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Review Article

Neurogenesis and brain-derived neurotrophic factor levels in herbal therapy

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ABSTRACT

Neurogenesis is the process of formation of new neurons from precursor cells that involves a series includes the proliferation, migration, differentiation, maturation and synapse formation. During the formation, some neurons will undergo a process of programmed cell death or apoptosis; it is related to the trophic factor / neurotrophin molecules of the substance that is to sustain life as BDNF cells found in the nervous system among other areas in the hippocampus. Problem neurogenesis is expected to reach 17% of the entire population, basic pathology due to reduced synapse, neurotransmitters and neuronal networks. Provision of adequate stimuli can trigger neurogenesis and synaptic plasticity in the nervous system. WHO estimates that 80% of the world population use herbal medicine for the treatment of major health considering safe and without side effects. Already many herb plants are currently used as a treatment for nerve. In a review of this article we try to give an overview illustration of our understanding of neurogenesis and BDNF with various problems related to the prospect of therapy for both of them, through the treatment of phytochemicals as an alternative treatment that is safe and effective, using several types of herbs below levels / doses used, how to work, and the methods used.

Keywords: BDNF, Herbal therapy, Neurogenesis

INTRODUCTION

In developing countries, herbal therapy is the first and basis form of treatment for most types of diseases. About 75–80% of the world's population prefers herbal therapy as a major treatment due to its better adequacy and satisfactoriness, which enhance human body's symmetry with minimal side effects. Fruits and plants have been presented from the past as promising tools in becoming natural agents.

The World Health Organization (WHO) estimates that 80 percent of the world's population presently uses herbal medicine for some aspect of primary health care, in Europe, the European Directive 2004/24/EC released in 2004 by the European Parliament and by the Council of Europe provides the guidelines for the use of herbal medicines.[1,2] Evidence for the potential protective effects of selected herbs is generally based on experiments demonstrating a biological activity in a relevant in vitro bioassay or experiments using animal models. In some cases, this is supported by both epidemiological studies and a limited number of intervention experiments in humans. Researchers from the Shanghai Institutes for Biological Sciences have found that a herb used in traditional Chinese medicine promotes neural progenitor

cell proliferation and neurogenesis.[3] Neurogenesis is the process of generating new nerve cells, including neurons, astrocytes, glia and others. Neuroplasticity refers to the ability of the brain and the central nervous system to adapt to environmental change, respond to injury and to acquire novel information by modifying neural connectivity and function.

Neurotrophins are molecules that support neuroplasticity and in particular, are capable of signalling neurons to survive, differentiate or grow and key intervention that trigger the processes through which neurotrophins mediate energy metabolism and in turn neuroplsticity, and substance to preserve the life of the cell like BDNF.[4-8] BDNF is most abundant in brain areas that are associated with cognitive and metabolic regulation the hippocampus and the hypothalamus.

In the hippocampus, the involvement of BDNF in neural plasticity and neurogenesis is important to learning and memory. BDNF stimulates the development and differentiation of new neurons and promotes long-term potentiation (LTP), which is widely considered to be one of the major mechanisms underlying memory acquisition, consolidation and storage in the brain.

It is also known to be controlled at the molecular level by the activation of a number of neuronal signalling pathways. It is generally accepted that BDNF has a wide repertoire of neuro-trophic and neuroprotective properties in the CNS and the periphery; namely, neuronal protection and survival, neurite expression, axonal and dendritic growth and remodelling, neuronal differentiation and synaptic plasticity and synaptic transmission efficacy.[9]

BDNF also plays a role in energy homeostasis, as BDNF deficiency is associated with increased weight gain in mice and humans, and hypothalamic BDNF administration can reduce food intake and increase energy expenditure, leading to lighter animals.[10] BDNF plays a central role in brain development and plasticity by opposing neuronal damage and promoting neurogenesis and cell survival. Similar to classical antidepressant imipramine, chronic curcumin treatment prevented stress-induced decreases in BDNF levels and neurogenesis across all hippocampal subfields.[11] The most abundant neurotrophin in the central nervous system involved in neuronal survival, growth, and proliferation is the brain-derived neurotrophic factor (BDNF).[12]

DISCUSSION

Polygonum multiflorum Thunberg complex composition {12 (PMC-12})

Polygonum multiflorum Thunberg complex composition-12 (PMC-12), which is a mixture of four medicinal herbs, that is, Polygonum multiflorum, Polygala tenuifolia, Rehmannia glutinosa, and Acorus gramineus, on hippocampal neurogenesis, learning, and memory in mice. PMC-12 was orally administered to male C57BL/6 mice (5 weeks old) at 100 or 500 mg/kg daily for 2 weeks. PMC-12 administration significantly was found to increase the proliferation of neural progenitor cells and the survival of newly-generated cells in the dentate gyrus. In the Morris water maze test, the latency times of PMC-12 treated mice (100 or 500 mg/kg) were shorter than those of vehicle-control mice. In addition, PMC-12 increased the levels of BDNF, p-CREB, and synaptophysin, which are known to be associated with neural plasticity and hippocampal neurogenesis.[13]

