

# Okadaic Acid Induces the Rats' Memory Impairment and Tau Protein Hyperphosphorylation And Intervened by Flavonoids from Stem and Leaf of *Scutellaria Baicalensis* Georgi



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**Abbreviations:** AD: ALZHEIMER'S DISEASE; NFTs: Neurofibrillary Tangles; P-Tau: Phosphorylated Tau; SP: Senile Plaques; PHF: Paired Helical Filament; CDK5: Cyclin-Dependent Kinase 5; Tyr: phosphorylation at tyrosine; Ser: serine; PKA: protein kinase; GSK3 $\beta$ : Glycogen Synthase Kinase 3 $\beta$ ; OA: Okadaic Acid

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive impairment. The neuropathology of AD is represented by widespread deposits of neurofibrillary tangles (NFTs) formed by phosphorylated tau (p-tau) protein and of senile plaques (SP) containing amyloid  $\beta$  (A $\beta$ ) protein. A series of epidemiological statistical results and the experimental study showed that solely SP cannot result in AD clinical dementia symptoms, while the formation and the number of NFTs is directly related to the occurrence of dementia. NFTs formation is due to excessive phosphorylated tau protein occurred after the formation of the structure of the double helix shape. Actually, tau, a microtubule-binding protein, primarily promotes microtubule stability and contains 2-3 phosphate groups per molecule in the normal brain. However, in the AD brain, tau protein hyperphosphorylated, containing 5-9 phosphate groups per molecule, has a decreased ability to combine with microtubules and dimerize.

Stable tau dimers form tau oligomers, which continue aggregating to form subunits of filaments called protomers. Two protomers wound around each other form a paired helical filament (PHF), and excessive PHF assembly leads to NFTs and eventually AD [1]. An imbalance between tau phosphorylation and dephosphorylation is critical to AD tauopathy. Several protein kinases, including cyclin-dependent kinase 5 (CDK5), cyclic AMP-dependent protein kinase (PKA) and glycogen synthase kinase

3 $\beta$  (GSK3 $\beta$ ) have been confirmed to phosphorylate tau protein at different sites, such as at serine (Ser) 199, Ser202, Ser262, Ser396, Ser214, Ser404, Thr231 and other sites of tau protein. These forms of p-tau protein are found in the AD brain. In addition, the phosphorylation of protein kinases at different sites can alter their kinase activity. For instance, GSK3 $\beta$  activity is inhibited by phosphorylation at serine (Ser) 9, and its activity is enhanced by phosphorylation at tyrosine (Tyr) 216. Hyperphosphorylated tau protein also results from the reduced activity of protein phosphatase (PP2A, PP2B, PP2C, PP1) that indicates a decisive role of PP in tangle formation in AD. Then any strategy that can maintain hyperphosphorylation of tau protein can be used to establish an AD-like animal model for studying pathophysiology process and drug screen with AD [2].

Okadaic acid (OA), a polyether toxin isolated from marine microalgae, is a selective inhibitor of PP and is neurotoxic. An AD-like animal model was developed by intracerebroventricular injection of OA, which resulted in learning and memory deficits, tau hyperphosphorylation, and NFT accumulation in the brain. This AD-like animal model can be regarded as an accurate simulation of the pathophysiology of AD in vivo [3]. SSF, a flavonoid isolated from the stems and leaves of *Scutellaria baicalensis* Georgi, has demonstrated beneficial effects towards cognitive improvement in animals with cognitive deficits induced by AlCl<sub>3</sub>, D-galactose and aggregated A $\beta$  [4-6]. The present study established an AD-like animal model via

the injection of OA into the right lateral cerebral ventricle of rats. We investigated the effects of SSF on memory impairment, neuron injury, NFT deposition, tau protein phosphorylation at Ser199, Ser202, Ser214, Ser262, Ser396, Ser404 and Thr231 in the brain and examined the effects of SSF on the regulatory mechanisms of CDK5, PKA, GSK3 $\beta$  and PP.

The results of the present study showed that the intracerebroventricular injection of OA to rats can result in the deterioration in rats' memory acquisition, memory retention and memory re-learning; damages in neuron structure; the increases of PHF, p-tau(Ser199), p-tau(Ser202), p-tau(Ser214), p-tau(Ser262), p-tau(Ser396), p-tau(Ser404), p-tau(Thr231) and pTyr216-GSK3 $\beta$  protein expression; as well as the decreases of PKA and pSer9-GSK3 $\beta$  protein expression. The protein expression of CDK5 was not significantly changed by OA treated. Concerning to the PP, the intracerebroventricular injection of OA to rats can markedly decrease protein expression of PP2A-C $\alpha$ , PP2A-C $\beta$ , PP2CB and PP1 of the brain. However, SSF treated the rats for 36 d to reverse OA-resulted in memory impairment, neuron injury, the increased PHF, p-tau(Ser199), p-tau(Ser202), p-tau(Ser214), p-tau(Ser262), p-tau(Ser396), p-tau(Ser404) p-tau(Thr231) and pTyr216-GSK3 $\beta$  protein expression, the decreased PKA, pSer9-GSK3 $\beta$ , PP2A-C $\alpha$ , PP2A-C $\beta$ , PP2CB and PP1 protein expression [7-9].

The current studies demonstrated that SSF is improved memory deficits and neuroprotective against OA primary from lowering the hyperphosphorylation of tau protein and regulative balance of protein kinases and protein phosphatase activities and then inhibiting PHF increase. These findings, coupled with our previous studies, indicate that the action of SSF is based on multiple targets, which may be predicted beneficial effects for the treatment of AD.

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