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Research Report

# Protective effect of L-theanine on chronic restraint stress-induced cognitive impairments in mice

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ABSTRACT

The present work was aimed to study the protective effect of L-theanine on chronic restraint stress (CRS)-induced cognitive impairments in mice. The stress was produced by restraining the animals in well-ventilated polypropylene tubes (3.2 cm in diameter × 10.5 cm in length) for 8 h once daily for 21 consecutive days. L-theanine (2 and 4 mg/kg) was administered 30 min before the animals subjected to acute immobilized stress. At week 4, mice were subjected to Morris water maze and step-through tests to measure the cognitive function followed by oxidative parameters and corticosterone as well as catecholamines (norepinephrine and dopamine) subsequently. Our results showed that the cognitive performances in CRS group were markedly deteriorated, accompanied by noticeable alterations in oxidative parameters and catecholamine levels in the hippocampus and the cerebral cortex as well as corticosterone and catecholamine levels in the serum. However, not only did L-theanine treatment exhibit a reversal of the cognitive impairments and oxidative damage induced by CRS, but also reversed the abnormal level of corticosterone in the serum as well as the abnormal levels of catecholamines in the brain and the serum. This study indicated the protective effect of L-theanine against CRS-induced cognitive impairments in mice.

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## 1. Introduction

In the competitive world of modern technology, mental and emotional stress has become an unavoidable part of life and is known to have deleterious effects on physical and mental well-being. Stress is a crucial determinant for maintenance of health and disease (Jacobson and Spolsky, 1991; Gilgun-Sherki et al., 2001). Stress either due to internal or external stimuli disturbs physiological homeostasis and causes neurobehavioral alteration (Masood et al., 2003; Masood et al., 2004). It has been reported that restraint stress is an easy and convenient method for psychological and physical stress resulting in restricted mobility and aggression (Romanova et al., 1994; Singh et al., 1999).

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Severe and prolonged stress precipitates affective disorders and causes impairment in learning and memory. The main physiological responses to chronic stress include the hypothalamic–pituitary–adrenal axis (HPA) and the sympatho-adrenomedullary system (SAM), through which the levels of corticosterone and catecholamine were altered (Cohen and Hamrick, 2003). Enhancement of corticosterone (CORT) levels via the hyperactivity of the HPA axis resulted in impaired performances of the cognitive function, including learning and memory, and spatial recognition (Beane et al., 2002; Harvey et al., 2006). However, the secretion of serum catecholamines conducted by the SAM system, e.g., noradrenaline (NA) and dopamine (DA), were considered as an immediate response in fighting against restraint stress (Sachser, 1987; Chen et al., 2011). Furthermore, there have been many reports (Shaheen et al., 1993; Kovacs et al., 1996; Liu and Mori, 1999; Olivenza et al., 2000) suggesting that free radicals play an aberrant role in the mechanism of stress. As previously shown (Shaheen et al., 1993; Liu and Mori, 1999; Matsumoto et al., 1999), stress can stimulate numerous pathways leading to an increased production of free radicals. Oxidative stress is widely accepted as a contributor to neuronal vulnerability (Langley and Ratan, 2004; Lin and Beal, 2006; Ohta and Ohsawa, 2006). The putative role of oxygen radicals and radical-derived reactive oxygen species in neurodegeneration and cognitive decline has been well reviewed (Sayre et al., 2008; Gallagher et al., 1996; Berr et al., 2000). The brain, though comprising a very small part of body mass consumes an appreciable amount of the oxygen, is extremely susceptible to reactive oxygen species induced damage.

