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Autophagy: Can It be a New Experimental Research Method of Neuropathic Pain?

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Neuropathic pain, which can be debilitating and life-destroying, has close relationships with inflammatory processes and neuroinflammation caused by a significant pathophysiological state within the nervous system; this is one of the main causes of neuropathic pain [1,2]. Development of neuropathic pain is associated with upregulation of neuroinflammatory responses with proinflammatory cytokines such as TNF-α, interleukin (IL)-1β and IL-6 after the initial nerve damage. There have been numerous studies to control the neural-immune interactions and cellular activation according to the pathogenesis of neuropathic pain states [3,4]. The features of a neuroimmune disorder are considered as opportunities for modification and management of neuropathic pain. Therapeutic trials which are targeted to reduce excessive inflammation such as anti-cytokine agents, cytokine receptor antibodies, and cytokine-signaling inhibitors can be a new opportunity for treatment of neuropathic pain [3].

However, the pathologic mechanisms of neuropathic pain are not completely understood because of its complexity and involvement of structural and physiological changes of the nervous system, thus, clinical treatment of neuropathic pain still remains challenging [3,5]. As a result, revealing new cellular and molecular mechanisms about neuroinflammation and neuropathic pain is indispensable for developing effective pharmacotherapy [5].

Autophagy, a lysosome-mediated intracellular catabolic process, is a cellular pathway involved in the degradation of damaged protein and organelles and occurs at basal, constitutive levels [5,6]. The difference between autophagy and apoptosis may be conceptualized as "self-eating" and "self-killing" [7]. Autophagy offers an alternative cell-death pathway as a stress adaptation. If cellular responses caused by stress have switched from apoptosis to autophagic responses, cells can avoid death [7]. Autophagy serves homeostatic functions and provides metabolic substrates when energy demands of cells are increased, and these properties of autophagy make it a cytoprotective mechanism [6]. Research of this 'self-eating' process have rapidly grown, and connections between autophagy and human disease or physiology have been discovered. Scientists also found that autophagic dysfunction is associated not only with cancer and aging but also with neurodegeneration. Autophagic dysfunction is associated with neurodegenerative diseases such as Huntington's disease, spinocerebellar ataxia, and Parkinson's disease, which are associated with an accumulation of toxic protein due to ineffective lysosomal clearance by autophagy [6]. The mice lacking Atg7 (autophagy-related 7, essential gene for autophagy) in the central nervous system showed

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massive neuronal degenerations in the cerebral and cerebellar cortices [8].

In this respect, Berliocchi et al. [9] investigated the changes of the autophagic process as consequences of nerve injury after spinal nerve ligation. They observed a degenerative pathway produced by a block in the completion of basal autophagy resulted in the accumulation of dysfunctional macromolecules and organelles. In addition, they concluded that the disruption of the autophagic process plays a role in pain processing. Although further investigation is required to find out details in the role and progress of autophagy in the neuroinflammation of chronic pain disease, autophagy seems to participate in microglial cell functions [10] which are related in the pathogenesis of neuropathic pain [11]. These immune cells express a variety of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6, which are related not only to hyperalgesia and allodynia but also to the development of neuropathic pain [10]. Autophagy can regulate inflammasome-dependent responses by controlling the levels of pro-inflammatory cytokine secretion, such as IL-1β [12]. When autophagy was activated by inflammatory signals, IL-1β production became limited. This regulatory effect of autophagy may be a new therapeutic target. Upregulation of autophagy can decrease the development of neuropathic pain.

Recently, epigenetic changes in the spinal cord and brain during chronic pain were introduced and these findings may guide fundamental advances in new treatments [13]. Autophagy can also be a tool for evaluating the effects of experimental therapeutic interventions targeted to epigenetic mechanisms. For example, recent findings showed a relationship was found between the activation of microRNAs (miRNAs, potent regulators of gene expression and cell survival) and the autophagic activation in the neuropathic pain [5]. The miRNA-195 has increased neuroinflammation and neuropathic pain by inhibiting autophagy activation after peripheral nerve injury. The research also found that miR-195 inhibitor treatment increased autophagy activation and suppressed neuroinflammation. Unfortunately, many patients are still troubled with chronic neuropathic pain because current pain management interventions are insufficient [13]. Incomplete understanding and complexity of pathologic mechanisms of neuropathic pain are obstacles to therapeutic strategies. Autophagy can be an experimental trial from a different angle. However, further research is still needed about the relationships of autophagy and the effects of drugs or therapeutic trials against neuropathic pain. It can be used as new research tools to discover the effect or reveal the mechanisms of treatments. Autophagy research in the light of basal cellular mechanisms may offer a new escape point from neuropathic pain.

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