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Baicalin may have a therapeutic effect in attention deficit hyperactivity disorder

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ABSTRACT

Baicalin is a flavonoid purified from *Scutellaria baicalensis Georgi*. It possesses a variety of pharmacological properties, such as anti-inflammatory, antioxidant, antiapoptotic, and neuro-protective properties, and provides protection against cerebral hemorrhage. However, it is seldom considered a therapeutic in mental disorders. Recent studies showed that baicalin protects cerebral functions against ischemia and has sedative and anxiolytic-like effects. Animal experiments showed that it protects dopaminergic neurons in the striatum, hippocampus and substantia nigra. It also has effects such as anti-depressive and anti-epileptic and offers resistance to Parkinson's disease. Attention deficit hyperactivity disorder (ADHD) pathogenesis is closely related to dopamine deficiency. However, the therapeutic effect of baicalin in ADHD has not been studied. We hypothesize that baicalin may protect dopaminergic neurons and increase brain dopamine levels, thus serving as an effective novel treatment for ADHD.

Introduction

Baicalin, is a flavonoid purified from the plant *Scutellaria baicalensis Georgi* [1]. It is the main medicinal component of the plant and its highest concentration is found in the radix scutellariae [2]. *Scutellaria baicalensis* has been widely used for thousands of years in traditional Chinese medicine to treat inflammation [3], fever [4], hepatitis [5], jaundice [6] and hypertension, and its safety has been proven in the clinic. The crystalline form of baicalin is pale yellow, odorless, and bitter and it has a melting point of 223 °C. Its molecular formula is $C_{21}H_{18}O_{11}$ and molecular weight is 446.35. Pharmacologically, baicalin has been used as an anticancer, anti-inflammatory and antioxidative agent. Besides, it has also been used as an adjuvant drug in the clinical treatment of hepatitis in encephalitis. However, it has not been used in the treatment of brain disorders.

Baicalin and the blood–brain barrier (BBB)

It is well known that the BBB protects the brain by preventing the passage of drugs into the brain. BBB permeability is a prerequisite for drugs used to treat brain disorders. Fortunately, a recent study on the effect of baicalin [7] and berberine on the transport of nimodipine (NMD) in primary-cultured, rat brain microvascular endothelial cells (rBMEC) showed that baicalin has a bidirectional effect on the uptake of NMD by rBMEC. A low concentration of baicalin (2–5 μg/mL) has a positive effect on the transport of NMD across the BBB, while a higher concentration had the opposite effect. Besides, Kwak and Liu obtained similar results [8,9] that indicated that baicalin has vascular barrier protective and nerve protective effects. The results also showed that baicalin could pass through the BBB in either direction. These reports indicate that baicalin is able to passes into the brain through the BBB. However, the target of baicalin in the brain and its mechanism of action need to be explored.

Numerous studies have indicated that baicalin has anticonvulsant and anti-anxiety effects. These studies give indirect evidence that baicalin can pass through the BBB. Through a selective anxiolytic profile of baicalin, its drug targets were identified as gamma-aminobutyric acid $(GABA)_A$ α2- and α3-containing receptor subtypes [10]. Generally, GABA is the main inhibitory neurotransmitter in the central nervous system. It is reasonable to implicate that GABA neurotransmission is implicated when attention deficit hyperactivity disorder (ADHD) can be viewed as a disorder of 'disinhibition' on dopamine (DA). Moreover, in accordance with this hypothesis, it has been proved that GABA receptors have a close connection to ADHD, and the GABA transporter subtype 1 (GAT1) gene knockout mice may be a new model for ADHD research and GAT1 may be a new target to treat ADHD [11,12]. These studies have shown that the anti-anxiety effect of baicalin

