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The Serotonergic System and Neuroplasticity are Implicated in the Effect of Phytochemicals on Mood and Cognitive Disorders

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1. Introduction

Studies has been established in the 1930s that any environmental changes, whether internal or external, that disturbs the maintenance of homeostasis can cause stress response, including psychological, neuronal, endocrine and immune system reactivity (B E Leonard, 2005). During chronic stress or long-term exposure to external stress, glucocorticosteroids induce the hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which produces an increase in plasma glucocorticoid level that then impairs the negative feedback mechanism, causing psychological disorders (Croes, Merz, & Netter, 1993; Henry, 1992). In stress-induced emotional and cognitive disorders, such as depression, anxiety and learning and memory impairment, the serotonergic system mainly exerts its regulatory functions through different subtypes of receptors. Research over the past decades have found that serotonin receptors, such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₄, 5-HT₆, and 5-HT₇ subtypes, are closely related to depression and memory deficits. Moreover, clinical investigation suggests that some of the agonists or antagonists of the 5-HT receptor subtypes can be used for treatment of depression. However, the detailed roles of serotonin receptors in these disorders remain unclear.

Neuroplasticity has been described as the ability of the brain to reorganize itself and form new neuronal connections throughout life. Depression is associated with a neuronal loss in specific brain regions, which has been proven by functional brain imaging and other neurobiological techniques. The dendritic abnormalities seen in the hippocampus in animal models of depression and in patients with depression and Alzheimer's suggest changes in hippocampal circuitry are involved in disorders involving depression, anxiety and learning and memory impairment. The morphological and functional changes of neurons may be reversed after treatment with antidepressants, such as some natural compounds. In this review, a connection between neuroplasticity and the antidepressant-like effects of phytochemicals that are currently being studied is brought into attention. Some phytochemicals, such as curcumin, are found to reverse impaired hippocampal

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neuroplasticity in chronically stressed rats by, for instance, increasing the dendritic length and the number of dendrites and axons. Compelling evidence now suggests a close relation between serotonin system and neuroplasticity in depression. For example, the reduced neuronal plasticity in chronically stressed rats is accompanied by down-regulation of 5-HT_{1A} receptor mRNA expression, which can be prevented by the administration of curcumin. Other intriguing findings suggest that 5-HT₇ receptor can even differentially regulate neuroplasticity in different brain regions after treatment with corticosterone and curcumin. With these findings, there has been a remarkable increase in interest regarding the use of phytochemicals in repairing the neuroplasticity related to central nervous system dysfunction.

Phytochemicals, particularly anti-oxidative natural compounds, are considered promising alternatives to conventional drugs, such as tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors (SSRI), and norepinephrine and dopamine reuptake inhibitors. This is not only because they are extracted from fruits and vegetables and affect biological activities with high potency and low systemic toxicity, but also because they can bind to multiple targets. Studies in the early 90s had a general focus on long-term dietary supplementation. For example, foods supplemented with strawberry extracts and spinach had beneficial effects in retarding functional age-related mood and neurodegenerative diseases, due to their potent anti-oxidative properties. In the following years, phytochemicals have been isolated from the antioxidant-rich foods and their biological activities are gradually being elucidated. Typical phytochemicals that are being studied include curcumin, resveratrol, fisetin, and berberine.

This review summarizes the series of studies on the involvement of serotonin system and neuronal plasticity in treatment of mood and cognitive disorders using Chinese medicine.

2. The 5-HT system in mood and cognitive diseases

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter in the central nervous system (CNS). Through activation or inhibition of its receptor subtypes, studies have demonstrated that 5-HT has multiple physiological functions and dysregulation of serotonergic system can cause stress-related diseases such as Alzheimer's Diseases (AD), anxiety, depression and cognitive disorders (Goddard et al., 2010; Ramanathan & Glatt, 2009). The neurons of the raphe nuclei release the majority of 5-HT in the brain and project onto many other regions of the brain, exerting the regulatory function of 5-HT on physiology. 5-HT expression in developing raphe nuclei neurons and the preferential generation of the nerve fiber projecting terminals during the formation of neuronal synapses demonstrated that 5-HT affects not only morphology and neural activity of embryonic neurons, but also neurogenesis and neuroplasticity after neuronal maturation, including proliferation, translocation, differentiation and synapse formation (Veenstra-VanderWeele et al., 2000). 5-HT is also involved in the development of cerebral cortex in mammals; during the early stages of sensory cortex development, temporary serotonergic fiber projections were detected, indicating that 5-HT might be helpful in conjugation and integration of the developing cortex (Nayyar et al., 2009). Brain serotonin synthesis, packaging, transportation, targeting, release, reuptake and degradation all affect the concentration of 5-HT and its functions. Proteins and related genes that are involved in regulating these physiological functions include speed-limiting enzyme TPH-1 and TPH-2 (Illi et al., 2009), Vmat2 (Fukui et al., 2007; Zucker, Weizman, & Rehavi, 2005), serotonin transporter (SERT or 5-HTT),

monoamine oxidase A (MAO-A) and 5-HT pre and post synaptic receptors (Paaver et al., 2007).

5-HT receptors are assigned to one of seven receptor families, 5-HT₁₋₇, comprising a total of fourteen structurally and pharmacologically distinct mammalian 5-HT receptor subtypes. With the exception of 5-HT₃ receptor, a ligand-gated ion channel, all receptors (5-HT_{1A-E}, 5-HT_{2A-C}, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇) are G protein-coupled receptors (GPCR) that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response. Activation of the specific G-protein can affect enzymes, such as adenylate cyclase, phospholipase A and C, mitogen-activated protein kinase, and cation channels, especially K⁺ and Ca²⁺ (Kushwaha & Albert, 2005). Recent literature has shown, in intact brain, the unequivocal participation of 5-HT receptors in specific physiological responses, ranging from modulation of neuronal activity and transmitter release to behavioral change, especially in psychological disorders like depression, anxiety, obsessive-compulsive disorder, and panic disorder (Ayala, 2009). Among the receptor subtypes, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₄, 5-HT₆, 5-HT₇ are associated with chronic stress-induced neural diseases, inhibition of learning and memory, and cognitive disorders (King et al., 2008; Meneses, 2007; Pérez-García et al., 2006).

