COMMENTARY

Augmenting glial cell-line derived neurotrophic factor signaling to treat painful neuropathies

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Pain in Peripheral Neuropathies

Peripheral neuropathies are a group of disorders affecting peripheral nerves, characterized by either distal axonal degeneration or dysfunction of the ensheathing Schwann cells. Depending on the type of peripheral nerve involvement, there are many different symptoms and examination findings in patients with peripheral neuropathy. However, neuropathic pain is probably the single most prevalent complaint that results in consultation with a doctor. Although symptomatic therapies exist for treating pain in peripheral neuropathies (1), none are very effective or specific to the underlying pathogenic mechanisms, often resulting in too many side effects. There is a desperate need in the field to develop pathogenesis-based specific treatments to treat painful symptoms in patients with peripheral neuropathies. In PNAS, Hedstrom et al. present convincing preclinical data to show that enhancement of glial cell-line derived neurotrophic factor (GDNF) signaling with a small molecule agonist offers such a hope (2).

Exact pathogenic mechanism(s) of neuropathic pain are still unknown. The complexity of neuropathic pain is exemplified with the recognition that in a given patient various painful symptoms may have different underlying pathogenic mechanisms, and over time, even for the same type of pain, the underlying molecular mechanism may change. This is partly due to the fact that sensory organs in the skin often encode multiple types of sensations and that a single type of stimulus such as heat may require multiple transduction pathways (3). Nevertheless, research in the last 20 y or so showed that neurotrophic factors play a critical role in generation and maintenance of neuropathic pain. Nerve growth factor (NGF), which plays a crucial role in development of nociceptor neurons in the dorsal root ganglia, may also play a critical role in generation and maintenance of neuropathic states in multiple experimental models of pain (4). Supporting these observations in animal models is that administration of recombinant human NGF in clinical trials of Alzheimer's disease and diabetic peripheral neuropathy results in painful paresthesias at sites of injection. In fact, blocking the NGF signaling is a promising molecular target for development of novel drugs to treat neuropathic pain (5). In contrast to the peptidergic, NGF-dependent nociceptive fibers, the nonpeptidergic C-fiber population in the dorsal root ganglia that is dependent on GDNF family of neurotrophic factors acts mainly as antinociceptive neurons. Signaling through the GDNF family of neurotrophic factors results in amelioration of neuropathic pain (6, 7).

Augmenting GDNF signaling is likely to be a potent mechanism to treat neuropathic pain, even if there is no deficiency of endogenous GDNF signaling.

GDNF Signaling in Neuropathic Pain

Hedstrom et al. take these observations further and demonstrate that overexpression of GDNF in keratinocytes prevents progressive small fiber sensory neuropathy in a transgenic mouse line (line-D) in which expression of the dominant-negative ErbB4 receptor in nonmyelinating Schwann cells results in progressive neuropathic pain behavior and loss of small unmyelinated sensory axons. This observation is not too surprising given that the line-D has reduced levels of GDNF in the peripheral nerves and perhaps supplementing GDNF can rescue the phenotype. Furthermore, others have shown that GDNF has therapeutic potential in diabetic peripheral neuropathy, delivered either intrathecally as recombinant protein (8) or as gene therapy with intramuscular injections (9). However, treatment of diabetic peripheral neuropathy or other neuropathic states with GDNF is going to be challenging as systemic administration of recombinant GDNF is poorly tolerated due to gastrointestinal side effects. What is more promising is that Hedstrom et al. demonstrate that topical application of XIB4035, a presumptive agonist of GDNF receptor GFRα1, rescues the neuropathy phenotype in both line-D mice and mice developing diabetic peripheral neuropathy after injection of streptozotocin (model of type 1 diabetes due to pancreatic β-cell death). XIB4035 was initially developed as a novel nonpeptidyl small molecular agonist for GFRα1 and was hypothesized to replace GDNF from its receptor (10). However, Hedstrom et al. did not observe any direct effect of XIB4035 on GFRα/RET signaling unless the neurotrophic factor ligand, GDNF, or artemin (a member of the GDNF family of neurotrophic factors) was present in the culture media. In fact, what they observed was that XIB4035 augmented ligand-induced GDNF receptor α (GFRα)/RET signaling, suggesting that XIB4035 acted as a modulator to augment GDNF-GFRα/RET signaling. This is an important observation and may allow relatively low doses of this molecule to show efficacy by augmenting down-regulated endogenous signaling pathways rather than activating new pathways. However, many caveats remain; to further develop XIB4035 or similar molecules for treatment of painful neuropathies, one will have to examine their effects on the gastrointestinal system where GDNF-GFRa/RET signaling plays an important role in enteric nervous system development and colonic function (11).

An interesting observation of the authors was that XIB4035 prevented the development of neuropathic pain in streptozotocin-treated

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mice but had no effect on loss of intraepidermal nerve fibers, a hallmark of painful small fiber sensory neuropathies (12). This was in contrast to the observation in line-D mice where it prevented both painful behaviors and pathologic loss of intraepidermal nerve fibers. The observation in line-D is not too surprising given that there is a decrease in GDNF levels in peripheral nerves, which may be a proximate cause of distal axonal loss in unmyelinated fibers, and that XIB4035 treatment just acted to augment this signaling to prevent axonal degeneration. However, in the streptozotocin-induced model of diabetic peripheral neuropathy, there is no peripheral loss of GDNF, and the distal axonal loss may not be a direct consequence of potential deficiency of GDNF signaling. It is possible that XIB4035 acted as an analgesic agent by augmenting endogenous GDNF signaling either at the periphery or centrally in the spinal cord. In fact, others have shown that intrathecal administration of GDNF prevents pain in multiple models of neuropathic pain induced by traumatic injury to the peripheral nerves (13, 14). Similarly, overexpression of GDNF in uninjured dorsal root ganglion (DRG) neurons, delivered via lentiviral injection, exerts analgesic effects on neuropathic pain following segmental spinal nerve ligation (15).

These observations, combined with the effects of XIB4035 seen in the article Hedstrom et al., suggest that augmenting GDNF signaling is likely to be a potent mechanism to treat neuropathic pain, even if there is no deficiency of endogenous GDNF signaling. Whether this can be accomplished with GFRa/RET modulators like XIB4035 or by local delivery of recombinant GDNF protein or directed genetic delivery of GDNF remains to be seen. Recent development of nonreplicating herpes simplex virus–based vectors to deliver genes to the DRG neurons (16) by peripheral injection into the target skin areas opens up other potential delivery methods to take advantage of the GDNF signaling pathway to treat neuropathic pain.

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