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Relationship between neuropathic pain and zinc ion

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Neuropathic pain characterized by spontaneous pain, pain sensation and tactile allodynia. The disease arising from peripheral or spinal nerve injury, diabetes, or infection with herpes virus is a result of the final product of an altered peripheral, spinal, and supraspinal process for which the usual analgesics are not effective and novel analgesics are desired.

The past study indicated that reduction of chloride gradient across the neuronal membrane, which in turn leads to reduction of anion reversal potential, occurred in neurons of the superficial dorsal horn following a peripheral nerve injury [1]. The mechanism of the change is down-regulation of K^+-Cl^--cotransporter-2 (KCC2), which is potassium-chloride exporter, in spinal lamina I [1]. Similarly, the anion gradient is induced by brain-derived neurotrophic factor (BDNF) in neuropathic pain model animals [2]. BDNF induce decrease of KCC2 expression *via* activation of TrkB receptor. This alteration is one of likely mechanism which contributes to the production of allodynia and hyperalgesia associated with neuropathic pain. It is believed that microglia released BDNF. Many reports indicated relationship between microglia and BDNF signaling in neuropathic pain [3]. It was indicated that microglia played an important role in onset/development of neuropathic pain. However, the upstream signaling of BDNF-TrkB-KCC2 cascade reaction is unclear. Although astrocytes are also considered to contribute to the initiation, rather to the maintenance of neuropathic pain, the role of astrocytes on development of neuropathic pain and underlying signaling cascades are not clear.

Recent reports suggested the relationship between zinc ion and neurodegenerative disease including spinal cord injury [4,5]. Zinc is an essential trace mineral that plays an important role such as growth and development, immune response, gene expression, wound healing, neurological function [6]. Zinc ion levels are strictly maintained by physiologic mechanisms. Transport of zinc ion requires specific zinc transporter proteins because zinc can't pass cellular membrane. In mouse, there are 14 *Zip* transporters that increase intracellular zinc levels and 9 *ZnT* transporters that decrease intracellular zinc levels [6].

The alteration of zinc transporter proteins in zinc homeostasis induces to biochemical and physiological change. For example, lactational zinc deficiency suppresses TrkB signaling pathway and induces neuronal apoptosis [5]. High concentration of extracellular zinc ion activates matrix metalloproteinases that convert pro-BDNF to mature-BDNF [7]. Zinc ion ionophore pyrithione inhibits KCC2 activity *in vitro* [8]. In other word, increase of zinc ion induces decrease KCC2 function. On the other hand, high synaptic zinc ion regulated by zinc transporter-3 elevates KCC2 activity via activation of metabotropic zinc ion sensing receptor [9]. These reports suggest that zinc ion concentration have an important relationship with KCC2 function. Moreover, it is considered that the alteration of zinc concentration modulates pain signaling.

Table 1. Relationship between neuropathic pain and zinc ion.

Researcher	Year	Summary
Ciubotariu et al.	2015	Zinc ion modulates opioid activity
Rodriguez-Muñoz et al.	2013	Zinc ion modulates opioid receptor
Lakhan et al.	2012	Zinc ion modulates pain via matrix metalloproteinases
Jiang et al.	2012	Zinc ion inhibits acid-sensing ion channel
Nozaki et al.	2011	Zinc ion modulates pain via NMDA receptor
Jo et al.	2008	Depletion of vesicular zinc ion increases pain

We previously detected by microarray method that partial sciatic nerve ligation surgery induces the decreased expression of *slc30a1* (zinc transporter 1, ZnT1) mRNA. The down regulation of ZnT1 gene was relationship with BDNF-TrkB-KCC2 cascade reaction in astrocyte [10]. The cascade reaction is that the down-regulated expression of ZnT1 increases intracellular zinc concentrations, enhances PKCα membrane translocation and NFκB nuclear translocation, up-regulates the expression of IL-6, increases the phosphorylation of CREB, and promotes the BDNF cascade reaction in astrocytes, all of which down-regulate the expression of KCC2 and induce neuropathic pain *in vivo* [10].

The essential trace mineral include zinc is interesting. Recently, a lot of studies focus on zinc ion (Table 1). However, I think that it is possibility that the alteration of other essential trace mineral concentration is the upstream signaling of BDNF-TrkB-KCC2 cascade reaction and/or playing key role of development of neuropathic pain.

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