3. Role of neuroplasticity in mood and cognitive disabilities: Protective effects of herbal medicines

Neuroplasticity is referred to as the ability of the nervous system to respond and adapt to environmental challenges as a result of one's experiences. It encompasses a series of functional and structural adaptation mechanisms that may lead to neuronal remodeling, including adding, removing or changing the strength of connections between nerve cells and glial cells. Failure of such adaptations might enhance the susceptibility to environmental challenges and ultimately lead to psychopathology. The brain may become more vulnerable by losing the ability to maintain homeostasis. In the case of depression, it is now well accepted to be characterized by profound alterations in brain function and responsiveness, which might be closely linked with neuroplasticity and the ability to modulate a cascade of events from intracellular signaling mechanisms to gene expression.

3.1 Structure change in mood and cognitive disorders

Recent neuroimaging and post-mortem morphometric studies of several brain regions, including limbic and non-limbic circuits, in individuals with mood disorders have begun to demonstrate that depression is accompanied by morphological changes at both the macro-anatomical and histological levels (Miguel-hidalgo & Rajkowska, 2002). Some researchers applying the most sensitive structural neuroimaging techniques to the brains of patients with major depressive disorder (MDD) or bipolar disorder have shown that they are associated with an enlargement of the lateral ventricles, reduction in the volume of grey and white matter in the prefrontal cortex, shrinkage of the hippocampus and decreased volume of the amygdala. Due to the scant access to post-mortem studies on patients, whether treated or untreated, with mood disorders, information on possible morphological alterations of brain regions is limited. Instead, cytomorphological changes associated with mood disorders in animal models, such as the number of neurons, the size and shape of their cell bodies, as well as dendritic and axonal components, have been greatly studied.

Studies in rodents and nonhuman primates demonstrate that exposure to stress can cause alterations in cytomorphology of neurons. Layer II/III pyramidal neurons in the medial prefrontal cortex showed dendritic retraction and reduction in spine number after several weeks of glucocorticoid administration or restraint stress (S. C. Cook & Wellman, 2004). In the hippocampus, repeated stress is reported to cause atrophy of CA3 pyramidal neurons and dentate gyrus. This is supported by a decrease in the number and length of apical tree, but not base tree (R S Duman, 2002). Volume reduction and, more importantly, a shift from neuronal processes to glial processes to make up for the volume decrease have also been observed. Distinct from the CA3 hippocampal region, 24 hr after a single forced swim stress rather than a 3-week period, apical dendrites showed fewer branches in medial prefrontal cortex (mPFC) (Izquierdo, Wellman, & Holmes, 2006). Moreover, the hippocampus is one of the first brain regions to suffer damage from Alzheimer's disease. The comparison of multiple brain regions provides an even more convincing proof of the relationship between neuroplasticity and stress-induced mood disorders: while chronic stress induces significant regression of the apical dendrites in both hippocampus and prefrontal cortex (PFC), it enhances synaptic plasticity in amygdala (Pittenger & Ronald S Duman, 2008). The latter change could both result from and contribute to over-activation of neuronal circuits within amygdala that control fear, anxiety, and emotion. These findings in the animal models with regard to cytomorphological alterations are consistent with several structural imaging studies in human patients with major depression or anxiety.

In learning and memory, synaptic plasticity is even more thoroughly studied. The theory postulating that changes at synapses within the brain underlie learning and memory was formalized in the 1950s. Two crucial terms involved in this theory are long-term potentiation (LTP) and long-term depression (LTD) (Howland & Y. T. Wang, 2008). LTP is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. LTD, on the other hand, is an activity-dependent reduction in the efficacy of neuronal synapses lasting hours or longer and occurs in many areas of the CNS. Both of them describe the ability of chemical synapses to change their strength, which is considered one of the major cellular mechanisms that underlies learning and memory. Cytomorphology of individual neurons and macro-morphology of brain support the normal functioning of synaptic plasticity which plays a direct role in regulating cognitive functions. The underlying mechanisms of morphological alterations during the onset and treatment of mood and cognitive disorders have not yet been clearly understood. However, a few studies show that in patients with MDD and bipolar disorder, there are changes in synaptic proteins that might be associated with morphological changes in related brain regions (Jørgensen & Riederer, 1985). It has also been revealed that antidepressant treatment have a reversing effect on the intracellular signaling, transcription factors and target genes. Neurotrophic factors (NTFs), particularly the neurotrophin family such as BDNF, are one of the activity-regulated gene expressions responsive to neuronal activity. It is possible that these treatments could oppose the adverse cellular effects, which may be regarded as a loss of neural plasticity, by blocking or reversing the atrophy of neurons and by increasing cell survival and function.

3.2 Herbal medicines able to restore neuroplasticity in some CNS malfunction

Antidepressant medications may act by correcting the dysfunction of neuronal adaptive responses, namely neuroplasticity. The most likely immediate cause of depressive

symptoms turns out to be changes in the synaptic availability of the monoamines such as noradrenaline (norepinephrine), serotonin and dopamine, or in the activity of their receptors. As a result, the best accepted pharmacological treatments for depression have been those that increase the availability of monoamines, particularly serotonin. These antidepressants also greatly correct dendritic abnormalities of patients with mood disorders. Dendrites and their spines undergo morphological changes after treatment with some antidepressants. For example, treatment with the selective serotonin reuptake inhibitors (SSRIs) produces a significant increase in dendritic spine density and total length of secondary dendrites in the CA1 region and dentate gyrus of the hippocampus (Norrholm & Ouimet, 2000).

Beyond the classical antidepressants, herbal medicines have been receiving mounting attention due to their ability to reverse or halt impaired neuroplasticity. A wide variety of herbal plants, including Panax ginseng, Zuoomei-to (ZMT), Gongjin-dan (GJD), their extracts, compounds and so on have, to date, already presented beneficial results when tested against known pathological neuronal morphology in some mood and cognitive disorders.

