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Ginkgo biloba and the central nervous system

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Abstract

In this paper the main features of the pharmacological effects exerted by *Ginkgo biloba* leaf extracts on central nervous system functions are reviewed.

Keywords: *Ginkgo biloba*; Herbal medicines; Neurotransmission; Oxidative stress; Cerebral ischemia

1. Introduction

The first publication concerning the therapeutic use of the leaves of *Ginkgo biloba* dates back to the 16th century in a text by Liu Wen Tai, a Chinese author. The extract of *G. biloba* leaves (EGb) is one of the most popular plant extracts used to alleviate symptoms associated with a range of cognitive disorders. The mechanism of action of this extract in the central nervous system (CNS) is only partially understood. In this short review some of the most significant effects of EGb on CNS will be treated.

2. Effects on neurotransmitter uptake

Several studies have been performed in order to characterize the effects of EGb on uptake of biogenic amines. It was firstly shown that EGb, at high concentra-

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tions, inhibits the uptake of tritiated norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT) into synaptosome-enriched fractions of rat brain [1]. Subsequent studies in synaptosomal fractions prepared from mice cerebral cortex demonstrated that EGb modified tritiated 5-HT in a biphasic manner. Between 4 and 16 μg/ml of this extract significantly increased 5-HT uptake, whereas at higher concentrations, 5-HT uptake was inhibited [2]. The inhibition of amine uptake has been considered aspecific, due to the high concentrations of EGb needed to obtain such effects, whereas the increase of 5-HT uptake, detected at 4–16 μg/ml is believed rather specific since at these concentrations, in striatal synaptosomes, DA and choline uptake is unchanged [2]. Since at the usual therapeutic doses of EGb the concentrations responsible for 5-HT uptake increase are likely to be reached in the brain, Ramassamy et al. [2] suggested that this effect could contribute to the therapeutic action of EGb. Other in vitro experiments have been performed in order to detect the component of EGb responsible for these effects on amine uptake. It was concluded that the flavonoid glycosides and/or proanthocyanidins are the active components.

An interesting property of EGb is that it can prevent the decrease of synaptosomal uptake of tritiated DA and 5-HT uptake, that occurs in conditions of prolonged (> 20 min) incubation in media of usual composition [3,4]. Rather than an effect on uptake mechanisms, this effect has been attributed to a free radical scavenging property. In fact, such a decrease of amine uptake in conditions of prolonged incubation has been considered as the consequence of the deleterious action of free radicals on uptake mechanisms through the peroxidation of membrane components. With regard to the extract components responsible for this effect of EGb that can be considered protective, both flavonoid containing fraction and quercetin have been shown to be effective, whereas the terpene fraction failed to show any activity.

3. Effects on neurotransmitter receptors during aging

In experimental animals the aging process is generally associated with a decrease in the B_{max} of most neurotransmitter receptors in several brain regions [5], whereas human studies have produced conflicting reports. Several authors have investigated the effects of EGb administration on the changes induced by the aging process on neurotransmitter receptors. Thus, Taylor [6] demonstrated that a 28-day administration of EGb was able to increase muscarinic receptor binding to hippocampal membranes of aged rats to the level found in young rats. The influence exerted by a subchronic treatment with EGb on the aging-induced changes in cholinergic pathway activity has been confirmed by results showing that a daily administration of EGb for 30 days caused a significant increase of high affinity choline uptake into hippocampal synaptosomes of old rats [7]. Analogous positive effects exerted by EGb treatment on age-induced changes have been demonstrated for noradrenergic

system. In fact, tritiated rauwolscine binding to α_2 adrenoceptors in cerebral cortex and hippocampal membranes is reduced in old rats and a treatment with EGb was able to significantly increase such binding whereas it did not alter rauwolscine binding in hippocampus of young rats [8]. Few studies have been performed in relation to the serotoninergic system. In particular, it has been shown that the binding of tritiated 8-hydroxy-2(di-*n*-propyl)tetralin to 5-HT_{1A} receptors in cerebral cortex membranes of old rats had a B_{max} lower than that found in young rats. The treatment for 21 days with EGb significantly increased B_{max} in old rats whereas it did not modify binding in young rats [9].