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is closely related to the central nervous system. Another report has shown that baicalin prevents the loss of tyrosine hydroxylase (TH) in positive neurons in the substantia nigra and the decrease of DA content in the striatum in Parkinson's disease model mice [13]. It prevented the loss of dopaminergic nerve cells in the substantia nigra and the reduction of DA in the striatum in mice with Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyr idine (MPTP), and showed neuroprotective effects, which may be due to its antioxidant properties [14]. In addition, a test from Tsinghua University showed that baicalin has some anti-depression effect related to the DA system. This test gives further evidence to prove the intimate connection between baicalin and DA [15]. Other similar studies have further shown that baicalin protects the mitochondria in the substantia and striatum nigra [16,17], which are the main distribution areas of DA. The same effect was confirmed in an a-amino-3-hydroxy-5-methyl-4-isoxaz-olepropio nic acid (AMPA) depression model mouse [18]. Another study found that baicalin induces regeneration of hippocampal neurons in a mouse model of ischemia injury [19]. Thus, baicalin has neuro-protective and therapeutic functions in brain disorders. However, the potential effect of baicalin in ADHD, a disease caused by reduced DA levels, has not been investigated.

DA and ADHD

ADHD is a common behavioral disorder in children, with a 5.9% global annual incidence [20]. The etiology of this disorder is unclear. Multidisciplinary studies have shown that environment, genetic factors, family education, and dietary habits are associated with ADHD. Its main symptoms are inattention, hyperactivity, and impulsiveness. These negative effects cause serious problems to the individual, family, and society. Several studies have shown that ADHD has a moderate association with criminal activity [21]. In addition, about a quarter to half of the people diagnosed with ADHD in childhood show persisting symptoms as adults. Studies have indicated that adults with ADHD are of significant risk for suicide and a negative effect on labor market outcomes [22,23]. Therefore, treating children with ADHD is important for the society. However, the pathogenesis of ADHD remains unclear. Swanson et al. found that ADHD is associated with the level of DA in the brain as people with ADHD have a decreased level of DA [24]. The theory of DA deficiency in ADHD is now commonly accepted. The clinical pharmacology of Ritalin has also proved this hypothesis. The emergence of symptoms is closely related to the reduction in brain DA levels. The theory of DA deficiency in ADHD has been demonstrated by experiments on rats and through clinical pharmacology [25].

Dopaminergic neurons are mainly distributed in the substantia nigra, hippocampus, and striatum. Numerous studies indicate that baicalin mainly affects these areas. A study, which determined the level of DA in the cerebral nuclei after an intravenous administration of flavonoids with HPLC—an electrochemical method to analyze the relation between baicalin and DA in the cerebral nuclei—found an obvious increase in the DA levels in the rat hippocampus and cortex. They showed that the DA system was another target which baicalin acted on [26]. An animal experiment has shown that a high dose of baicalin effectively improved rotarod performance and prevented the reduction of striatal DA levels and TH contents in the striatum and substantia nigra [27]. About 70% of dopaminergic neurons are distributed in the substantia nigra and striatum. Meanwhile, TH is a rate-limiting enzyme in the synthesis of DA. These results indicate that baicalin is closely related to DA. Mu et al. [28] found that baicalin can be a promising candidate for the prevention or treatment of Parkinson's disease, and that it can increase the number of dopaminergic neurons and impart a neuroprotective effect. A Tsinghua University doctoral dissertation by Zhang [29] describes that baicalin could pass through BBB immediately after intravenous administration of total flavonoids from Scutellariae radix. Baicalin inclined to the striatum and hippocampus after being distributed into the cerebral nuclei which indicated that the striatum and hippocampus would be the most potential target of total flavonoids. The DA system was significantly affected by the total flavonoids, which showed a high consistency to the distribution regulation of baicalin in the cerebral nuclei and the DA nerve distribution. Moreover, a study from the USA indicates that baicalin exerts potent neuroprotective effect on dopaminergic neurons [30]. Accordingly, we hypothesized that baicalin may protect the dopaminergic neurons and increase brain DA levels. Thus, it could be an effective and novel treatment for ADHD.

Hypothesis

Our hypothesis is that baicalin may be an effective and novel treatment for ADHD via protecting dopaminergic neurons and increasing the content of DA in the brain. Our theory is unique because the effect of baicalin on the brain's DA system has not been reported so far.

