:627–629
8. 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

9. Tyrrell L, Renganathan M, Dib-Hajj SD, Waxman SG. Glycosylation alters steady-state inactivation of sodium channel Nav1.9/NaN in dorsal root ganglion neurons and is developmentally regulated. J Neurosci 2001;21:9629–9637
10. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev 2001;53:597–652
11. Baron R, Tölle TR, Gockel U, Brosz M, Freynhagen R. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. Pain 2009;146:34–40
12. 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 appears in Nat Med 2012;18:1445]. Nat Med 2012;18:926–933
13. Klein CJ, Wu Y, Kilfoyle DH, et al. Infrequent SCN9A mutations in congenital insensitivity to pain and erythromelalgia. J Neurol Neurosurg Psychiatry 2013;84:386–391
14. Malmberg AB, O'Connor WT, Glennon JC, Ceseña R, Calcutt NA. Impaired formalin-evoked changes of spinal amino acid levels in diabetic rats. Brain Res 2006;1115:48–53
15. Romanovsky D, Cruz NF, Dienel GA, Dobretsov M. Mechanical hyperalgesia correlates with insulin deficiency in normoglycemic streptozotocin-treated rats. Neurobiol Dis 2006;24:384–394
16. Calcutt NA, Freshwater JD, Mizisin AP. Prevention of sensory disorders in diabetic Sprague-Dawley rats by aldose reductase inhibition or treatment with ciliary neurotrophic factor. Diabetologia 2004;47:718–724
17. Chan AW, MacFarlane IA, Bowsher D. Short term fluctuations in blood glucose concentrations do not alter pain perception in diabetic-patients with and without painful peripheral neuropathy. Diabetes Res 1990;14:15–19
18. Frøkjaer JB, Søfteland E, Graversen C, Dimcevski G, Drewes AM. Effect of acute hyperglycaemia on sensory processing in diabetic autonomic neuropathy. Eur J Clin Invest 2010;40:883–886
19. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Ann Neurol 2010;67:534–541