E. longana, H. cordata and D. japonica

The herbal mixture used in the present study demonstrated an inductive effect on the expression of BDNF, pCREB and pAkt. These herbs have been used as a therapeutic agent for cerebral disease especially in Korea. That oral administration of herbal mixture in both doses (206 and 618 mg/kg) alleviated stress induced learning and memory deficits for mice by remaining in the well-lit side of a two compartment apparatus and not entering the dark where it received the electrical stimulus.

The present study investigated BDNF protein levels in hippocampus and cortex of mice under stress and compared values with herbal mixture fed mice under stress. Treatment with herbal mixture showed a significant increase in BDNF translation level. The administration of herbal mixture significantly increased BDNF protein expression in mouse hippocampus and cortex.[14]

Curcumin

Curcumin is a lipophilic compound that can easily cross the blood-brain barrier and directly induce neuroprotection probably through its antioxidant ability to inhibit lipid peroxidation and neutralize ROS and RNS.[15] In addition, curcumin can affect number of cellular pathways on molecular level and via anti-inflammatory properties it can inhibit cyclooxygenase 1 and cyclooxygenase 2 and influence many other signalling pathways leading to cell protection and enhancement of cell survival.[16]

Curcumin effects in restoring BDNF protein levels is important in the context of BDNF signalling in adult neurogenesis, shown to increase neuronal differentiation, survival, and dendritic arborisation.[17-19] Furthmore, chronic curcumin treatment resulted in increased BDNF expression in the hippocampus.

Since BDNF has been directly implicated in cell survival and neurogenesis, and alterations in hippocampal neurogenesis have been linked to depression, it may be suggested that at least some of the antidepressant effects of curcumin may be mediated via enhanced neurogenesis in the hippocampus.[20,21] The learning and memory

deficits associated with chronic stress may be alleviated by novel therapeutic strategies involving dietary and medicinal phyto-antioxidants. One such nutraceutical is turmeric, which has been used throughout Asia as a food additive and a traditional herbal medicine. The active substance in turmeric is curcumin, the yellow pigment extracted from the rhizoma of Curcuma longa.[22]

Brain-derived neurotrophic factor (BDNF) was shown involved in this neuroprotective effect of curcumin. Detailed mechanisms by which curcumin regulate the expression of BDNF that the effects of polyphenols in vivo may be different from the effects in vitro, as in vivo rather metabolites of polyphenols are active than original substances. For example, curcumin, a nonflavonoid phenolic compound present in Curcuma longa, known and used in Indian traditional medicine, after administration significantly decreased depression-like behaviour in rats probably through improvement of the BDNF level.[23]

Curcumin is also reported to significant several studies have shown that different polyphenols including flavonoids such as genistein, quercetin, liquiritin from *Glycyrrhizae radix* plant, isorhamnetin (a flavonolaglycone from *Ginkgo biloba* plant and acetylated flavonoid glycosides from *Scopariadulcis* as well as the stilbenoid compound resveratrol (a polyphenol present in grapes and red wine cause a significant enhancement of neurotrophin (nerve growth factor [NGF] and brain-derived neurotrophic factor [BDNF])-mediated neurite outgrowth in PC12 cells.[24-28]

The effects of curcumin treatment on brain-derived neurotrophic factor (BDNF) levels in the hippocampus and frontal cortex (FC) of diabetic *db/db* mice (DM) and in sera of obese humans. Thus, DM was treated daily with 50 mg/kg of curcumin during an 8-week period. Obese human were treated daily with 500 and 750 mg of curcumin that was administered orally for 12 weeks; BDNF levels in sera were determined at in weeks 0, 2, 6 and 12 of treatment. BDNF levels decreased in hippocampus and FC of DM as compared with untreated wild-type mice.

Curcumin improved or restored BDNF levels to normal levels in DM, but curcumin did not have any effect on BDNF levels in sera of obese humans. Present results suggest a therapeutic potential of curcumin to decrease oxidation caused by obesity in humans and also show that curcumin restores BDNF levels in DM.[29]

The effects of curcumin on hippocampal neurogenesis in chronically stressed rats. We used an unpredictable chronic stress paradigm (20 days) to determine whether chronic curcumin treatment with the effective doses for behavioral responses (5, 10 and 20 mg/kg, p.o.), could alleviate or reverse the effects of stress on adult hippocampal neurogenesis. Our results suggested that curcumin administration (10 and 20 mg/kg, p.o.) increased hippocampal neurogenesis in chronically stressed rats, similar to classic antidepressant imipramine treatment (10 mg/kg, i.p.). Our results further demonstrated that these new cells mature and become neurons, as determined by triple labeling for BrdU and neuronal- or glial-specific markers. In addition, curcumin significantly prevented the stress-induced decrease in 5-HT (1A) mRNA and BDNF protein levels in the hippocampal subfields, two molecules involved in hippocampal neurogenesis.

