

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 ion 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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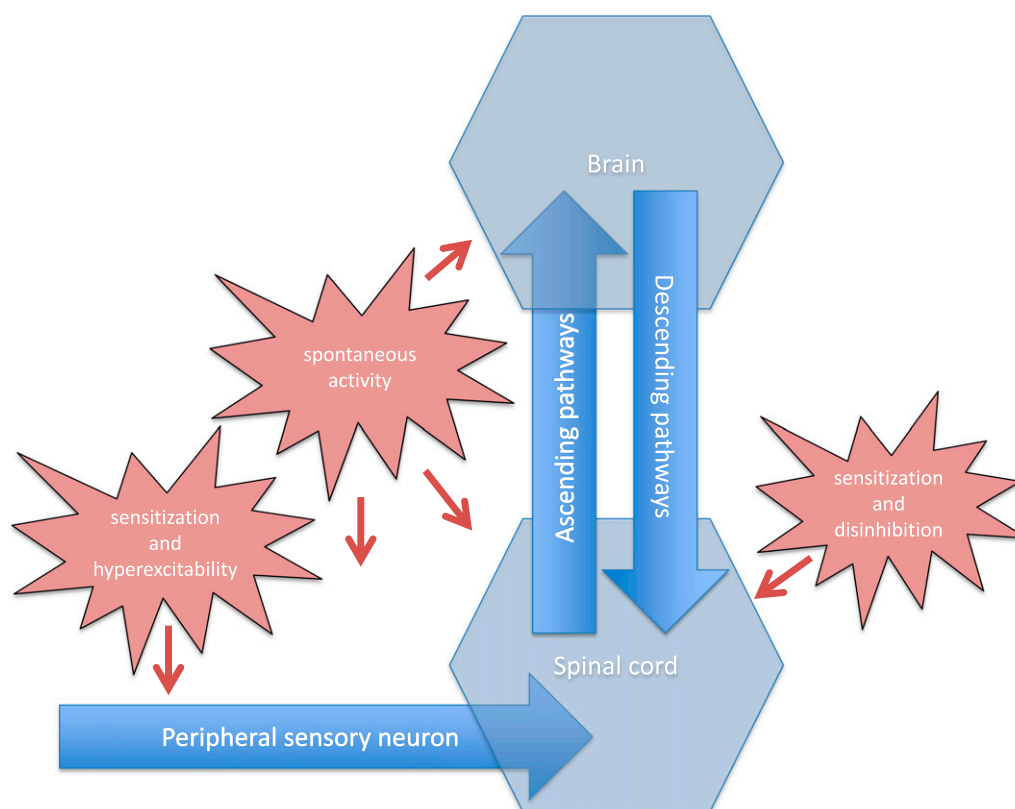


FIG. 1. The location of potential generator and amplifier sites for neuropathic pain in diabetes includes peripheral sensory neurons, the spinal cord, and the brain.

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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