A Brief Discussion of Mechanism of Butylphthalide in Treatment of Ischemic Cerebrovascular Disease and its Potential Clinical Application in Treatment of Multiple Sclerosis

Abstract
A Chinese traditional medicine Butylphthalide (NBP) has been proved effects in ischemic cerebrovascular disease. Here we discuss the mechanism of NBP in treatment of ischemic stroke, and find its capability in penetrating and modulating Blood-brain barrier (BBB), reducing harmful inflammation and formation of scars in injury CNS tissue, which implicate the potential application of NBP in treatment of Multiple Sclerosis (MS).

Keywords: Butylphthalide; Blood-Brain Barrier; Neovascularization; Center Nervous System, Inflammation; Multiple Sclerosis; Treatment; Ischemic Cerebrovascular Disease

Introduction
Butylphthalide (NBP) is a group of new drugs isolated from celery’s seeds, originally used for anti-hypertension traditional Chinese medicine [1], has been developed for anti-ischemia treatment in brain infarction [2]. Its function in improvement of outcome of cerebral ischemia infarction had been approved [3,4]. More and more patients get benefits from administrating Butylphthalide. However, the working mechanism of Butylphthalides is far unknown. Here, we literately review the research achievement so far that are related to application of Butylphthalides in cerebrovascular disease in vivo and in vitro. Surprisingly, we found that the metabolites of butylphthalidemay pass through blood-brain barrier [5], and butylphthalide may protect the integrity of BBB and reduce the permeability of BBB injured by reperfusion following hypoxic condition of brain tissue, thereby, reduce the inflammation and water content of brain, prevent brain edema [6]. Understanding the working mechanism of Butylphthalide will widen the future application of Butylphthalides and increase clinic efficacy on treatment and diagnosis of vascular and inflammation diseases in center nervous system (CNS).

Mechanism of Butylphthalides in treatment of cerebral ischemia infarction
I. Butylphthalide modulate inflammation by increasing circulation endothelium progenitor cells (EPCs) [7] and reducing the infiltration of neutrophils to injured post-ischemic brain tissue. Yip HK et al. [8] studied the prognostic value of circulating EPCs in acute ischemia stroke (IS) with 130 consecutive patients and found that circulating EPCs is the independent factor for prognosis of outcome of acute IS. The bone marrow-derived EPCs migrate following the blood stream to injured lesion, differentiate to mature endothelial cells for angiogenesis in situ. It has been reported that Butylphthalide administration increase the level of EPCs in blood stream that associate with the outcome of IS in a clinical study with 170 stroke patients [7]. The results suggest that somehow Butylphthalide increase EPCs passing through BBB to ischemic lesions for injured brain tissue healing process. On the other hand, Butylphthalide inhibit the infiltration of neutrophils to injured lesions of ischemic-reperfusion after transient focal cerebral ischemia in rats that decrease the inflammation [9]. Therefore, Butylphthalide improve the healing of post-ischemic brain tissue through migrating immune healing cells.

II. Butylphthalide promote angiogenesis with increasing expression of pro-angiographic factors:
A chick embryonic chorioallantoic membrane assay shows the profound effect of angiogenesis of DL-NBP with increased expression of pro-angiographic factors: growth factors, vascular endothelial growth factor (VEGF), VEGF receptor and basic fibroblast growth factor (bFGF) [10]. In a middle cerebral artery occlusion (MCAO) model with Stroke-prone renovascular hypertensive rats, NBP treatment rescues brain tissue after ischemic stroke by enhancing angiogenesis with up-regulation of VEGF and hypoxia inducible factor 1 (HIF1) alpha [11]. Therefore, angiogenesis induced by pro-angiographic immune factors play an important role in the mechanism of NBP in treatment of ischemic cerebrovascular diseases.

