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The Effects of Gingko Biloba on Learning and Memory

By Andres deLuna

ABSTRACT

Gingko Biloba and its extract, EGb761, have been widely promoted for a variety of functions, including the enhancement of learning and memory. A review of the results of studies in animals supports this assertion, but studies in humans have not had the statistical requirements for any definite conclusions. Multiple mechanisms of action have been proposed, most focusing on effects on the hippocampus; however, the exact nature of the effects of Gingko Biloba has yet to be determined. Because Gingko Biloba has various side effects, more research is needed in order to determine if supplementation would be truly beneficial.

KEY WORDS

Gingko Biloba, EGb761, Rat, Mouse, Hippocampus

Gingko Biloba has played a large role in traditional Chinese medicine for millennia. Recently, Gingko Biloba and its extract, EGb761, have become widely distributed throughout the European Union and the US (1,2). Nowadays, it has become noticeably more difficult to escape the deluge of mass media advertisements and shelves of Gingko Biloba extract bottles at local supermarkets and pharmacies. There are many reasons for this excitement. Gingko Biloba has been praised as a drug to supposedly improve circulation, treat asthma, increase attention, improve learning, and enhance memory, especially in elderly patients with age-related neurological deficits (3,10). This paper will present animal and clinical studies focused on the latter two claims, as well as present the putative mechanisms for its actions.

Studies on learning and memory

Animal models

Multiple studies have examined the effects of Gingko Biloba extract, EGb761 on learning and memory in rats and mice. A few noteworthy studies are examined below.

An important study by Winter 1991 (4) studied the effect of EGb761 on the ability of mice to acquire, practice, and retain knowledge of a two lever response sequence. In this experimental setup, the mouse was rewarded food each time the correct sequence of levers was pressed. Supplementation of EGb761 for four or eight weeks prior to the beginning of the operant conditioning period was compared with controls. Data measurements included number of correct responses and speed of acquisition, as measured by the day the animal made more correct than incorrect responses and maintained such behavior for four or more days. Correct responses were greater for treatment groups (34.8+/- 3.4) as compared to control groups (24.8+/-2.8, 26.4+/-2.9). It is interesting to note that there is no dependency of performance on the time treatment was started, i.e. both four week and eight week treatment groups had the same number of correct responses. Speed of acquisition data showed that experimental group mice learned faster (13 d, 14 d) as compared to the control group (17 d), indicating that EGb761 treated mice learned faster than controls. Thus, Winter's study showed the positive effects of EGb761 on the ability of mice to learn, practice, and remember a new skill.

The study by Cohen-Salmon et al. 1997 (5) provided insight to the possible benefits of EGb761 on young adult and aged mice. The relevant experiments tested the ability of mice to learn using a T-maze. In such a maze, a mouse could learn to either choose a light or a dark alley, of which the trainers chose the latter. If the mouse stepped into the light alley, an incorrect response was recorded and the mouse received electric foot shocks until the mouse escaped the maze. Both young adult (6 months old) and aged mice (22 months old) were tested. The treatment groups received intraperitoneal injections of EGb761 in saline prior to the training. The control groups received an injection of saline for the same period of time. Two strains of mice C57BL/6J and DBA/2J were used. DBA/2J are notable for their inability to learn in old age. Both groups of treated aged mice performed better than corresponding controls, the most significant effects surprising being on the intractable DBA/2J aged mice. Interestingly, although treated young DBA/2J mice performed better than corresponding controls, EGb761 had a negative effect on performance for the C5BL/6J mice. Thus, the Cohen-Salmon study supports the fact that EGb761 has a positive effect on learning in aged mice, although the results for younger mice were inconclusive.

Wirth et al. 1999 (2) studied the effects of both acute and chronic treatment of EGb761 on young and aged

rats, using an olfactory recognition test. Rats have been shown to increase their exploratory behavior in the presence of a new odor, i.e. they will attempt to "sniff" more of the new odor; however, if they recognize the odor from previous experiences, they will lose interest and decrease this type of behavior. Measurements were conducted to see how the behavior would change with chronic administration of EGb761, which was administered EGb761 was administered over a 30 day course prior to testing (chronic group). Acute effects of EGb761 were also measured by administration of the drug two hours before testing (acute group). Finally, EGb761 was administered to aged rats 10 minutes (aged group) before the start of the exposure to the scent. Rats were then exposed to the odor four times, the first three times as part of a "learning phase" and the fourth time constituting the "test phase," which occurred after a delay. All three groups showed decreased exploratory behavior compared to controls with administrations of EGb761 of 60mg/kg or greater. Thus, Wirth et al. showed that both acute and chronic administration of EGb761 enhanced the short-term memory of both young and aged rats.

