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Leptin: New hope for the treatment of post-operative cognitive dysfunction?

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Leptin plays a critical role in neuronal development and also promotes structural and functional activities in the central nervous system. Recent studies have demonstrated that leptin could produce therapeutic effects for cognitive impairments of patients with Alzheimer's disease (AD). Post-operative cognitive dysfunction (POCD), defined as a significant dysfunction in cognitive performance for several weeks after surgery, probably has a pathogenesis similar to that of AD. Specifically, they are both characterized by cognitive impairment. In this regard, we hypothesized that leptin probably has a therapeutic benefit of alleviating symptoms of patients with POCD, and the leptin signaling pathway may be involved in the pathogenesis of POCD.

MeSH Keywords: **Alzheimer Disease • Autophagy • Leptin • Postoperative Complications**

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 573  —  —  24

Background

Cognitive dysfunction is a disturbing event. Elderly individuals are at a greater risk for cognitive dysfunction following surgery [1]. This manifestation, widely known as post-operative cognitive dysfunction (POCD), is characterized by disordered thinking and impaired consciousness with later onset and fluctuating course [2–4]. POCD, as mentioned above, is common in elderly patients, and probably has a pathogenesis similar to that of AD and may even evolve into AD [5]. Unfortunately, it has been demonstrated that 41.4% of aged patients have POCD at hospital discharge [6,7]. The underlying mechanisms of POCD, however, have not been fully elucidated.

Leptin is synthesized and secreted by adipocytes, and has been recognized as having an important role in coordinating the peripheral and central signals, ultimately regulating food intake and body weight [8–11]. Although the biological effects of leptin are thought to regulate eating behavior and energy expenditure [12], a prospective clinical study with 785 participants showed that higher circulating levels of leptin contribute to reduce AD incidence [13]. A preclinical study has shown that leptin can reduce pathology and improve memory in a transgenic mouse model of AD. Collectively, these findings indicate that leptin has unique therapeutic effects on cognitive dysfunction, which is the primary pathological feature of AD. In addition to POCD, it is also characterized by cognitive dysfunction and shares similar pathogenesis with AD. Consequently, we hypothesized that leptin may have therapeutic effects on POCD.

Hypothesis

We hypothesized that leptin has prophylactic and therapeutic effects on POCD, and that the leptin signaling pathway may be involved in the pathogenesis of POCD. A previous study by Doherty et al. [14] indicated that leptin prevents hippocampal synaptic disruption and neuronal cell death induced by amyloid- β (A β). A study by Marwarha et al. [15] has shown that

leptin treatment reversed the 27-hydroxycholesterol-induced increase in A β and tau phosphorylation (p-tau). AD, a progressive neurodegenerative disease, is characterized by the accumulation of A β peptide-containing neuritic plaques and neurofibrillary tangles composed of p-tau [16]. In this regard, POCD is also characterized by abnormal deposition of A β and p-tau. These findings strongly support the hypothesis that leptin may have beneficial effects for the treatment of POCD by down-regulation of A β and dephosphorylation of p-tau.

AMP-activated protein kinase (AMPK), a Ser/Thr kinase, has a critical role in the maintenance of energy metabolism at cellular and body levels [17,18]. Thornton et al. [19] verified that the activation of AMPK suppresses tau binding to microtubules. Furthermore, leptin is capable of decreasing the levels of tau phosphorylation by activation of AMPK in rat cortical neurons [20]. It is widely known that POCD and AD are both aging-related diseases, and slowing the aging process may have therapeutic effects. AMPK is a major regulator, which can activate the autophagic pathway, while activation of AMPK inhibits mTOR, an inducer of autophagy [21,22]. Our recent study proposed a hypothesis that inhibiting mTOR activates the autophagic pathway, thereby leading to therapeutic effects for POCD [23]. Leptin probably has prophylactic and therapeutic effects in POCD, and the leptin signaling pathway may be involved in the pathogenesis of POCD.

Conclusions

Further investigations are needed to determine whether leptin has unique effects in the treatment of POCD, and to make certain whether leptin signaling pathway is involved in the pathogenesis of POCD. If our hypothesis is correct, leptin may be a promising treatment for POCD.

Conflict of interest statement

The authors declare that they have no conflicts of interest in this work.

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