Ginsenosides are extracts from Panax ginseng root that are widely used as a tonic medicine throughout the world and in the treatment of amnesia. In animal models, such as brain-damaged rats and aged rats, a significant improvement in learning and memory has been observed using ginseng powder, which contains the major ginseng saponins, ginsenoside Rb1 and Rg1 (Zhong et al., n.d.). Beyond all doubt, change of neuronal cells morphology underlies the above-mentioned beneficial effects of ginseng saponins. In the 1980s, Sugaya et al. was one of the earliest groups to show that ginseng saponins can improve neurite extension (A. Sugaya et al., 1988). In their study, rat cerebral cortex neurons were cultured. Cytochalasin-B induced disappearance of the growth cone and looping phenomenon were both blocked by administration of crude saponin extract. A proliferative effect of neurite extension, about 1.5 fold in ganglioside content, of cultured neurons was observed, indicating that ginsenosides can promote neurite extension and protect neurons against cytochalasin-B-induced cell lesion. However, this study did not clarify which component within the crude saponin extract of ginseng roots played the most significant role. Later studies screened out ginsenoside Rb1, Rb3, notoginsenoside R4 and Fa as the active compounds that caused the outgrowth and maturation of neurites and they could possibly recover the function of degenerated brains (Nishiyama, Cho, Kitagawa, & Saito, 1994; Tohda, N. Matsumoto, Zou, Meselhy, & Komatsu, 2002).

Zuoomei-to (ZMT, or Xu Ming Tan in Chinese), composed of traditional Chinese and Japanese herbal drugs, has long been used in treating postapoplectic sequelae, clinically indicating that it might reactivate neuronal function in degenerated neuronal circuits. Based on this speculation, the effects of ZMT on memory impairment and synaptic loss in an Alzheimer's mouse model were investigated (Tohda et al., 2003). In this study, synaptophysin, a vesicle protein located at the presynaptic membrane, was used as a marker for synaptic loss. Mice brain slices stained with anti-synaptophysin antibody showed that ZMT prevented synaptic loss induced by A β (25-35) in the CA1 region and dentate gyrus of the hippocampus and the parietal cortex. Neuron densities were also measured in CA1, CA3, and dentate gyrus of the hippocampus and the parietal cortex of mice brains treated with A β (25-35) only or both ZMT and A β (25-35). However, no significant difference was observed, suggesting that synaptic reconstruction rather than neuronal death was involved here.

Gongjin-dan (GJD) is a multi-herbal formula containing different parts of up to six botanicals. It has been used clinically in Korea as an anti-fatigue and anti-aging agent for hundreds of years. GJD was proven to have beneficial effects not only on promoting neurite outgrowth but also on preventing neuronal cell death (Moon et al., 2009). GJD was used on PC12 cells and stressed mice models either as a mimetic or inducer of nerve growth factor (NGF), a small protein commonly reported to stimulate cholinergic neurons, improve memory loss, and increase long-term potentiation and learning tasks. PC12 cells exhibited extended neurite outgrowth after treatment with GJD, although not as obvious as after treatment with NGF. Moreover, NGF level in the cell culture media was elevated. The effect of GJD on survival of neurons was examined by immunostaining microtubule-associated protein-2 (MAP-2), which is a key player in neurogenesis. In the hippocampus of immobilization stressed rats, neuronal cell death was greatly triggered, and GJD was able to decrease this neuronal loss. Since NGF is also required for the survival of the neurons, it is highly possible that GJD exert its neuroprotective function, both in neuroplasticity and neuronal cell survival, by activating the secretion of NGF or simply acting as a mimetic of NGF.

Herbal medicines that have similar effects on the shape and structure of the CNS are not limited to the above-mentioned examples. In later sections of this chapter, more natural compounds, such as curcumin, resveratrol and others, will be discussed with respect to their tonic effects on CNS and operating mechanisms, especially when the 5-HT system is involved. Most of them appear to prevent morphological alterations induced by stress insults. Even though individual studies might have slightly different outcomes due to different cell types or animal models, herbal medicine generally proves to be a promising in treating CNS-related disorders.

4. The antioxidative effects of neuroprotective natural compounds

4.1 Oxidative stress and the 5-HT system

Oxidative stress is a result of a build-up of reactive oxygen species (ROS) due to reduced ability of a biological system to detoxify the reactive intermediates or to repair the resulting damage. ROS are a group of chemically-reactive molecules containing oxygen. They are generated by enzymatic and non-enzymatic reactions in the mitochondria and cytoplasm. In humans, oxidative stress is involved in many diseases including those in the CNS. Oxygen radicals initiate neurotoxicity such as build up of Abeta, leading to neurodegenerations. For example, neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, are commonly accompanied by oxidative stress markers. Environmental stress can lead the body into pathological conditions, in which ROS levels can increase dramatically, activating enzymes including proteases, phospholipases, and nucleases that result in significant damage to cell morphology. As a result, there is increasing attention to develop nutritional therapies to combat these age-related oxidative processes. Mounting focus has been placed on compounds extracted from botanicals in vegetables, fruits, grains, roots, flowers and so on. Polyphenolics, like resveratrol from grape and red wine and curcumin from turmeric, are becoming recognized for their antioxidative effects against neurodegenerative diseases, possibly by restoring the neuronal cell morphology, as mentioned earlier in this chapter.

The 5-HT system is involved with the oxidative process in several aspects. First, the process interferes with 5-HT system's precursor tryptophan. ROS and reactive nitrogen species (RNS), excluding NO, oxygen and superoxide anion, rapidly react with many tryptophan

derivatives, thus gradually eliminating the important neurotransmitter serotonin (Peyrot & Ducrocq, 2008). Second, serotonin and oxidative stress have a counterbalance effect in synthesizing NO. NO, as an endothelium-derived relaxing factor, is synthesized by the endothelial isoform of nitric oxide synthase (eNOS). This process involves pertussis-toxin-sensitive G protein that responds to serotonin and can be inhibited by oxidative stress (Michel & Vanhoutte, 2010). Third, 5-HT receptor subtypes interact with components of the oxidative process. For example, NADPH oxidase is necessary for the activation of 5-HT₂ receptors (MacFarlane et al., 2011). NADPH oxidase is recognized for its dual-edge roles in health and disease. Altered NADPH oxidase function has been linked to neurological disorders such as AD, as it is present in Abeta-induced ROS production (Lambeth, 2007). Superoxide produced by NADPH oxidase may interact with NO to form the toxic peroxynitrite, which is normally associated with neuronal death (Brown, 2007). All in all, oxidative stressors impair neuronal plasticity while concurrently altering neurotransmission, contributing to CNS diseases.

