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Chinese Traditional Medicine and Adult Neurogenesis in the Hippocampus

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ABSTRACT

Adult neurogenesis is an important therapeutic target in treating neurological disorders. Adult neurogenesis takes place in two regions of the brain: Subventricular zone and dentate gyrus in the hippocampus. The progressive understanding on hippocampal neurogenesis in aging and mood disorders increases the demand to explore powerful and subtle interventions on hippocampal neurogenesis. Traditional Chinese herbal medicine provides an abundant pharmaceutical platform for modulating hippocampal neurogenesis. Recent progress in exploring the effects of Chinese herbal medicine and the related mechanisms opens a new direction for regeneration therapy. The current review gives a thorough summary of the research progress made in traditional Chinese herbal formulas, and the effective compounds in Chinese herbs which are beneficial on hippocampal neurogenesis and the possible mechanisms involved.

Key words: Active components, Hippocampal neurogenesis, Neural progenitor cells, Traditional Chinese herb

INTRODUCTION

Adult neurogenesis is a continuous bioactivity in certain brain regions. This activity is highly reserved during revolution, from oscines to rodents and primates. In mammals, there are two regions in brain continuously generating the new neurons during adulthood, the subventricular zone and the dentate gyrus.[1]

It had been a long-term ambiguity whether adult neurogenesis in the dentate gyrus had substantial functions. In 2008, clear evidence proved that the newly generated neurons in the dentate gyrus projected axons and established synapses with hilar interneurons, mossy cells, and CA3 pyramidal cells, and released glutamate as their main neurotransmitter.[2] The process of maturation and synapse formation of the adult-born dentate granule cells was causally linked to memory and learning in the brain.[3] For instance, many factors known to be beneficial for memory (e.g. running, environment enrichment) also increased the number of new neurons;[4-7] likewise, factors that impaired memory, such as aging, stress, and several diseases, were associated with lower neurogenesis levels.[8,9] In addition to learning and memory, adult neurogenesis in the dentate gyrus was proved to be involved in psychological disorders such as depression[4] and anxiety.[5] An impairment of adult neurogenesis in the dentate gyrus could be one of the critical factors in the etiology of certain psychiatric disorders.[6]

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Given the significance of the adult neurogenesis in the hippocampus, pharmacological interventions on adult neurogenesis are believed to be one of the key strategies to treat psychological disorders and to improve the cognitive functions during aging. In China, over more than 3200 herbs and 300 mineral and animal extracts are used in more than 400 different formulas.[7] Although there exists distinct theories in the history of drug development between the oriental world and the western world,[7] these Chinese herbs and extracts provide an abundant database for the drug screening and development using the modern technologies in modern bioscience research. Great efforts had been made in the last decade to explore the effects of Chinese herbal medicine on promoting adult neurogenesis, and recent progress indicates that these medicines hold promising potential for neural regeneration therapy. This review tries to give a summary and comparison on the recent research articles focusing on the Chinese herbs and adult neurogenesis in the hippocampus.

