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BRAIN RESEARCH

Research Report

# Oral supplementation of catalpol ameliorates diabetic encephalopathy in rats

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ABSTRACT

Diabetes mellitus can cause dysfunction of the central nervous system called "diabetic encephalopathy." Although insulin and various oral drugs are used to treat diabetes, they do not completely prevent the development of diabetic encephalopathy, and novel strategies for the prevention and treatment are urgently needed. Catalpol, an iridoid glycoside, has properties of anti-inflammation, antioxidant and decreasing blood glucose level and thus has the possibility of treating diabetic encephalopathy. Therefore, the study was designed to investigate the effects of catalpol on diabetic encephalopathy in rats. A single dose of 65 mg/kg streptozotocin was injected intraperitoneally to induce diabetes. Intragastric infusion of catalpol was performed for 6 weeks with the doses of 10, 50 and 100 mg/kg, respectively. The Y-type maze test, biochemical measurement, Nissl staining and the terminal deoxynucleotidyl transferase-mediated UTP nick end labeling methods were used to evaluate the neuropathological changes and the effects of catalpol on diabetic rats. The results showed that streptozotocin-induced diabetes produced obvious neuron damage and cognitive dysfunction coupling with markedly increased oxidative stress in the brain. Long-term oral supplementation of catalpol improved neuronal injury and cognitive dysfunction by attenuating oxidative stress. The effects that catalpol could both increase the nerve growth factor concentration and decrease the blood glucose level were related with the function of defending against oxidative stress of catalpol. The study suggested that oral supplementation of catalpol might be a potential therapeutic strategy for the treatment and/or prevention of diabetic encephalopathy.



## 1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterized by chronic hyperglycemia and is associated with long-term complications and produces various dysfunctions in the body. Besides the most common complication of the peripheral neuropathy (Bloomgarden, 2007), there are much more evidences, which demonstrate that diabetes may also have negative impacts on the central nervous system and can cause dysfunction of the central nervous system (Biessels

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*Abbreviations:* STZ, streptozotocin; TUNEL, terminal deoxynucleotidyl transferase-mediated UTP nick end labeling; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; CAT, catalase; MDA, malondialdehyde; NGF, nerve growth factor

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et al., 2006; Mijnhout et al., 2006; Tuzcu and Baydas, 2006). Cognitive dysfunction in diabetic subjects has been recognized since the early 20th century. A wealth of studies described a series of neuropathological and neurobehavioral changes in both type 1 and type 2 diabetic subjects, such as cognitive dysfunction and decline in memory and mental speed (Awad et al., 2004; Reaven et al., 1990; Ryan et al., 1993; Stewart and Liolitsa, 1999; Strachan et al., 1997). The cognitive deficiency was more pronounced in the elderly (Sinclair et al., 2000) and in whom the incidence of dementia appeared to be doubled (Ott et al., 1999). These slowly progressive alterations in cerebral function and structure that occur in association with diabetes are referred to as "diabetic encephalopathy," which has been recognized as a complication of diabetes.

Oxidative stress (Mastrocola et al., 2005) and inflammation (Somfai et al., 2006) were proved to play a central role in diabetic encephalopathy. Alongside the increment of reactive oxygen species level during hyperglycemia (Baydas et al., 2002), the activities of glutathione peroxidase and superoxide dismutase are reduced (Fukui et al., 2001). The increased oxidative stress in diabetes produced the damage of hippocampus and cortex, which contributed to the morphological abnormalities and memory impairment (Fukui et al., 2001). The enhanced free radicals either directly damaged the cellular proteins, lipids and nucleic acids to cause cell necrosis or indirectly affected cellular signaling pathways and gene regulation to induce neuronal apoptosis; this contributed to the neuropathology associated with diabetes (Greene et al., 1999). Antioxidants have been shown to protect neurons against a variety of experimental neurodegenerative conditions. Melatonin and vitamin E (Tuzcu and Baydas, 2006) were reported to prevent diabetes animals from learning and memory deficiency. To date, antioxidant therapy is the most promising approach to the prevention of diabetic neuropathy. However, the efficacy of the treatment has not been established in clinical trials.

Catalpol (Fig. 1), an iridoid glycoside, has properties of anti-inflammation, antioxidant and decreasing blood glucose level. Our previous studies showed that catalpol used by injection could increase the anti-oxidative and anti-inflammatory capacities in the brain and protect DNA against singlet-oxygen-induced strand breaks and lipids from peroxidation in cerebral ischemia and dementia animals (Li et al., 2004a,b, 2005; Jiang et al., 2008). Whether oral administration of catalpol has also the neuroprotective activity is still not clear up to now. With the above background, the study was designed to investigate the effects of oral supplementation of catalpol on diabetic encephalopathy in rats.

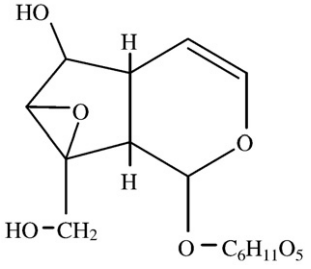


**Fig. 1 – Structure of catalpol.**

## 2. Results

### 2.1. *The animals used for the experiment*

Six rats among 55 were excluded from this experiment according to the result of a behavioral training. The remaining 49 rats were used to perform further experiment. Four animals (three came from the STZ-treated group and one came from the 10 mg/kg catalpol-treated group) died during the experiment, so their data were removed and the remaining 45 animals, 9 animals in each group, were submitted to the final analysis for cognitive determination as well as biochemical, histopathological and NGF assay.

### 2.2. *Effect of catalpol on body weight and blood glucose level*

STZ-treated rats exhibited significant increase in blood glucose level and decrease in body weight as compared with age-matched normal control rats. Long-term oral supplementation of catalpol with either dose of 50 or 100 mg/kg significantly improved the blood glucose level and the body weight of diabetic rats, but catalpol used with the dose of 10 mg/kg did not show any influence on the rat body weight and the blood glucose level as presented at Tables 1 and 2.

### 2.3. *Effect of catalpol on cognitive function*

The cognitive function was assessed in Y-type maze. The results showed that the cognitive function of STZ-treated diabetic rats was markedly impaired; oral supplementation of catalpol could significantly improve their cognitive ability. STZ-treated diabetic rats needed 63±3 trials to arrive the training criterion, while normal control rats only needed 23±3 trials to reach the same aim. The difference between the two groups was significant statistically. Oral administration of catalpol significantly improved the cognitive function of diabetic rats. 50±4, 37±4 and 22±4 trials were needed in the animals treated with catalpol at the doses of 10, 50 and 100 mg/kg, respectively, as presented in Fig. 2.

### 2.4. *Effect of catalpol on hippocampal histology*

Microphotographies of the hippocampal CA1 subfield in each group were shown in Fig. 3. In normal control animals, CA1 pyramidal neurons were laid in three to four layers and presented round and large nuclei and clear nucleoli. Widespread damage was evident in STZ-treated diabetic rats. Pyramidal neurons either presented a densely stained shrunken appearance with minimal cytoplasm or disappeared. In contrast, the majority of the CA1 neurons were rescued in the rats treated with catalpol. The survival neuronal densities of CA1 subfield were 167±12 and 60±9 cells/mm in the normal control and STZ-treated diabetic rats, respectively. The diabetic rats treated with catalpol showed an obvious increase in the number of intact CA1 neurons when compared with STZ-treated diabetic rats. The neuronal densities were 92±11, 125±9 and 165±10 cells/mm in the animals treated with catalpol at the doses of 10, 50 and 100 mg/kg, respectively, as shown in Fig. 3. Numerous of TUNEL-positive cells in the CA1