4.2 Natural compounds as antioxidants

Plant-derived supplements for improving mental health are gradually gaining popularity because they are natural and thus considered to be safer and produce fewer side effects than chemically synthesized antioxidants. One of the most commonly studied type is the polyphenols, which have a wide array of phenol ring structures, as one of the first antioxidative natural compounds to catch attention. They are divided into different groups according to the number of phenol rings and the chemical groups attached to them, among which flavonoids are the largest and most well-known group. The capacity of flavonoids to act as an antioxidant, i.e. scavenging free radicals, depends on their molecular structure. In general, polyphenols are rapidly converted to their glucuronide derivatives upon ingestion and transported to the circulatory system, where they can cross the blood brain barrier.

4.2.1 Resveratrol

Dietary supplement of polyphenols extracted from grape skin and seeds had been reported to ameliorate oxidative damage in synaptic membrane of brain cells (G. Y. Sun et al., 1999). Later on, trans-resveratrol was found to be the most effective extract from grape skin and seed, as well as a variety of other plants such as peanuts and berries, that produces beneficial health effects. To assess its role as an antioxidant, resveratrol was compared with the classical antioxidative vitamins C and E in a 1977 study (Chanvitayapongs et al., 1997). In this study, oxidative stress was induced by addition of Fe²⁺ and t-butyl hydroperoxide to the cultured PC12 cell medium. Even though the combination of the three antioxidants exhibited the greatest effect, when used alone, resveratrol is more effective than vitamins C and E combined.

Several studies have demonstrated the ability of resveratrol to protect neurons against Abeta-induced oxidative toxicity in vitro. In a rat model of sporadic AD induced by intracerebroventricular streptozotocin, in which both oxidative stress and cognitive impairment were present, trans-resveratrol significantly prevented the cognitive deficits (Sharma & Gupta, 2002). Red wine, with a high content of resveratrol, was also reported to markedly attenuate AD-type deterioration of spatial memory function and Abeta neuropathology (Jun Wang et al., 2006). The mechanism by which resveratrol fights against Abeta-induced oxidative stress mainly lies in its ability to inhibit not only the secretion of

Abeta, but also formation and extension of Abeta fibrils and to destabilize the fibrilized Abeta (Marambaud et al., 2005; Ono et al., 2006).

The antidepressant-like activity of resveratrol, which involves the inhibition of monoamine oxidase (MAO) isoform activity, also attributes to its potent antioxidative effects (Ying Xu et al., 2010). MAOs are mitochondrial-bound isoenzymes that catalyze the oxidative deamination of dietary amines and monoamine neurotransmitters, such as 5-HT, noradrenaline, dopamine and other trace amines. In a PCPA-induced serotonin-depleted mice model, treatment with resveratrol significantly improved the performance of mice in forced swimming and tail suspension tests. In the meantime, serotonin levels were dramatically increased, accompanied by inhibition of MAO-B activity. The involvement of 5-HT system in neuroprotective effects of resveratrol was also confirmed by an electrophysiological study (Lee et al., 2011). It was reported that resveratrol is able to mediate current flow in the cell by regulating 5-HT₃ receptor activity, possibly through interactions with the N-terminal domain of the receptor.

There are different modes of administration of resveratrol, such as i.p. injection or supplementation with grape powder formulation. Studies to examine bioavailability indicate that resveratrol is rapidly conjugated to its glucuronide derivative and can be transported to the circulatory system. Once in the circulatory system, it can pass through the blood brain barrier. This renders a possibility that resveratrol can be developed into drugs for use in clinical trials.

4.2.2 Curcumin

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* (Ying Xu et al., 2009). In this study, the effects of curcumin on restraint stress-induced spatial learning and memory dysfunction in a water maze task were investigated, and related neuroendocrine and plasticity changes were measured. The results showed that memory deficits were reversed with curcumin in a dose-dependent manner, as were stress-induced increases in serum corticosterone levels. These effects were similar to those seen with positive antidepressant imipramine. Additionally, curcumin prevented adverse changes in the dendritic morphology of CA3 pyramidal neurons in the hippocampus, as assessed by the changes in branch points and dendritic length. Moreover, curcumin protected primary hippocampal neurons against corticosterone-induced toxicity.

Curcumin supplementation has also been recently considered as an alternative approach to reduce oxidative damage associated with AD (Wu et al., 2006). High-fat diet has been shown to induce oxidative stress as an intrinsic component that can exacerbate the damage caused by traumatic brain injury (TBI). The group of rats feeding on curcumin supplemented high-fat diet performed better in the cognition tests than the group of rats feeding on high-fat diet only, when both groups were subjected to a mild fluid percussion injury. Synaptic plasticity also changed in accordance with the cognition results. Brain-derived neurotrophic factor (BDNF) was shown involved in this neuroprotective effect of curcumin. Detailed mechanisms by which curcumin regulate the expression of BDNF will be discussed in a later section of this chapter. Moreover, curcumin, but not ibuprofen, a conventional non-steroidal

anti-inflammatory drug, was also able to prevent the synaptic loss related to Abeta-induced oxidative damage (Frautschy et al., 2001).

The impact of curcumin on the 5-HT system has been extensively studied. One study showed that curcumin protected against arsenic-induced neurobehavioral toxicity by modulating oxidative stress and dopaminergic functions in rats; the serotonin level was restored to normal if the rats were treated with both curcumin and arsenic, compared with the group of rats treated with arsenic only (Yadav et al., 2010). A similar phenomenon was found in a stressed mice model (Ying Xu et al., 2005): neurochemical assays showed that curcumin produced a marked increase in serotonin levels at 10 mg/kg in both the frontal cortex and hippocampus.