III. Butylphthalide inhibit the activation of microglia and astrocytes, reduce pro-inflammation factors produced by microglia and astrocytes in injured brain territory to decrease the scar area, improve the restoration of ischemic lesions
of brain tissue. The astrocytes and microglia-mediated neuroinflammation play a central role in pathogenesis of ischemic brain injury by releasing inflammatory mediators. Over-activated microglia releasing excessive pro-inflammatory factors cause over immune reaction in the lesions, which lead to less function restoration from ischemic stroke. Suppression of activation of microglia is a therapeutic strategy in improving the outcome of stroke [12]. Astrocytes also modulate the permeability of BBB by interacting with endothelial cells with released immune mediators [13]. Zhao et al. [14] found that NBP attenuate neuroinflammation by inhibiting the microglia activation in lipopolysaccharide-treated mice [14]. In the culture system of primary astrocytes isolated from cerebral cortex of rats, NBP attenuate the inflammatory responses induced by amyloid-beta through inhibiting activation of astrocytes and proinflammatory products [15]. These results implicate that NBP may improve the restoration of neurological function through reducing neuroinflammation mediated by microglia and astrocytes and their pro-inflammation products.

Potential application of butylphthalide in treatment of multiple sclerosis (MS)

Multiple Sclerosis (MS) is a demyelination disease affecting 2.5 million people worldwide and no cure has been reported up to date. Patients with MS relapse presenta variety of physical, mental neurological disorders, even death as the disease advances. MS is well known as most common autoimmune disease occurring in CNS. The leakage of BBB is a common pathological property in multiple sclerosis (MS) [16]. Genetics or environmental factors like infection of microbes combined with immune system disorder induce the dysfunction of BBB and the entry of immune cells and antibodies passing through BBB into tissue of brain and spine cord. Immune cells invasion and their secreted cytokines, chemokines and antibodies attack the neuron supporting and myelinating cells, such as oligodendrocytes, astrocytes, pericytes and neuroglia, disrupt the myelin sheath of nerve cells, eventually damage then eurrons. Between the two relapses, remyelination may occur, but unsuccessfully remyelinated lesions form scar-like plaques where permanently lose neurological functions. The overlaps of mechanism of Butylphthalides in treatment of ischemia cerebrovascular diseases with the pathological process of MS lead us to consider the clinical feasibility and efficacy of application of Butylphthalides in treatment of MS. We hypothesis that NBP may reduce pro-inflammation cells, increase mature endothelia cells in the MS lesions to mild the inflammation responses in relapsing phase; NBP may increase angiogenesis with angiographic factors for restoration of neovascularization in MS lesions; NBP may inhibit the pro-immune activation of microglia and astrocytes so that reducing formation of scars, improving remyelinating of neurons. Taken together, the mechanism of NBP implicates great potential in the healing of MS.

Brain and spine cord are known as immune privilege organ in certain ways because blood-brain barrier (BBB), the neuroimmune structure between blood vessels and brain tissue, blocks the ‘antigens’ and immune cells entering CNS tissue for prevention from inflammation [17]. In normal condition, there are very few immune cells existing in brain and spine cord tissue. The main elements of BBB structure include tightly connected endothelium cells, basal membrane and astrocytes, terminal of neurons. Depending on the characteristics of the brain specific structure, only brain essential nutrition like glucose, oxygen, small amino acids and so on can pass through this brain-specific structure to provide the original energy materials for brain tissue survival and brain specific functions. This feature protects CNS tissue but at same time bring difficulties to treatment and precise diagnosis of CNS diseases. For instance, neuron protective drugs hardly locate to brain tissue become functional. Therefore, the studies about BBB have significant meaning to neurological diseases. The discovery of capability of Butylphalide and its metabolites in mild passing through BBB not only lighten the way for improvement of outcome of ischemic cerebrovascular diseases and MS, but also give us hope for find cures for other deadly CNS disorders like degenerative diseases and tumor by combining with nanotechnology [18].