Collectively, the mentioned results seem to suggest that EGb might restore age-induced decrease in neurotransmitter receptor binding.

4. Effect on oxidative stress-induced neuronal injury

Recent evidence has focused on the role played by oxidative stress in various acute and chronic neurodegenerative diseases. However, the precise mechanism by which oxidative stress can trigger the degenerative process is still a matter of debate. Different in vitro models have been proposed in order to mimic the deleterious effects on cell viability of oxidative stress, thus allowing the evaluation of the protective properties of pharmacological agents. In one of these models the effect of EGb on dissociated rat cerebellar neurons suffering from oxidative stress induced by hydrogen peroxide was examined. Hydrogen peroxide increased the number of dead neurons in a time-dependent manner. Pre-treatment of neurons with EGb greatly delayed such time-dependent increase of dead neurons during exposure to hydrogen peroxide. When the extract was added to the cells immediately or 60 min after the starting of oxidative stress, it was less effective [10]. During oxidative stress neurons die, generally, for apoptosis, that is thought to play a crucial role in the pathogenesis of neurodegenerative disorders. Ni et al. [11] investigated the effect of EGb on the oxidative stress-induced apoptosis in cerebellar neuronal cells. Cells were exposed to hydroxyl radicals that produced neuronal apoptotic death. Pre-treatment of neurons with EGb reduced the percentage of dead cells. Since it has been demonstrated that EGb and its flavonoid constituents reduce the production of reactive oxygen species (ROS) [12], it has been suggested that the protective effects exerted by EGb on oxidative stress-induced cell death may occur via the direct scavenging of hydroxyl radicals.

5. Effect on cerebral ischemia

In humans, cerebral ischemia, regardless of the origin (thrombosis, spasm, hypotension or elevation of intracranic pressure), triggers a sequence of vascular and metabolic events, which is difficult to mimic in experimental animals. Among

the available animal models, experimental ischemia, obtained through unilateral ligation of the carotid artery in the gerbil, is the most widely used. By using this model, Spinnewyn et al. [13] showed that oral or intraperitoneal administration of EGb induced the normalization of mitochondrial respiration, a diminution of cerebral oedema, correction of the accompanying ionic perturbations, and practically total functional restoration, revealed by a normal neurological index. In another gerbil model of ischemia (bilateral forebrain ischemia) daily administration of EGb for 14 days before inducing ischemia exerted a protective action. In fact, a significant increase of the area of preserved neurons occurred [14]. These results suggest that EGb treatment can prevent the occurrence of those processes leading to neuronal degeneration during this kind of ischemia.

In rat models of focal and global cerebral ischemia it has been demonstrated that the neuroprotective effects may be due to the PAF-antagonistic properties of ginkgolides. Thus, Prehn and Krieglstein [15] showed that the combined pre- and post-treatment with the ginkgolides A and B significantly reduced ischemia-induced neuronal damage of hippocampal areas. Presently, it is thought that in the mechanism underlying the neuroprotective effect of EGb during ischemia, the free radical scavenging and antioxidant activities of its constituents, including flavonoids, ginkgolides with anti PAF and antioxidant activities and bilobalide, could be involved.

6. Clinical trials

Although a number of clinical trials of *Ginkgo biloba* have been conducted, few were well designed. Most of these studies did not include a sufficient number of subjects or adequate efficacy measures. These studies focused on a variety of diseases, but the majority addressed the possible effects of *G. biloba* extracts on cognitive dysfunction. Particularly interesting is a recently published placebo-controlled, double bind, randomized trial on the effects of EGb in dementia [16]. The objective of this study was to assess the efficacy and safety of EGb in Alzheimer disease or multi-infarct dementia. The primary outcome measures assessed changes in three areas: (1) cognitive impairment assessed by a performance-based cognitive test that objectively evaluates memory, language, praxis and orientation; (2) daily living and social behavior; and (3) general psychopathology. The authors' conclusion was that EGb was safe and appeared capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year.

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