Alterations in 5-HT transmission are associated with changes in adult cell proliferation, since 5-HT depletion results in significant decreases in the number of newborn cells in the hippocampus. In order to further clarify the mechanism by which curcumin interacts with the 5-HT system and affects neuronal cells morphology, different 5-HT receptor subtypes were studied. A study aimed to investigate the effects of curcumin on hippocampal neurogenesis in chronically stressed rats used an unpredictable chronic stress paradigm (Ying Xu et al., 2007). It found that 5, 10 and 20 mg/kg, p.o. chronic treatment for 20 days could alleviate or reverse the effects of stress on adult hippocampal neurogenesis, denoted by BrdU labeling. This result was similar to 10 mg/kg, i.p. classic antidepressant imipramine treatment. In addition, curcumin significantly prevented the stress-induced decrease in 5-HT_{1A} mRNA and BDNF protein levels in the hippocampal subfields. These results suggest that curcumin treatment overcomes the stress-induced behavioral abnormalities and hippocampal neuronal damage by increasing cell proliferation and neuronal populations.

Moving on to neuroplasticity, the 5-HT system also plays a significant role in the neuroprotective effects of curcumin. In a 2011 study, exposure of cortical neurons to corticosterone resulted in decreased mRNA levels for the 5-HT receptor subtypes 5-HT_{1A}, 5-HT_{2A} and 5-HT₄, but no change for the 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₆ and 5-HT₇. Pretreatment with curcumin reversed this decreased mRNA level for the 5-HT_{1A} and 5-HT₄ receptors, but not the 5-HT_{2A} receptor. Moreover, curcumin exerted a neuroprotective effect against corticosterone-induced neuronal death. This observed effect was partially blocked with the separate application of 5-HT_{1A} receptor antagonist p-MPPI and 5-HT₄ receptor antagonist RS 39604, and completely blocked with the simultaneous application of the two antagonists. Curcumin was also found to regulate corticosterone-induced morphological changes, such as increases in soma size, dendritic branching and dendritic spine density, as well as elevate synaptophysin expression in cortical neurons. Again, p-MPPI and RS 39604 reversed these effects of curcumin to prevent the morphological changes of neurons (Ying Xu et al., 2011).

4.2.3 EGCG

Green tea polyphenols (GTPs) are the most active antioxidative constituents in green tea. Among the 5 isoforms of GTPs, EGCG has the greatest potential beneficial effects in the CNS. In male Wistar rats undergoing restraint stress for 3 weeks, EGCG-treated groups performed better in the open field test and step-through test than the stress group. Similar results were observed in the crude GTP-treated group. Moreover, plasma levels of serotonin in both EGCG- and GTP- treated groups were elevated closer to the normal groups,

compared to the stress group (Chen et al., 2010). This supports the involvement of the 5-HT system in the mechanism of the antioxidative effects of many neuroprotective herbals.

4.2.4 Other herbal supplements

Ginkgo biloba, also known as the maiden tree, contains compounds with antioxidant properties that protect neuron membranes, regulate neurotransmitters and retard cell degeneration. Standardized Ginkgo biloba extract EGb 761 was shown to improve neurogenesis and cognitive function in both young and old transgenic mice model TgAPP/PS1 with AD (Tchantchou et al., 2007). Later studies however suggested that Ginkgo biloba aids cognition only when subjects have AD rather than preventing AD. The neuroprotective effects of EGb 761 pertaining to the serotonin system and depression were also examined (P. Rojas et al., 2011). Not surprisingly, EGb 761 exerted its antidepressant property, as assessed by the forced swimming test, via its antioxidative effects. Moreover, serotonin level in the midbrain was increased in the EGb 761-treated group of mice, compared to the stress group. This indicates that ginkgo biloba can modulate serotonergic neurotransmission. A recent study suggests that ginkgo biloba is able to block the 5-HT₃ receptor channel, further attesting to its function on the serotonin system (Thompson et al., 2011).

Huperzine A (HupA) is an alkaloid compound extracted from the Chinese moss *Huperzia serrata*. Besides its role as a natural acetylcholinesterase inhibitor in treating AD, HupA also has potent antioxidative effects. It has been found to protect against Abeta-induced cell lesion and abnormal morphology in the primary cultured rat cortical neurons (Xiao et al., 2002). HupA treatment reduced ROS formation and caspase 3 (a protein regulating cell apoptosis) activity in a dose-dependent manner in cortical neurons. In PC12 cells, cell death triggered by oxygen-glucose deprivation (OGD) was alleviated by HupA treatment as well (Zhou et al., 2001). Moreover, it prevented the change in cell morphology caused by OGD. After 30 min OGD exposure, PC12 cells developed a mild cell body swelling and neurites retraction or even complete loss. Cells pre-treated with HupA, however, maintained their morphology almost at the same level as normal control. Regarding cognitive behavior, HupA also exhibited beneficial effects. For instance, daily administration of HupA produced significant reversals of the Abeta-induced deficit in learning and memory tasks (R. Wang et al., 2001).

There are other natural antioxidants outside of the above-mentioned ones that are being used to treat or prevent some CNS diseases, such as withania somnifera from a small evergreen shrub; apocynin from *Picrorhiza kurroa*, a creeping plant native to the mountains of India, Nepal, Tibet and Pakistan; and Coenzyme Q, enriched in a number of diets, all of which have neuroprotective effects via oxidative stress reduction in mammalian brains. Natural antioxidants are advantageous for use, because they can cross the blood brain barrier, have low toxicity to the overall health being, and can be easily administered. Many antioxidant studies have indicated their interactions with the 5-HT system, including serotonin and the 5-HT receptor subtypes. More attention to these interactions may bring promise to the development of drugs treating depression and neurodegenerative diseases caused by oxidative stress.