CHINESE HERBS IN FORMULA AND ADULT NEUROGENESIS

In the history of traditional Chinese medicine (TCM), majority of the TCMs are found to be applied as formulas. Several formulas of TCM have been found to be able to promote adult neurogenesis in the dentate gyrus in stressed animals.[8-10] Liu-Wei Dihuang Tang (六味地黄汤 Liū Wèi Dì Huáng Tāng), a Chinese herbal formula used to treat complications of diabetes and glomerulonephritis, was proved to promote hippocampal neurogenesis in adult rats at a dose of 100 mg/kg, which was thought to be associated with improvement in cognitive function in eight radiating arms.[8] More recently, researchers found that oral treatment of Kami-ondam-tang (加味溫膽湯 Jiā Wèi Wēndǎn Tāng) at a dose of 50 mg/kg increased the number of the doublecortin-positive cells in the dentate gyrus in naïve rats, and consequently improved the cognitive functions in mice treated for 2 weeks.[10] Another study using kami-shoyo-san (加味逍遙散 Jiā Wèi Xiāo Yáo Sǎn) reported that in stressed rats, 20 times of standard dose of kami-shoyo-san was able to reverse the impaired neurogenesis in the hippocampus.[9] The above three studies provide evidence that TCM formulas could enhance neurogenesis in the dentate gyrus, both in physical and pathological conditions. However, each formula contained several components based on the theory of TCM. For example, kami-shoyo-san consisted of nine herbal plants [Paeoniae Radix (白芍 Bái Sháo) 4 g, Bupleuri Radix (柴胡 Chái Hú) 4 g, Atractylodis Macrocephalae Rhizoma (白朮 Bái Zhú) 4 g, Liriopis tuber (麥冬 Mài Dōng) 4 g, Angelicae Gigantis Radix (當歸 Dāng Guī) 4 g, Hoelen (茯苓 Fú Ling) 4 g, Menthae Folium (薄荷腦葉 Bò Hé Não Yè) 2 g, Glycyrrhizae Radix (甘草 Gān Cǎo) 2 g, and Zingiberis Rhizoma (生薑 Shēng Jiāng) 6 g].[9] The complex composition of TCMs in formula makes it difficult to further explain which component or components in the formula are beneficial for neurogenesis. It is also unknown whether the effective components have synergistic or antagonistic effects.

EFFECTIVE COMPONENTS IN CHINESE HERBS AND HIPPOCAMPAL NEUROGENESIS

According to the principle of "Jun-Chen-Zuo-Shi (君-臣-佐-使)" in the traditional Chinese medical theory, every component in a certain Chinese medicine formula is essential and plays its own respective role. In view of the complex composition in Chinese medicine formulas, popular research direction in the modern science to promote the application of Chinese herbs for neurogenesis has been carried out to study the effective components in Chinese herbs which are able to stimulate neurogenesis in the dentate gyrus. Therefore, the effects of extracts of Chinese formulas on neurogenesis are widely investigated. Table 1 summarizes that active components from different Chinese herbs that have been proved to enhance the hippocampal neurogenesis under naïve and pathological conditions.

In addition, a few interesting comparison studies were carried out to screen the useful components in a certain Chinese formula. For instance, Buyang Huanwu Decoction (補陽還五湯 Bǔ Yáng Huǎn Wǔ Tāng) is a classic formula that has been used for post-stroke disability for 300 years.[11] It contains Radix Astragali Membranaceus (黃芪根 Huáng Qígēn), Radix Angelicae Sinensis (白芷 Bái Zhǐ), Radix Paeonia Rubra (赤芍 Chì Sháo), Rhizoma Chuanxiong (川穹 Chuān Qióng), Semen Persicae (桃仁 Táo Rén), Flos Carthami (紅花 Hōng Huā), and earthworm (蚯蚓 Qiū Yǐn). The components are mixed in order in the ratio of 120:10:10:10:10:10:4.5 (dry weight). Either with or without earth-

Table 1: Effective component in Chinese herbs beneficial to hippocampal neurogenesis

Effective components	Name of Chinese herbs	Animals/cell types	References
Curcumin	Curcuma longa (薑黃 Jiāng Huáng)	Stressed mice; Adult neural progenitor cells	[30] [40]
Salvianolic acid B	Salvia miltiorrhiza (丹參 Dān Shēn)	MCAO rats; Adult neural progenitor cells	[41,42] [39]
Baicalin	Scutellaria baicalensis Georgi (黃芩 Huáng Qín)	MCAO mice; C17.2 cell/ embryonic stem cells; MCAO rats	[43] [34] [44]
Panax Notoginseng Saponins	Panax Notoginseng (田七 Tián Qí)	Hippocampal progenitor cells	[45]
Polysaccharides	Wolfberry (枸杞子 Gǒu Qí Zī)	Stressed rats C17.2 cells	[26] [46]
Fuzi polysacchrides	Fuzi (附子 Fù Zī)	Stressed mice	[28]
Mori Fructus extracts	Mori Fructus (森喜朗山萸 Sēn Xī Lǎng Shān Yú)	Naïve mice	[31]
Cornel iridoid glycoside	*Cornus officinalis* (山茱萸 Shān Zhū Yú)	MCAO rats	[29]

MCAO: Middle cerebral artery occlusion