Lack of satisfactory treatment of the cognitive deficits usually accompanying stress, depression, and associated mental problems present a constant challenge for psychopharmacology research. Anti-anxiety or hypno-sedative agents, commonly used for the management of stress, have several disadvantages and ill effects. Therefore, employment of safe natural products can be an ideal choice. L-theanine, one of the major amino acids contained in green tea, has been a focus of attention due to its biochemical characteristics, Yokogoshi et al. (1998a, 1998b) reported that L-theanine could pass through the blood-brain barrier, and that it increased by 1 h at the latest in serum, the liver, and the brain after administration, thereafter decreasing sharply in the serum and liver but only beginning to decrease in the brain 5 h after administration. Furthermore, another study reported that L-theanine could influence the secretion and function of neurotransmitters in the central nervous system even at 30 min after oral administration (Terashima et al., 1999). L-theanine has also been demonstrated to have anti-oxidative properties (Serrano and Klann, 2004; Yokozawa and Dong, 1997; Cho et al., 2008) and neuroprotective effects against ischemia (Nishida et al., 2008; Kakuda, 2002; Egashira et al., 2004) and Parkinson-related neurotoxicants (Yokozawa and Dong, 1997). In further support, L-theanine has been shown to improve memory function (Egashira et al., 2007; Nathan et al., 2006) and prevent memory impairment induced by cerebral ischemia (Yamada et al., 2008), moreover, L-theanine is known to block the binding of L-glutamic acid to glutamate receptors in the brain and oral intake of L-theanine could cause anti-stress effects via the inhibition of cortical neuron excitation (Kimura et al., 2007). However, the protective effect of L-theanine on CRS-induced spatial cognitive impairments and the mechanisms of cognitive improvement are yet to be reported. Therefore, the aim of this study was to evaluate the neuroprotective effect of L-theanine on stress-induced cognitive impairments in mice. Meanwhile, the neuroendocrine changes and alterations in anti-oxidative status associated with chronic restraint stress were also determined.

## 2. Results

### 2.1. *Effects of L-theanine on behavioral assessment*

#### 2.1.1. *Spatial recognition and learning*

To examine whether L-theanine could attenuate the CRS-induced cognitive impairments, we tested the learning and memory using the Morris water maze (MWM) test and the results are shown in Fig. 1. The mean escape latency for the trained rats was decreased over the course of the learning trials in all the groups (Fig. 1A), and from the third day onwards there was a significant difference in transfer latency

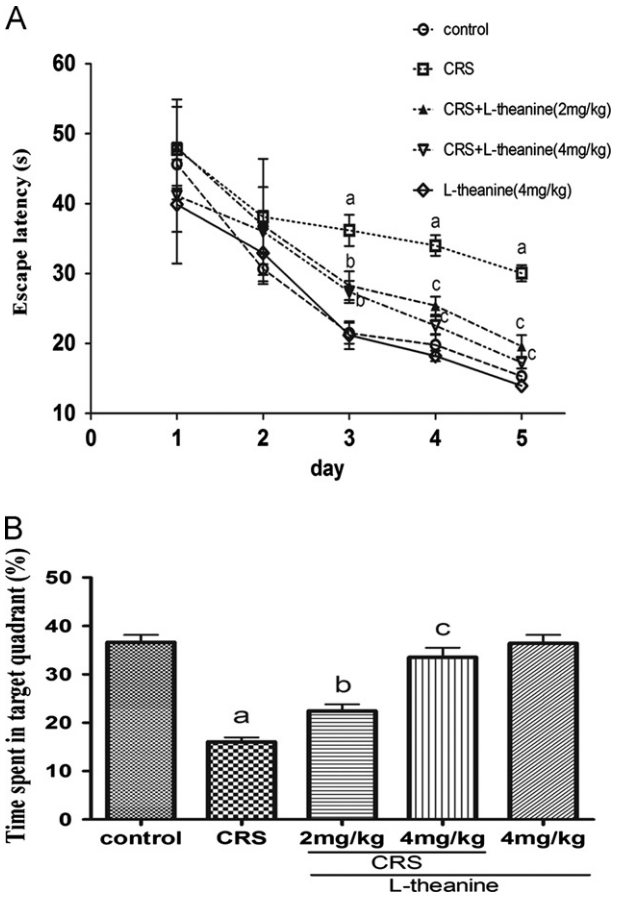


**Fig. 1 – (Section 2.1.1). Effects of L-theanine on the spatial learning and memory in MWM test. Escape latency appeared during the training and the probe sessions (A). The percentage of time spent in the target quadrant during the probe trial (B). Data are reported as mean ± SEM ($n = 10$). $^{a}P < 0.001$, as compared with the control group; $^{b}P < 0.05$, $^{c}P < 0.001$, as compared with the CRS group.**

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