5. Beyond the antioxidants

Even though the biological actions of most neuroprotective natural compounds have been attributed to their antioxidant properties, namely their abilities to scavenge free radicals or

through their impact on the intracellular redox status, studies have also argued that at least some of these compounds' bioactivity *in vivo* is not due to their classical H-donating antioxidant property. This is mainly because of their relatively low level in the brain. Instead, the neuroprotective actions might be exerted through the modulation of the expression of genes that control neuronal survival, death and differentiation; interactions with mitochondria; structural similarities to other hormones in the body and so on.

5.1 Natural compounds used as estrogen replacement

Natural estrogen, also known as the female sex hormone, is a group of compounds belonging to the steroid hormones that exist in humans and other animals. The actions of estrogen are mediated by the estrogen receptors (ER). One of the key functions of estrogen in women is the maintenance of mental health. Withdrawal and fluctuating or low levels of estrogen correlate with significant mood lowering. For example, animal behavioral studies have shown that ovariectomy may lead to the development of cognitive dysfunction, accompanied by changes in neuronal architecture. And estrogen replacement can prevent these changes (Birge, 1996). As a result, there has been increasing interest in the cognitive preserving effects of soybean isoflavones, mainly in post-menopausal women, due to their structural similarity to estrogen and ability to mimic the actions of estrogen in the brain (Henderson, 2006; Kritz-Silverstein et al., 2003). Resveratrol, like soy products and other polyphenols, has free hydroxyl groups and phenolic ring structures that are important for estrogen receptor binding. Indeed, resveratrol can ameliorate neuronal damage induced by acute and chronic stress in different neuronal cell types by interacting directly with both estrogen receptors alpha and beta, though stronger with ER-beta (Robb & Stuart, 2010). Ginsenoside Rb1 also proved to have comparable effects with estrogen on improving behavioral performance in ovariectomized mice (K. Hao et al., 2011). After treatment with ginsenoside Rb1, there were increased TPH (an enzyme in the synthesis of 5-HT) level, decreased MAO activities, and finally elevated 5-HT levels in the mice brains, all to a similar extent observed using estrogen treatment. Additionally, estrogen receptor clomiphene blocked the effects of both ginsenoside Rb1 and estrogen, confirming that ginsenoside Rb1 shares similar pathways with estrogen.

5.2 Increase in the expression of growth factors

Neurotrophic factors are a family of proteins responsible for the growth and survival of developing neurons, thus maintaining the normal function and integral plasticity of the brain. There are three families involved: neurotrophins, glial cell-line derived neurotrophic factor family ligands (GFLs), and neuropoietic cytokines, among which neurotrophins is the most commonly studied. In this family, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT 4/5) are basic components. Regulated by the transcriptional factor CREB, 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 (Y. Xu et al., 2007). Malonylginsenoside Rb1 (GRb1-m) extracted from dried root of *Panax ginseng* C.A. Meyer and ginsenoside Rb1 had a synergizing effect on NGF (Nishiyama et al., 1994). They potentiated the effect of NGF on promoting the neurite outgrowth, eliminating the glial cells when they are co-cultured with neurons, and prolonging the duration of neuronal survival.

Vascular endothelial growth factor (VEGF) is an important signaling molecule that induces proliferation and migration and reduces apoptosis of endothelial cells. It has also gained attention for its beneficial effect on the physiological function of the brain, such as increasing angiogenesis in the ischemic area and enhancing neurogenesis in the hippocampus, which leads to improved cognitive performances (Q. Zhao et al., 2010). Kangen-karyu, a traditional Chinese medicine prescription consisting of six different herbs, upregulates not only BDNF, but also VEGF levels in SAMP8 mice brains. As a result, anxiety-like behaviors as observed in the elevated plus-maze test and impairment in learning and memory as measured in the object recognition/location tests were reduced.

5.3 Increase in blood flow

Learning and memory have long been connected with neurogenesis, i.e. new neuronal growth, increases in the spine density and morphology, especially in the hippocampal area. New hippocampal cells are not only observed to be stimulated by neurotrophic factors, but also cluster near blood vessels, where they proliferate in response to vascular growth factors (Palmer et al., 2000). A brain imaging study showed that cocoa flavanol are able to enhance the cortical blood flow, indicating its potential ability to increase angiogenesis and neurogenesis (Dinges, 2006). Indeed, though flavanol (-)epicatechin did not increase the number of new born cells in the dentate gyrus of the hippocampus in this case, it was reported to increase angiogenesis and neural spine density (H. van Praag et al., 2007). In this study, behavioral tests were also conducted to confirm the effects of neurogenesis. Retention of spatial memory in the water maze test increased in both sedentary and wheel-running performance. Cognition, too, was enhanced, though to a greater extent in the wheel-running group.

6. The signaling pathways

Synaptic plasticity is often involved in stress-induced brain injury, neuroinflammation, and neurocognitive performances. There are several signaling pathways linked with the neuroprotective effects of natural compounds that preserve normal synaptic plasticity. It is likely that the neuroprotection process is carried through selective activation or inhibition of different components, as well as change of gene expression, within a number of protein kinase and lipid kinase signaling pathways, including the mitogen-activated protein kinase (MAPK), protein kinase A (PKA), phosphatidylinositol-3 kinase (PI3K), protein kinase C (PKC) and CaMK pathways. The activation of these pathways commonly result in the activation of the cAMP response element-binding protein (CREB) and a variety of downstream responses, including neurotrophin expression, dendritic spine remodeling and synaptic plasticity such as LTP. Moreover, most flavonoids can bind to the ATP-binding sites of a large number of proteins (Conseil et al., 1998), such as mitochondrial ATPase and Ca²⁺ plasma membrane ATPase. This binding leads to a three-dimensional structural change, followed by series of kinase inactivation, thus preventing the formation of pro-apoptotic proteins in the neurons.

