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Review

Activated microglia in the spinal cord underlies diabetic neuropathic pain

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ABSTRACT

Diabetes mellitus is an increasingly common chronic medical condition. Approximately 30% of diabetic patients develop neuropathic pain, manifested as spontaneous pain, hyperalgesia and allodynia. Hyperglycemia induces metabolic changes in peripheral tissues and enhances oxidative stress in nerve fibers. The damages and subsequent reactive inflammation affect structural properties of Schwann cells and axons leading to the release of neuropoietic mediators, such as pro-inflammatory cytokines and pro-nociceptive mediators. Therefore, diabetic neuropathic pain (DNP) shares some histological features and underlying mechanisms with traumatic neuropathy. DNP displays, however, other distinct features; for instance, sensory input to the spinal cord decreases rather than increasing in diabetic patients. Consequently, development of central sensitization in DNP involves mechanisms that are distinct from traumatic neuropathic pain. In DNP, the contribution of spinal cord microglia activation to central sensitization and pain processes is emerging as a new concept. Besides inflammation in the periphery, hyperglycemia and the resulting production of reactive oxygen species affect the local microenvironment in the spinal cord. All these alterations could trigger resting and sessile microglia to the activated phenotype. In turn, microglia synthesize and release pro-inflammatory cytokines and neuroactive molecules capable of inducing hyperactivity of spinal nociceptive neurons. Hence, it is imperative to elucidate glial mechanisms underlying DNP for the development of effective therapeutic agents. The present review highlights the recent developments regarding the contribution of spinal microglia as compelling target for the treatment of DNP.

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1. Introduction

Peripheral neuropathic pain is caused by a primary injury or dysfunction in the peripheral nervous system. Abnormal spontaneous impulse generated in primary afferents and dorsal root ganglia in response to damage in peripheral nerve axon results in neuronal plasticity changes in the spinal cord leading to the enhancement of nociceptive information transmitted from sensory nerves to spinal nociceptive neurons, called central sensitization (Baron, 2000). Diabetes mellitus is one of the major causes of peripheral neuropathy. Diabetic neuropathic pain (DNP) is defined as pain arising as a direct consequence of abnormalities in peripheral somatosensory system in people with diabetes (Treede et al., 2008). DNP is a chronic and length-dependent sensorimotor neuropathy, which develops as a result of glucose toxicity associated with local metabolic and microvascular changes in both type I and type II diabetes mellitus (Tesfaye et al., 2010). Approximately 30% of diabetic patients display neuropathic pain (Davies et al., 2006; Tavakoli and Malik, 2008), which can manifest as spontaneous pain, allodynia (pain to normally innocuous stimuli) and hyperalgesia (increased pain perception to noxious stimuli). DNP exerts a substantial impact on the quality of life, particularly by interfering with sleep and enjoyment of life (Galer et al., 2000), but also on the prognosis of diabetic patients (Vinik et al., 2000). In addition to causing pain, diabetic neuropathy together with microangiopathy is responsible for the first cause of foot ulcer and amputation. Similar to traumatic neuropathic pain, DNP is refractory or partially responsive to the existing and conventional analgesics (Veves et al., 2008). This is mainly due to our poor understanding of the underlying mechanisms.

2. Putative mechanisms underlying DNP

The mechanisms underlying the development and maintenance of DNP involve multiple biochemical and anatomical alterations in the peripheral and the central nervous systems (CNS). Several possible mechanisms have been proposed including chronic hyperglycemia (Obrosova, 2009a), increased aldose reductase (Yagihashi et al., 2001; Oates, 2008), enhancement of Na^+ currents in peripheral nerve axons (Misawa et al., 2009), generation of advanced glycation end products (Sugimoto et al., 2008), activation of protein kinase C (Eichberg, 2002), RhoA/Rho kinase pathway (Ohsawa et al., 2011), oxidative stress (Ozkul et al., 2010; Naziroglu et al., 2012) and thalamic dysfunction (Fischer and Waxman, 2010). Importantly, DNP is shown to be accompanied by a progressive increase in c-Fos expression, a marker of neuronal activation (Harris, 1998), in the spinal dorsal horn (Morgado and Tavares, 2007; Morgado et al., 2010). Moreover, inhibition of pain hypersensitivity is associated with the inhibition of spinal neuronal activity (Pertovaara et al., 2001; Morgado et al., 2010). These studies indicate an important role of hyperactivity in the spinal dorsal horn neurons in the pathogenesis of DNP.