These results raise the possibility that increased cell proliferation and neuronal populations may be a mechanism by which curcumin treatment overcomes the stress-induced behavioral abnormalities and hippocampal neuronal damage. Moreover, curcumin treatment, via up-regulation of 5-HT (1A) receptors and BDNF, may reverse or protect hippocampal neurons from further damage in response to chronic stress, which may underlie the therapeutic actions of curcumin.[11]

Centella asiatica (CA)

CA is herbal plant, growing in moist places in Asian countries, *CA* is widely used as a herbalplants in traditional medicines in many countries inAsia. Some omportant chemical constituents found in *CA* are triterpenoids and flavonoids.[30] Twenty male rats (Spraque dowley were divided divided into four groups: control/aquades group and groups treated with different doses (mg/kg) of *CA*: 150 (*CA* 150), 300 (*CA* 300), 600 (*CA* 600). Each rat underwent memory exercise for nine days before and after electrical stress and oral administration of ethanol extracts of *CA* for twenty-eight days.

Blood sampling was taking serially from rats tail for four times: (1) before memory exercise, (2) after memory exercise (before stress), (3) after chronic stress, and (4) after memory exercise (following chronic stress). Concentration of serum BDNF was assessed using ELISA. Results: There was no significant difference in serum BDNF concentration between groups in first and second serum sampling, which was prior to chronic stress and administration of different treatments.

There was significant difference in third and fourth serum sampling between groups. Ethanol extracts of CA Leaf increases serum BDNF concentration in rats after chronic stress.[31] Induction of CA extract concentration. Of 100 ppm pd cerebrum cells, cortical cells of mice aged 3 days in culture medium DMEM (Dulbecco's Modived eagle's medium) for 6 days, can promote the growth of axons long and has a tendency to induce neurogenesis.[32]

Spraque dowley male rats by intraoral asiatic acid 30 mg/kg day for 28 days to prevent spatial memory and improvements in neurogenesis in animal studies presented (valproic acid) anticonvulsant and mood stabilizers in the treatment of epilepsy and bipolar

disorder.[33] Research on stem cells isolated from embryo mouse and cell line PC12 presented 100 μm H_2O_2, cell growth was analyzed using the MTT assay and cell death were analyzed using western blotting, the results are cells in the treatment of CA 1ug / ml seen growing neurites that with subsequent long neurites growth and an increase in BDNF compared with controls, said that CA has influence in supporting neurogenesis.[34]

CONCLUSION

Plants, herbs, and ethnobotanicals have been used since the early days of humankind and are still used throughout the world for health promotion and treatment of disease. Plants and natural sources form the basis of today's modern medicine and contribute largely to the commercial drug preparations manufactured today. About 25% of drugs prescribed worldwide are derived from plants. Still, herbs, rather than drugs, are often used in health care. For some, herbal medicine is their preferred method of treatment. For others, herbs are used as adjunct therapy to conventional pharmaceuticals.

However, in many developing societies, traditional medicine of which herbal medicine is a core part is the only system of health care available or affordable. Many studies suggest that BDNF has a significant role in the process of learning and memory, such as development of patterned connections, growth and complexity of dendrites in the cerebral cortex. BDNF plays a significant role in neurogenesis, administration in chronically stressed rats increased hippocampal neurogenesis via modulation of the HPA axis and upregulation of BDNF and 5-HT 1A receptors in the hippocampus.

Curcumin administration in chronically stressed rats increased hippocampal neurogenesis via modulation of the HPA axis and upregulation of BDNF and 5-HT 1A, receptors in the hippocampus. Curcumin effects in restoring BDNF protein levels is important in the context of BDNF signalling in adult neurogenesis, shown to increase neuronal differentiation, survival, and dendritic arborisation. PMC-12 increased the levels of BDNF and hippocampal neurogenesis.

Treatment with herbal mixture *E. longana*, *H. cordata* and *D. japonica* showed a significant increase in BDNF translation level. Treatment with Centella can seen long neurites growth accompanied by growth next neurites and increased levels of BDNF, said that CA has influence in upport neurogenesis. A better understanding of the neurotrophic effects and the molecular mechanisms of action of these compounds could help design better agents for management of neurodegenerative diseases and other disorders of the nervous system.

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