6.1 Mitogen-activated protein kinase (MAPK) signaling cascade

MAPK is mainly responsible for transducing various extracellular stimuli into intracellular responses. There are three levels of regulation: a MAP kinase kinase kinase (MAPKKK), a

MAP kinase kinase (MAPKK) and a MAPK, each regulating the following element. Each MAPKK can be activated by more than one MAPKKK, thus increasing the complexity and diversity of MAPK signaling. The three best characterized pathways involved in the neuroprotective effects of most natural compounds are: the mitogenic extracellular signal-regulated protein kinase (ERK) pathway, the stress activated, c-Jun N-terminal kinase (JNK) pathway, and the p38 pathway (Schroeter et al., 2002). The activation of these MAP kinases phosphorylates their downstream proteins and transcription factors, leading to change in gene expression, as well as neuronal activities.

6.1.1 ERK1/2

ERK1/2 are usually associated with pro-survival signaling such as upregulation of the anti-apoptotic protein Bcl-2. ERK1/2 are activated by upstream MAPKKs, such as MEK1/2, and MAPKKKs, such as c-Raf. Phosphorylation of ERK usually occurs at 2 sites, threonine 202 and tyrosine 204, within the tripeptide motif TEY, and activates a series of transcription factors that regulate neuronal cell differentiation, survival and plasticity. Flavonoids have not only been reported to modulate the phosphorylation state of ERK1/2, but also to have an effect on upstream kinases and membrane receptors. This might be due to their structural homology to specific inhibitors of the ERK signaling. For example, PD 098059 is a flavone that has the ability to bind to the inactive MEK, preventing its activation by upstream MAPKKK and thus inhibiting the pro-survival process (Alessi et al., 1995). Compared to the neurotoxic properties of flavones through the ERK1/2 pathway, the neuroprotective effects are even more intriguing. Curcumin, mentioned multiple times previously, also has an influence on the ERK1/2 pathway. Administration of curcumin alleviated corticosterone-induced cytotoxicity in PC12 cells, with an increase in the ERK1/2 phosphorylation (H. Zhou et al., 2009). Moreover, elevation of phosphorylated ERK1/2 was only visible at a certain time period, 15-90 min in this case, indicating that other mechanisms are also involved in the ERK-regulated cell morphology. There is also evidence of the involvement of 5-HT system in this pathway: serotonin was able to increase ERK1/2 phosphorylation, possibly involving 5-HT_{1A}, 5-HT_{2B} and 5-HT_{2C} receptors (Debata et al., 2010; B. Li et al., 2010).

6.1.2 JNK

JNK is considered to oppose the effects of ERK, in that they generally promote neuronal apoptosis rather than neuronal survival. JNK cascade is strongly activated by stress signals such as oxidative stress, inflammatory cytokines and UV radiation. Regulated by GTPases such as Rac1, MAPKKKs such as MEKK1/4 and ASK1 activate MAPKKs, such as MKK4/7, which go on to regulate the JNK1/2/3. Activated JNK then enters the nucleus and activates or inhibits a series of downstream gene expression, including c-jun and AP-1 proteins that transduce the apoptotic signaling. Similar to ERK, JNK is dually phosphorylated at threonine138 and tyrosine185 within the motif pTppY. Since changes in the cellular redox status may result in the activation of JNK, and oxidative stress can more or less be alleviated by many antioxidative plant extracts, massive studies are investigating whether JNK pathway is involved in the neuroprotective process of these plant extracts. Oxidized low-density lipoprotein (oxLDL) can be used to induce oxidative stress in cultured striatal neurons (H Schroeter et al., 2001). The neurotoxicity was characterized by the activation of JNK, which phosphorylates c-jun, as measured by western blots. Flavonoid epicatechin

strongly inhibited this activation. JNK is also necessary for the serotonin-induced cell proliferation, for this was blocked with exposure to a specific JNK inhibitor. Furthermore, 10min of serotonin addition maximally activated of JNK. Blockade of 5-HT1B and 2A receptors abolished the stimulatory effect of serotonin in JNK (Wei et al., 2010).

6.1.3 P38

p38 shares some of the upstream MAPKKs with the JNK, i.e. MEK1/4 and ASK1, which regulates MKK3/4/6 (MAPKKs). Downstream transcription factors include ATF-2, Max and MEF2. p38 MAP kinase is activated by cellular stresses, including osmotic shock, inflammatory cytokines, UV radiation and growth factors. An isoflavonoid from soybean, genistein, was found to induce the activation of p38, followed by downregulation of Cdc25C, thus preventing the dividing MCF-10F, a nonmalignant human mammary epithelia cell line, from entering mitosis. In other words, genistein can inhibit cell proliferation by activating p38, indicating that it may be able to induce neural effects via this pathway (Frey & Singletary, 2003). However, the precise sites of action within the p38 pathway and the specific elements involved in regulating stress-induced neuronal death remain unknown.

6.2 PKA pathway

PKA is a family of enzymes that have several functions in the cell by phosphorylating other proteins and altering their function. It is also known as cAMP-dependent protein kinase, because its activity is only dependent on the level of cyclic AMP (cAMP). In the activation process, activated alpha subunit of G-protein binds to the enzyme adenylyl cyclase (AC), which catalyzes the conversion of ATP into cAMP, which further leads to the activation of PKA. Once PKA is activated, a series of proteins gets phosphorylated, including the transcription factor CREB. Since PKA exists in different types of cell, where they exert different biological functions, it is plausible that the same compound may have different regulatory effects on the activity of PKA. Curcumin was reported to inhibit the growth of several tumor cell types, in which hyperactivated PKA might play an important role in unlimited cell division, prompting a study on the mechanism by which curcumin may inhibit different types of phosphatases (Reddy & Aggarwal, 1994). Indeed, curcumin was able to inhibit the activity of PKA in tumor cells, even though not to a very high extent. However, in neurons, curcumin activated the PKA pathway rather than inhibited it, and this effect involved the 5-HT system (Y Xu et al., 2011). Treatment of the primary cortical cultured neurons with curcumin significantly increased the cAMP level, PKA activity and pCREB level, compared with the corticosterone-treated only group. Cell morphology parameters, including the soma size, total number of branching points, dendritic length and spine density, were also positively regulated by curcumin compare with the corticosterone-treated group. Addition of 5-HT4 receptor antagonist, RS 39604, blocked the elevation of cAMP level, while 5-HT1A antagonist, p-MPPI, inhibited the increase in PKA activity and pCREB. These findings suggest that the neuroprotection and modulation of neuroplasticity exhibited by curcumin might be mediated, at least in part, via the 5-HT receptor-cAMP-PKA-CREB signal pathway.

