Neurobiology of Disease

Low-Level Laser Therapy Rescues Dendrite Atrophy via Upregulating BDNF Expression: Implications for Alzheimer's Disease

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Downregulation of brain-derived neurotrophic factor (BDNF) in the hippocampus occurs early in the progression of Alzheimer's disease (AD). Since BDNF plays a critical role in neuronal survival and dendrite growth, BDNF upregulation may contribute to rescue dendrite atrophy and cell loss in AD. Low-level laser therapy (LLLT) has been demonstrated to regulate neuronal function both *in vitro* and *in vivo*. In the present study, we found that LLLT rescued neurons loss and dendritic atrophy via upregulation of BDNF in both Aβ-treated hippocampal neurons and cultured APP/PS1 mouse hippocampal neurons. Photoactivation of transcription factor CRE-binding protein (CREB) increased both BDNF mRNA and protein expression, since knockdown CREB blocked the effects of LLLT. Furthermore, CREB-regulated transcription was in an ERK-dependent manner. Inhibition of ERK attenuated the DNA-binding efficiency of CREB to BDNF promoter. In addition, dendrite growth was improved after LLLT, characterized by upregulation of Rac1 activity and PSD-95 expression, and the increase in length, branching, and spine density of dendrites in hippocampal neurons. Together, these studies suggest that upregulation of BDNF with LLLT by activation of ERK/CREB pathway can ameliorate Aβ-induced neurons loss and dendritic atrophy, thus identifying a novel pathway by which LLLT protects against Aβ-induced neurotoxicity. Our research may provide a feasible therapeutic approach to control the progression of AD.

Introduction

Neurotrophins exert biological actions primarily on cells of the nervous system (Lewin and Barde, 1996). In addition to their classical role in supporting survival of neuronal populations, brain-derived neurotrophic factor (BDNF), in particular, is a strong candidate to modulate dendritic structure and potentiate synaptic transmission in the CNS (Katz and Shatz, 1996; Connor and Dragunow, 1998; Murer et al., 2001). In patients with AD, neurites atrophy and synaptic loss are considered the major causes of cognitive impairment (Einstein et al., 1994; Masliah et al., 2001; Selkoe, 2002). Recent evidence suggests Aβ-associated neurotoxicity and dendrite atrophy may be a consequence of BDNF deficiency. Several studies indicate that the cortex and hippocampus exhibit both extensive amyloid pathology and decreased levels of BDNF in Alzheimer's disease (AD; Hu and Russek, 2008; Zuccato and Cattaneo, 2009). Learning and memory deficits exhibited by transgenic mouse models of AD can be rescued by BDNF delivery (Nagahara et al., 2009). Increasing BDNF expression may be an important manner to attenuate dendrite atrophy in the CNS during AD pathology.

In recent times, low-level laser therapy (LLLT) constitutes a novel intervention shown to regulate neuronal function in cell cultures, animal models, and clinical conditions (Eells et al., 2003; Rojas et al., 2008). The mechanism of LLLT at the cellular level has been ascribed to the acceleration of electron transfer reactions, resulting in increase of reactive oxygen species and Ca^{2+} as versatile second messengers (Lavi et al., 2003; Lan et al., 2012). Previous studies have shown that the application of LLLT could have an influence on cellular process including altering DNA synthesis and protein expression (Feng et al., 2012; Yazdani et al., 2012), biomodulation in cytoskeleton organization (Ricci et al., 2009; Song et al., 2012), and stimulating cellular proliferation (Zhang et al., 2009; Feng et al., 2012). Studies have shown that Aβ-induced cell apoptosis was significantly diminished with light irradiation (Liang et al., 2012; Zhang et al., 2012). LLLT can efficiently penetrate into biological tissue including the CNS, producing noninvasive beneficial photobiomodulation effects such as promoting nerve regeneration and increasing ATP synthesis (Anders et al., 1993; Mochizuki-Oda et al., 2002). Such properties support that LLLT, or interventions with similar neurobiological effects, may have a role in the treatment of neurodegeneration, a phenomenon that underlies debilitating clinical conditions.

Dendritic growth is crucially dependent on targeted changes in the cytoskeleton. Activation of the Rho-family GTPases, in-

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