References

1. Lu HC (1986) Chinese System of Food Cures: Prevention and Remedies. Sterling Publishing, New York, USA.
2. Zhang JT (2002) New drugs derived from medicinal plants. Therapie 57(2): 137-150.
3. Du R, Teng JF, Wang Y, Zhao XY, Shi ZB (2015) Clinical study of Butylphthalide combined with XueShuan Tong on serum inflammatory factors and prognosis effect of patients with cerebral infarction. Randomized controlled trial. Pak J Pharm Sci 28(Suppl): 1823-1827.
4. Cui LX, Zhu YC, Gao S, Wang JM, Peng B, et al. (2013) Ninety-day administration of dl-3-n-butylphthalide for acute ischemic stroke: a randomized double-blind trial. Randomized controlled trial. Chin Med J (Engl) 126(18): 3405-3410.
5. Diao XX, Zhong K, Li XL, Zhong DF, Chen XY (2015) Isomer-selective distribution of 3-n-butylphthalide (NBP) hydroxylated metabolites, 3-hydroxy-NBP and 10-hydroxy-NBP, across the rat blood-brain barrier. Acta Pharmacol Sin 36(12): 1520-1527.
6. Chong ZZ, Feng YP (1999) dl-3-n-butylphthalide attenuates reperfusion-induced blood-brain barrier damage after focal cerebral ischemia in rats. Zhongguo Yao Li Xue Bao 20(8): 696-700.
7. Zhao H, Yun W, Zhang G, Cai X, Li X (2016) Mobilization of circulating endothelial progenitor cells by dl-3-n-Butylphthalide in Acute Ischemic Stroke Patients. J Stroke Cerebrovasc Dis 25(4): 752-760.
8. Yip HK, Chang LT, Chang WN, Lu CH, Liou CW, et al. (2008) Level and value of circulating endothelial progenitor cells in patients after acute ischemic stroke. Stroke 39(1): 69-74.
9. Xu HL, Feng YP (2000) Inhibitory effects of chiral 3-n-butylphthalide on inflammation following focal ischemic brain injury in rats. Acta Pharmacol Sin 21(5): 433-438.
10. Zhang L, Lu L, Chan WM, Huang Y, Wai MS, et al. (2012) Effects of DL-3-n-butylphthalide on vascular dementia and angiogenesis. Neurochem Res 37(5): 911-919.
11. Liao SJ, Lin JW, Pei Z, Liu CL, Zeng JS, et al. (2009) Enhanced angiogenesis with dl-3-n-butylphthalide treatment after focal cerebral ischemia in RHRSP. Brain Res 1289: 69-78.
12. Yuan Y, Fang M, Wu CY, Ling EA (2016) Scutellarin as a potential therapeutic agent for microglia-mediated neuroinflammation in cerebral ischemia. Neumolecular Med.
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13. Abbott NJ (2002) Astrocyte-endothelial interactions and blood-brain barrier permeability. J Anat 200(6): 629-638.

14. Zhao CY, Lei H, Zhang Y, Li L, Xu SF, et al. (2016) L-3-n-Butylphthalide attenuates neuroinflammatory responses by downregulating JNK activation and upregulating Heme oxygenase-1 in lipopolysaccharide-treated mice. J Asian Nat Prod Res 18(3): 289-302.

15. Wang HM, Zhang T, Huang JK, Sun XJ (2013) 3-N-butylphthalide (NBP) attenuates the amyloid-beta-induced inflammatory responses in cultured astrocytes via the nuclear factor-kB signaling pathway. Cell Physiol Biochem 32(1): 235-242.

16. LeVine SM (2016) Albumin and multiple sclerosis. BMC Neurol 16(1): 47.

17. Banks WA (2015) The blood-brain barrier in neuroimmunology: Tales of separation and assimilation. Brain Behav Immun 44: 1-8.

18. Mangraviti A, Gullotti D, Tyler B, Brem H (2016) Nanobiotechnology-based delivery strategies: New frontiers in brain tumor targeted therapies. J Control Release.