6.3 PI3K/Akt signaling cascade (PKB pathway)

PI3Ks are a family of enzymes involved in cellular functions, such as cell survival, growth, proliferation, differentiation and motility. Activation of PI3K by extracellular signals

catalyzes the production of phosphatidylinositol-3,4,5-triphosphate (PIP3), phosphatidylinositol-4-phosphate (PIP) and phosphatidylinositol-4,5-bisphosphate (PIP2). PIP3 then activates phosphoinositide-dependent protein (PDK1/2), which plays a role in many signal transduction pathways by activating Akt (also known as protein kinase B, or PKB). Akt can promote cell survival mainly by inhibiting some important apoptosis-inducing proteins such as Bad (Cardone et al., 1998; Zha et al., 1996). Quercetin has been reported to dose dependently regulate neuronal cell fate. At lower doses, quercetin may activate the MAPK pathway and exert its protective mechanism. However, high concentrations of quercetin inhibit the PI3K pathway and thus stimulate the pro-apoptotic pathway (Kong et al., 2000). The relationship between serotonin and PI3K/ Akt signaling has also been studied. 5-HT-induced phosphorylation of Akt in different cell types was blocked either by PI3K inhibitors or 5-HT_{1A} antagonist, indicating the necessary presence of both elements in the proliferation and migration activities of cells (Dizeyi et al., 2011).

6.4 PKC pathway

PKC is a family of enzymes responsible for phosphorylating other proteins at the hydroxyl groups of serine and threonine residues, and plays an important role in several signal transduction cascades that regulate growth, differentiation and tumorigenesis. Signals such as an increase in the diacylglycerol or Ca²⁺ levels can initiate this signal cascade. The PKC pathway shares some components with the PI3K/ Akt pathway, such as the intracellular signaling molecules PI3K and PDK1. Flavonoids have been reported only to have an inhibitory effect on the PKC activity, rather than activation or a dual effect. TPA is a potent tumor promoter often employed to activate PKC, and consequently PKC is considered as a cellular receptor for TPA. In a brain-purified mixture of PKC isoenzymes, flavonols, in particular fisetin, quercetin and myricetin, and flavones, in particular luteolin, were found to be the most potent inhibitors for PKC. They also inhibited PI3K activity (Agullo et al., 1997; Ferriola et al., 1989). Since PKC is expressed in different cell types, the same compound may have varying extent of inhibitory effects on its activity (Y. T. Huang et al., 1996).

6.5 CaMK pathway

Ca²⁺/calmodulin-dependent protein kinases II or CaM kinases II are serine/threonine-specific protein kinases that are regulated by the Ca²⁺/calmodulin complex. CaMKII is intricately involved in memory formation and synaptic plasticity in the hippocampus. The phosphorylation of CaMKII at Thr286 switches the kinase into an active biochemical state required for synaptic plasticity and learning, including spatial learning. However, CaMKII over phosphorylation may produce some degree of neurotoxicity to the cells and alter some biochemical pathways involved in memory processing. It should be noted that mice that expressed a constitutively active CaMKII lacked low frequency LTP and were not able to form stable place cells within the hippocampus (Ying Xu et al., 2009). In hippocampal neurons, pCaMKII levels were significantly increased in response to corticosterone exposure, though no changes were found in total CaMKII levels. These results are similar to the changes elicited by the immobilization stress, which was previously reported (Suenaga et al., 2004). This elevation of pCaMKII was reversed by curcumin administration at different dose ranges from 0.62 to 2.5 mM (Ying Xu et al., 2009).

6.6 Other cascades

Signaling cascades involved in the neuroprotection effect of natural compounds may not be limited to the above-mentioned pathways. Besides the common transcription factor CREB of these pathways, there is FoxO1, an important target for insulin and growth factor signaling in the regulation of metabolism and cell proliferation. FoxO1 can mediate an autofeedback loop regulating SIRT1 expression (Xiong et al., 2011), a protein previously discussed to be regulated by resveratrol as well. A lot of the flavonoids also modulate the functions of the mitochondria by binding to the ATP-binding sites (Conseil et al., 1998). More or less, these pathways involve the 5-HT system, as well as its different receptor subtypes, and together they regulate gene expressions that are responsible for neuronal cell survival or inhibition of abnormal cell proliferation under stress insults. Other than behavioral tests, the most effective way to observe their function is to assess the cell morphology. Indeed, most neuroprotective natural compounds are able to morphologically restore the neurons close to normal conditions.

7. References

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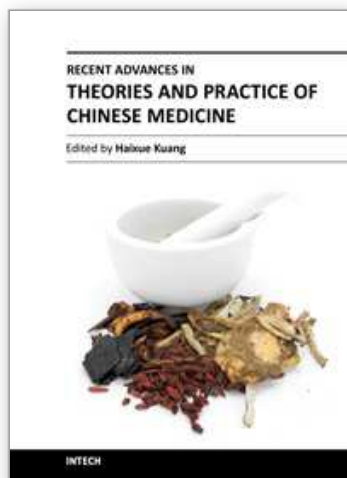
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During the recent years, traditional Chinese medicine (TCM) has attracted the attention of researchers all over the world. It is looked upon not only as a bright pearl, but also a treasure house of ancient Chinese culture. Nowadays, TCM has become a subject area with high potential and the possibility for original innovation. This book titled Recent Advances in Theories and Practice of Chinese Medicine provides an authoritative and cutting-edge insight into TCM research, including its basic theories, diagnostic approach, current clinical applications, latest advances, and more. It discusses many often neglected important issues, such as the theory of TCM property, and how to carry out TCM research in the direction of TCM property theory using modern scientific technology. The authors of this book comprise an international group of recognized researchers who possess abundant clinical knowledge and research background due to their years of practicing TCM. Hopefully, this book will help our readers gain a deeper understanding of the unique characteristics of Chinese medicine.

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