Our hypothesis is based on the discovery that baicalin can pass through the BBB and is associated with the striatum and substantia nigra which are enriched with DA neurons. Baicalin protects and regulates the DA system in numerous animal models such as models of Parkinson's disease, depressive disorder, and cerebral ischemia [31]. It also improves spatial learning ability in global ischemia/reperfusion rats [32]. A drug metabolism study showed that baicalin distribution was very high in the DA system [29]. The DA system is the target brain system for baicalin [26]. Children with ADHD have low levels of DA in the brain [24], as is the case in mice [25], while baicalin protects and regulates the DA system and increases the level of DA. A study showed [33] that baicalin has a dopamine neuroprotective effect to prevent methamphetamine (METH)-induced striatal damage in mice, and that baicalin may attenuate the loss of the DA transporter (DAT), which plays an important role in the pathogenesis of ADHD in the striatum. The study provides further evidence that baicalin significantly influences DA levels and DAT in the striatum. All the evidence proves that baicalin may have a therapeutic effect in ADHD and it would be meaningful and worthy of being studied.

Anshen Dingzhi Ling (ADL) is a Chinese herbal compound composed of 12 kinds of traditional Chinese medicine including *S. baicalensis*, *Radix bupleuri*, *Radix curcumae*, and *Acorus gramineus*, et al. It has been used to treat children with ADHD in China for more than 20 years, and the clinical curative effect is stable and reliable. We have performed experiments on spontaneously hypertensive rats (SHR), which is a recognized ADHD model mouse [34]. Animal experiments have shown that ADL has the potential to decrease the expression of DAT mRNA and protein in the SHR rat striatum, and up-regulate the expression of DA receptor-D1 (DRD1) and DRD2 mRNA and protein in the prefrontal cortex and striatum in SHR rats. ADL has therapeutic effects in ADHD and has a similar effect on DA receptors and transporters as Ping-Ho Wu's research [33]. We have an on-going research project under the National Natural Science Foundation of China (NSFC) namely "Regulatory mechanism of Anshen Dingzhi Ling (ADL) on the D1R/D2R signaling pathway and receptor desensitization/resensiti zation in ADHD". In the early stages, in order to find out the main effective components, we detected the active ingredients in ADL with HPLC. It indicated that baicalin is the most abundant and stable element in ADL water decoction. Currently, baicalin which is the most abundant and stable element in ADL is being subjected to further research using SHR mice, and we expect to make contri-

butions to the treatment of children with ADHD through our studies.

Currently, Ritalin, an amphetamine derivative is the first choice and first-line medical treatment for ADHD in both adults and children. It has been used for over 50 years in the treatment of ADHD [35]. It has a significant effect on controlling the core symptoms of ADHD such as inattention, impulsiveness, and hyperactivity [36]. However, as a central nervous system stimulant, Ritalin has its side-effects, such as depression, anxiety, obsessive–compulsive symptoms and health-related reduction in quality of life during methylphenidate treatment in children with ADHD [37]. Moreover, it also has been shown to have addictive potential [38,39], bad influence on sleep and underlying circadian clock [36,40,41]. These adverse reactions have limited clinical applications of this drug. On the other hand, baicalin is an active ingredient from the plant, and depending on the studies, baicalin may be a novel treatment for ADHD via protecting dopaminergic neurons and increasing the content of DA in the brain. It is a natural drug instead of being a central nervous system stimulant, which is readily accepted. Besides, it is safe and shows no drug-induced liver and kidney damage while having a protective effect [42–44]. In addition, baicalin also exhibits biphasic effects on sleep–wake regulation [45,46]. Baicalin and Ritalin could be a novel drug combination strategy to treat children and adults with ADHD. They may complement each other briefly, baicalin may be a new alternative therapy for patients with ADHD, and we are doing further research in the field.

Based on the existing data, our hypothesis is that baicalin may be an effective, and novel treatment for ADHD via protecting dopaminergic neurons and increasing the content of DA in the brain. Baicalin, a natural ingredient extracted from plants could bring hope to children with ADHD. With further research, many more central nervous system diseases as Parkinson's disease, autism and depressive disorder may benefit from baicalin. Based on the hypothesis stated here, we will soon carry out experiments on SHR mice.

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Conflict of interest statement

None declared.

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