3. The distinct characteristics of DNP

DNP shows some characteristics that are different from traumatic neuropathic pain. DNP displays elevated levels of nitrite and tumor necrosis factor-α (TNF-α) (Tiwari et al., 2011) in the blood and/or peripheral nerves (Kumar et al., 2011; Negi et al., 2011; Tiwari et al., 2011; Chauhan et al., 2012). Moreover, the high level of nitric oxide is attributed to the increase in inducible nitric oxide synthase (iNOS) (Kumar et al., 2011; Negi et al., 2011), instead of the increase in neuronal NOS in traumatic neuropathic pain (Guan et al., 2007; Kim et al., 2011). Notably, DNP is closely associated with the high level of blood glucose or hyperglycemia because insulin treatment can prevent (Calcutt and Chaplan, 1997) and partially attenuate (Chopra et al., 2010; Tiwari et al., 2011) the pain hypersensitivity in diabetic rats. Moreover, insulin treatment also potentiates anti-hypersensitive effect induced by antioxidants (Chopra et al., 2010; Tiwari et al., 2011).

As hyperglycemia disrupts homeostasis of peripheral tissues damaging nerve fibers (Obrosova, 2009a), diabetic neuropathy shares some histological features and underlying mechanisms with traumatic neuropathy. However, spinal sensory neurons are not mainly driven by nociceptive input from primary afferents because sensory input to the spinal cord decreases rather than increasing in diabetes (Calcutt, 2002). The peripheral sensory nerves do not exhibit spontaneous activity or increased responsiveness to peripheral stimuli in diabetic rodents. Hyperglycemia even induces a decrease in Na^+/K^+-ATPase activity in peripheral nerve (Raccah et al., 1994; Catanzaro et al., 2013). This reduction in Na^+/K^+-ATPase activity in nerve tissue can result from the oxidative stress associated with hyperglycemia. The resultant incomplete repolarization of membrane potential of nerve fiber could lead to the impairment of nerve conduction. Spinal microdialysis study also shows that sensory input to the spinal cord is decreased in diabetes. In contrast to normal animals, the release of glutamate and GABA in the spinal cord is paradoxically decreased and increased, respectively, under resting conditions in diabetic rats (Malmberg et al., 2006). Although intraplantar injection of formalin produces hyperalgesia in diabetic rats (Calcutt et al., 1994), the release of the excitatory neurotransmitters glutamate (Malmberg et al., 2006) and substance P (Calcutt et al., 2000) in the spinal cord is actually less than that in normal animals. Moreover, formalin injection even increases GABA release in diabetic rats (Malmberg et al., 2006), which is in contrast to that occurred in non-diabetic neuropathic pain (Mertens et al., 2000). These studies suggest that the afferent inputs from the nociceptive peripheral nerve stimuli are not the major source to drive hyperactivity of spinal neurons in diabetes. A decrease in the number of mechano-responsive nociceptors of C-fibers and the presence of probable degenerated fibers without responsiveness to mechanical or heat stimuli have been demonstrated in DNP patients (Orstavik et al., 2006).

Central sensitization plays a pivotal role in the pathogenesis of pain hypersensitivity (von Hehn et al., 2012) and its development results from augmented spontaneous and burst discharges in primary sensory neurons in non-diabetic neuropathic pain (Amir et al., 2002). Since activity in primary afferents is decreased in diabetes, the development of hypersensitivity of spinal nociceptive neurons in DNP must involve some mechanisms that are distinct from traumatic neuropathic pain. Glucose toxicity on local site of spinal cord can contribute to the development of spinally mediated hyperalgesia (Calcutt, 2002). The high concentration of glucose results in pain hypersensitivity (Pabreja et al., 2011; Barriere et al., 2012) probably by disrupting the functions of cell mitochondria and subsequent generation of reactive oxygen species (Stevens et al., 2000; Ho et al., 2006) and oxidative stress