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Severity of Diabetes in Patients with Allodynia and Hyperalgesia as Major Symptoms

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Description

Diabetic Neuropathy and Diabetic Neuropathic Pain (DNP) are common complications of long-term diabetes. DNP severs an intractable and characterized by spontaneous painful sensations (e.g., burning or sharp pain) cutaneous allodynia and hyperalgesia, impacting patients' quality of life and causing mood disturbances. There is no treatment for diabetic neuropathy and disturbingly long history of therapeutic approaches showing promise in preclinical studies in which failing to translate the clinic [1]. Hyperglycemia-induced nerve damage has been considered as a pivotal role in the pathophysiology of DNP. Damaged myelination in afferent nerve fibers which may induce dysfunction in nociceptive transduction, resulting in hyperalgesia and allodynia. Myelin abnormalities have been observed in patients with diabetes and animal models of DNP.

Do the myelin abnormalities represent the severity of diabetes in patients with allodynia and hyperalgesia as major symptoms I which molecules may regulate the myelin alteration? The findings presented in the research recently published in Aging and Diseases support the notion that axonal demyelination plays a key role in the development of DNP and may represent the severity of diabetic painful symptoms manifested as allodynia and hyperalgesia [2]. The myelin damage may be used as markers for diagnosis diabetic neuropathy. The underlying molecular signaling Matrix Metalloproteinase-9/2 (MMP-9 and MMP-2) can be potential targets for development of novel drugs.

There are three interesting and important observations.

The first, severity of diabetic painful symptoms and the axonal demyelination in the peripheral nerves and Dorsal Horn (DH) of the spinal cord in rats and mice with Streptozotocin (STZ) induced diabetes and DNP. Electron micrographs show that the axons exhibit signs of severe pathological axonal abnormalities, such as reductions in the axon diameter and myelin thickness. The detailed changes in axonal degeneration as well as myelin and mitochondria abnormalities analyzed include the decreased g-ratio (axonal diameter divided by the fiber diameter), decreased proportion of large myelinated fibers, which physiologically inhibit nociceptive afferents in the gelatinosa in DH as suggested by the gate-control theory of pain, and signs of mitochondrial swelling in the DH. Reduced damage of the axons results in greatly reduced painful symptoms manifested as allodynia and hyperalgesia. Our recent unpublished data further show that the severity of painful allodynia and hyperalgesia corresponds to the severity of axon damage in the different stages of the development of diabetes with painful symptoms. These findings demonstrate the relationship between axonal demyelination and painful symptoms, suggesting a diagnostic marker of diabetic neuropathy and, vice versa, the severity of diabetic painful symptoms probably help to evaluate the severity of axonal damage in the early stage in clinic. Mechanistically, MMP-9 plays a critical role in diabetic axonal demyelination. Targeted mutation of MMP-9 can prevent or reverse the axonal dysfunction and protect myelin homeostasis of the peripheral fibers and DH and thus reduce DNP in STZ mice.

The second, MMP-9 and MMP-2 in the Dorsal Root Ganglion (DRG) and DH play important roles in development of diabetes and DNP. MMP-9 may contribute to DNP by increasing the phosphorylation of NMDA receptors and the subsequent activation of $Ca_{2\pm}$ dependent downstream signaling pathways, in addition to inducing myelin abnormalities as described above however, MMP-2 may serve as a negative regulator. These findings demonstrate that, mechanistically, roles of MMP-9 and MMP-2 in DNP and diabetic axonal demyelination are different from that in neuropathic pain after peripheral nerve injury where the initial spinal MMP-9 and MMP-2 derives from axonal transport in DRG are positively involved in production and maintenance of neuropathic pain, respectively [3]. Further, MMP-9, but not MMP-2, originating primarily locally within spinal central neurons is positively involved in the enhancement of pain following morphine withdrawal, while both MMP-9 and MMP-2 are important in chronic and/or acute morphine tolerance [4]. In addition, our recent studies also show that ephrinB-EphB receptor signaling and Wnt signaling play critical roles in the production and maintenance of neuropathic and cancer pain, but only involve with less extent in the maintenance, not production of DNP [5]. These findings support an idea that the underlying mechanisms of DNP are different from neuropathic pain induced by other forms of injury or diseases. This may explain at least partly why some drugs work effectively for certain chronic pain due to direct nerve injury or bone cancer, but not for DNP.

The third, (±)-α-Lipoic Acid (α-LA) is a natural antioxidant synthesized in the mitochondria and derived from food with excellent clinical safety history and low cost and effective in alleviating diabetic complications in humans. We show that α-LA can greatly suppress DNP by regulating MMP-9 and MMP2, i.e., inhibiting the increased MMP-9 and rescuing the decreased MMP-2 in the DRG and DH. This finding provides mechanistic insights into the action of a therapeutically promising compound derived from natural products.

Additionally, this study shows among the animals that received i.p STZ, only approximately 56%~60% of rats or mice developed DNP, confirming our previous observation [5]. This limited success rate of STZ-induced DNP reminds that the painful symptoms need to be examined and confirmed in each of the experimental animals before we can go further to the next investigation so to avoid confusing and misleading outcomes and to increase the success rate of research and development of new treatment approaches for DNP.

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