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CHOLINERGIC EFFECTS OF SAGE (*SALVIA OFFICINALIS* L.) LEAVES

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ABSTRACT

The cholinergic basal forebrain (CBF) has been implicated in cognitive functions including learning, memory, and attention. The role of the basal forebrain cholinergic system in learning has been widely debated. Early studies are supported a role for the basal forebrain cholinergic system in general learning and memory mechanisms.

The leaves of *Salvia officinalis* L. (sage) are well known for their antioxidative properties. There is increasing evidence to suggest that many degenerative diseases, such as brain dysfunction, cancer, heart diseases, and weakened immune system, could be the result of cellular damage caused by free radicals, and antioxidants present in human diet may play an important role in disease prevention.

Keywords: Sage, acetylcholine, cholinergic effect

ÖZET

Öğrenme, bellek ve dikkat gibi algısal işlevler ön beyin tabanındaki kolinerjik nöronlarla ilişkilidir. Ön beyin tabanındaki kolinerjik sistemin öğrenmedeki rolü çok tartışılmıştır. Yakın zamanlarda yapılan çalışmalar genel öğrenmede ve hafıza mekanizmasında ön beyin tabanındaki kolinerjik sisteminin etkin bir rolü olduğunu desteklemektedir.

Salvia officinalis L. (adaçayı) yaprakları iyi bir antioksidan olarak bilinir. Beyin fonksiyon bozukluğu, kanser, kalp hastalıkları ve immün sistem zayıflığı, serbest radikallerin neden olduğu hücresel yıkım gibi çoğu dejeneratif hastalıklarda kullanımı tavsiye edilmektedir. Diyetle alınması hastalıkların engellenmesinde bir antioksidan olarak önemli bir rol oynayabilir.

Anahtar Kelimeler: Adaçayı, asetilkolin, kolinerjik etki

1. INTRODUCTION

In the last few decades, drugs targeting cholinergic function have been suggested as therapeutic treatments for cognitive

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dysfunction in neurodegenerative and neuropsychiatric disorders, as well as potential cognitive enhancers in normal subjects. Cholinergic effects on cognition were thought to pertain to learning and memory, but this view was challenged by several experiments showing that cholinergic effects on mnemonic or learning processes vary as a function of attention (Rusted and Warburton, 1992).

The cholinergic basal forebrain projects throughout the neocortex, exerting a critical role in modulating plasticity associated with normal learning. Cholinergic modulation of cortical plasticity could arise from 3 distinct mechanisms by 1) "direct" modulation via cholinergic inputs to regions undergoing plasticity, 2) "indirect" modulation via cholinergic projections to anterior, prefrontal attentional systems, or 3) modulating more global aspects of processing via distributed inputs throughout the cortex (Conner et al., 2010).

The cholinergic basal forebrain complex provides widespread and topologically organized cholinergic inputs to diverse brain regions, including the whole cortical mantle, the hippocampus, and the amygdala (Bigl et al., 1982).

The cholinergic projections, consisting of the nucleus basalis magnocellularis (NBM) efferents to the neocortex and the amygdala, as well as the medial septum projections to the hippocampus, are affected in Alzheimer's disease (AD) patients. Because the cognitive deficits in AD correlate with the extent of CBF degeneration, rodent models with cholinergic deficits are used to test strategies for alleviating cognitive impairments associated with CBF damage (DeKosky et al., 1992; Lehericy et al., 1993).

Although most have not been researched pharmacologically, many prescriptions used in Chinese herbal medicines include Salvia species for the treatment of disorders such as depression, epilepsy and age-related memory loss (Cho et al., 1994; Chung et al., 1994; Dhawan, 1994).

The anticholinesterase activity of essential oils and extracts of *Salvia officinalis* and *S. lavandulaefolia* has been previously demonstrated in vivo and in human postmortem brain tissue. Oral administration of the essential oil of S. lavandulaefolia to young rats has been shown to result in AChE inhibition in selected brain areas.

Compared to the control group, there was a significant decrease in AChE activity in the striatum but not the hippocampus at the lower dose. At the higher dose, there was a significant decrease in AChE activity in both the striatum and the hippocampus (Tildesleya et al., 2003; Perry et al., 1997; Perry et al., 2002).

Sage is generally safe and advised by the U.S. Food and Drug Administration. But, some species of sage can affect the nervous system. Especially, they contain thujone. Extended use of sage extract or essential oil may result in restlessness, vomiting, vertigo, tremors, seizures, and kidney damage. Ingesting 12 drops or more of the essential oil is considered a toxic dose (Bouaziz, et al. , 2009).