Clinical trials

Most of the studies reviewed have suffered from a lack of adequate sample sizes, with treatment and control groups consisting of four to six subjects (6,7,9). With sample sizes of this quantity, random error precludes any definitive statements of efficacy. Two studies are presented, showing the effects of EGb761 on learning and memory, although they both suffer from this shortcoming.

Allain et al. 1993 (6) investigated the effects of EGb761 on information processing by using a dual coding test in a group of 18 elderly volunteers with slight age-related memory problems. In the dual coding test, a series of words and drawings was shown to the subject at decreasing presentation times. A recall test immediately followed the presentation of each series. The time at which dual coding appears, when subjects recall more drawings than words, is an indicator for speed of information processing. Dual coding appeared earlier (960 ms) in the EGb761 treated group as opposed to the control (1920 ms), implying an increase in the speed of processing new information. If it did not suffer from a small sample size, the study by Allain et al. would imply that the speed of processing new information, an important component for learning, is increased by EGb761 extract.

More recently, Rigney et al. 1999 (7) studied the effects of EGb761 on memory and psychomotor performance in a randomized, double-blind, placebo-controlled study, in which different dosages of EGb761 were used. A psychometric battery test was given pre-treatment and at multiple intervals (up to 11 hrs) post-treatment. The results show that EGb761 has an effect on memory, although the effects are not necessarily dose-dependent. The authors report that the effects were more appreciable among the more elderly patients, but the sample size of this group does not allow one to draw any definite conclusions

The studies reviewed in the literature have supported the beneficial effects of Gingko Biloba and its extract on learning and memory; however, clinical experiments seem to have suffered from a lack of sample size.

Possible mechanisms for action

The mechanism for action of Gingko Biloba remains largely unknown, although several speculations have been advanced. These putative ideas include neurotrophic/ neuroprotective effects, changes in neurotransmitter receptor expression, and effects on cerebral circulation. EGb761's neuroprotective effects are thought to arise from its antioxidant properties, which are due to its partial flavonoid composition. EGb761 has the ability to scavenge superoxide, hydroxyl radicals, and other damaging free radicals to prevent lipid peroxidation, particularly in the hippocampus (1,5). Studies on the neurotrophic effects of EGb761 have also shown that EGb761 may induce neural sprouting in the hippocampus after age-related neuronal cell loss occurs, particularly granule cells of the dentate gyrus (8). Increases in the number of cholinergic receptors in the hippocampus has also been demonstrated. Interestingly, it has been shown that attention and memory are related to the cortical acetyl choline levels, thus implying an improvement by an ACh dependent process (2,5). Finally, EGb761 can influence neural function by increasing circulation, perhaps by inhibiting platelet activating factor, and by increasing glucose consumption in hypoxic or ischemic situations (1). Thus, Gingko Biloba may increase learning and attention by enhancing neural perfusion/substrate utilization, neurotransmission, neuroprotection, and/or neural plasticity, particularly in the hippocampus.

Conclusion

Positive effects of Gingko Biloba on memory and learning have been widely advertised in the US and the European Union; however, sound scientific evidence in medical literature seems inadequate for the formulation of such a definite conclusion. Although the studies reviewed above on rats and mice indicate that the extract can enhance learning and memory, this finding is obviously not necessarily applicable to humans. In addition, the experiments published in the literature that have been conducted with human subjects have had too small sample sizes to draw any definite conclusions. Even if the aforementioned studies had adequate sample sizes and statistically significant data, not much is known about the exact nature of the mechanism(s) of EGb761. For example, no research has demonstrated whether or not one can use the

effects of Gingko Biloba selectively. One could imagine that although the effects of Gingko Biloba on memory and learning would be very helpful for exams, these same effects could be very detrimental if they enhanced the memory of a negative experience, e.g. the tragic death of a loved one. Alternatively, high doses of Gingko Biloba have been reported to cause diarrhea, restlessness, nausea, and even sub-arachnoid hemorrhage. Thus, if Gingko Biloba does indeed have positive effects, care must be taken to choose an appropriate dosage for individual concerns. In short, more research should be conducted to determine if Gingko Biloba causes the desired effects on memory and learning.

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