2. THE MECHANISMS OF ACTION

Degeneration of septohippocampal cholinergic neurons results in memory deficits attributable to loss of cholinergic modulation of hippocampal synaptic circuits. A remarkable consequence of cholinergic degeneration is the sprouting of noradrenergic sympathetic fibers from the superior cervical ganglia into hippocampus (Scheiderer et al., 2006).

Cholinergic dysfunction is thought to play a central role in the mnemonic disturbances observed in Alzheimer's disease (AD) patients. The rationale is that cholinergic transmission is greatly impaired in the early stages of AD, when these memory deficits are first apparent (Davies and Maloney, 1976; Bartus et al., 1982).

It is concluded that the ethanolic extract of salvia officinalis potentiated memory retention and also it has an interaction with muscarinic and nicotinic cholinergic systems that is involved in the memory retention process. Results showed that sage ethanol extracts increased memory retention in rats and that pilocarpine and nicotine potentiated memory improvement, whereas scopolamine and mecamylamine had an attenuating effect. It is concluded that sage extracts have a mnemonic effect in adult male rats and interact with nicotinic and muscarinic cholinergic systems (Eidi et al., 2006).

The overall pattern of results is consistent with a dose-related benefit to processes involved in efficient stimulus processing and/or memory consolidation rather than retrieval or working memory efficiency (Scholey et al., 2007).

The ability of S. lavandulaefolia to inhibit the activity of AChE in the hippocampus is consistent with the reported memory-enhancing properties of sage. It is also of potential significance in improving cognitive function in AD as this area plays a major role in memory processing and is severely affected in the disorder.

Improvements on cognition following single doses of cholinesterase inhibitors have also been demonstrated (Almkvist et al., 2001).

In vitro anticholinesterase activities of eight commercially available terpenoid constituents of Salvia lavandulaefolia have been investigated. These included 1,8-cineole, camphor, α-pinene, β-pinene, borneol, caryophyllene oxide, linalool and bornyl acetate. Dose-dependent inhibition of acetylcholinesterase (AChE) by these chemical constituents was determined using the method of Ellman (Ellman et al., 1961).

The ethyl acetate and methanol extracts from 16 Salvia L. species were screened for their inhibitory activity against acetylcholinesterase, butyrylcholinesterase, lipoxygenase, and tyrosinase; the enzymes linked to neurodegeneration. The extracts exerted weak cholinesterase and tyrosinase inhibition, and remarkable inhibition against lipoxygenase (13.07 ± 2.73–74.21 ± 5.61%) at 100 μg ml $^{-1}$ (Orhan et al., 2012).

Their data indicates that nonpolar extracts of Salvia species for anticholinesterase activity and the polar extracts for antioxidant activity are worth further phytochemical evaluation for identifying their active components (Orhan et al., 2007).

3. DISCUSSIONS AND SUGGESTIONS

The revised role of the forebrain cholinergic system in learning and memory is more global than originally proposed: ACh regulates a number of cognitive/behavioral processes such as, arousal, attention, temporal processing all of which are important to learning and memory functioning. ACh appears to have a modulatory rather than central role in the production of behavior related to learning and memory processing (Sarter and Bruno, 1997; Gold, 2002).

Regardless of the mechanism of age-related atrophy and loss in neuronal systems, growth-factor delivery reverses these changes in

the primate basal forebrain cholinergic system, supporting a potential rationale for growth-factor delivery in the context of such neurodegenerative disorders as Alzheimer's disease (AD) (Hefti F et al., 1986). Further insights into basic mechanisms of age-related dysfunction in the brain will contribute to the design of the most rational approaches for treating age-related pathological neuronal degeneration.

S. lavandulaefolia and *S. officinalis* have similar compositions with the exception of the thujone content. *S. officinalis* has a much higher concentration of thujone which is toxic in large doses (Leung and Foster, 1996), so it has been suggested that *S. lavandulaefolia* may be a more suitable treatment (Mantle D et al., 2000).

The primary symptom of AD is a loss of memory. The encouraging memory-enhancing properties of Salvia in this acute administration paradigm and the favourable pharmacological profile suggest that Salvia is potentially a novel therapeutic treatment for AD.

More globally acting cholinergic mechanisms provide additional support for the acquisition of skilled motor behaviors, beyond those associated with cortical map reorganization.

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