

## Research report

# Acupuncture ameliorates inflammatory response in a chronic unpredictable stress rat model of depression



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## ABSTRACT

Depression is one of the most common psychiatric disorders. Chronic inflammatory response has been viewed as a key factor in depression. Acupuncture in Chinese medicine has been shown to be an effective treatment for depression. In the present study, we investigated the mechanism underlying antidepressant effect of acupuncture. The rats were subjected to chronic unpredictable mild stress (CUMS) for 28 days to induce depressive-like behaviors. Acupuncture treatment was applied once every other day during the 28-day stress period. The behavioral tests (body weight, sucrose consumption and locomotor activity) were performed. The expressions of nitric oxide (NO), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and nuclear factor kappa B (NF-κB) were determined in the rat hippocampus and prefrontal cortex. CUMS induced depressive-like behavior in rats, which was alleviated by acupuncture treatment. The increased levels of NO, PGE<sub>2</sub>, iNOS and COX-2 induced by CUMS, were all significantly decreased in the hippocampus and prefrontal cortex by acupuncture. Moreover, acupuncture markedly inhibited the activation of NF-κB in rats. These findings showed that the antidepressant-like effect of acupuncture might be mediated by inhibition of inflammatory mediators via modulation of NF-κB in the brain regions.

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## 1. Introduction

Depression is a common and debilitating psychiatric disorder in modern society, characterized by a pervasive low mood and loss of interest in usual activities (Kessler, 2012). Antidepressants dominate current treatment in clinical practice. There are three main kinds of classical antidepressants, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). However, some of these drugs show undesirable side effects. Meanwhile, less than 50% of depression patients achieve remission with the available antidepressants (Berton and Nestler, 2006). Therefore, there is no doubt that alternative medicines with safety and efficacy are needed to treat depression.

Acupuncture in traditional Chinese medicine has become a widely accepted alternative therapy. The specific effects of

acupuncture on central nervous system are attracting more and more interest. For example, acupuncture plays an important role in protecting the central nervous system from neuronal damage (Tao et al., 2016; Yang et al., 2016). Moreover, clinical trials have demonstrated that acupuncture could alleviate depressive symptoms (Chan et al., 2015; Leo and Ligot, 2007; MacPherson et al., 2013; Duan et al., 2008), and modulate the corticostriatal reward circuitry in major depressive disorder (Wang et al., 2016). Previous studies have shown that acupuncture could have antidepressant-like effect by modulating hypothalamic-pituitary-adrenal axis, enhancing hippocampal serotonin system (Le et al., 2016), modulating dopaminergic neuroactivity (Kwon et al., 2012), and reducing pro-inflammatory cytokines (Lu et al., 2016).

In recent years, chronic inflammatory response has been viewed as a key factor in depression. The expressions of many inflammatory mediators, such as pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), are regulated by nuclear factor kappa B (NF-κB) (Natoli, 2010; Smale, 2011). NF-κB can be activated by a number of stimuli, including lipopolysaccharide or stress. After activation, NF-κB induces

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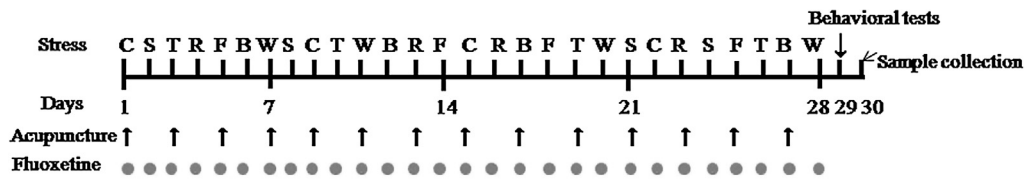


Fig. 1. A schematic diagram of protocol design, including schedule of chronic unpredictable mild stress, acupuncture and drug treatment.

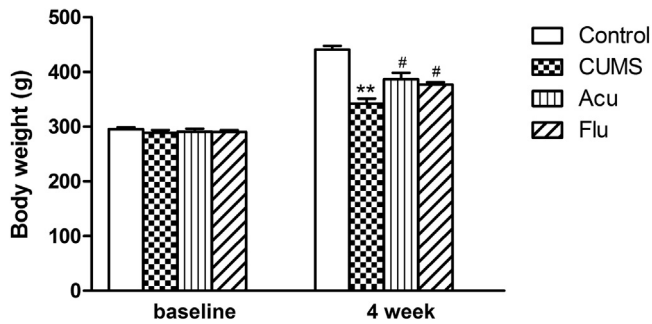


Fig. 2. Body weight in the following groups (N=8 per group): Control, chronic unpredictable mild stress (CUMS), CUMS+Acupuncture (Acu), CUMS+Fluoxetine (Flu). Data are means ± SEM. \*\*P<0.01 as compared with the control group, #P<0.05 as compared with the CUMS group.

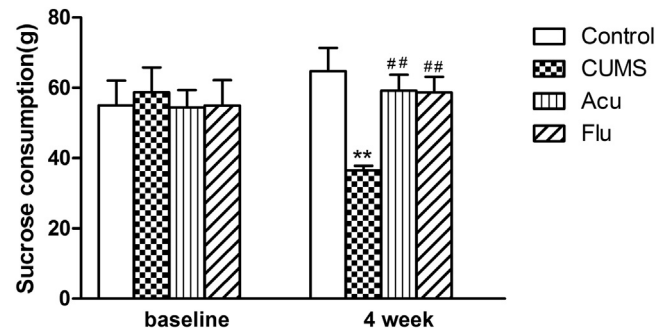


Fig. 3. Sucrose consumption in the following groups (N=8 per group): Control, CUMS, CUMS+Acupuncture (Acu), CUMS+Fluoxetine (Flu). Data are means ± SEM. \*\*P<0.01 as compared with the control group, ##P<0.01 as compared with the CUMS group.

the transcription of the inflammatory mediators involved in inflammatory response (Munhoz et al., 2006; FitzGerald, 2003). Therefore, NF-κB pathway play a vital role in regulating inflammatory responses in depression (Wichers and Maes, 2002; Karin and Greten, 2005; Yu et al., 2014). For example, it has been reported that chronic stress enhanced the activation of NF-κB (Munhoz et al., 2006; Koo et al., 2010), and increased expression of COX-2 (Seybold et al., 2003; Guo et al., 2009), as well as iNOS in the rat model of depression (Christopherson and Bredt, 1997; Stokes et al., 2002; Olivenza et al., 2000; Peng et al., 2012). The increase of COX-2 and iNOS expression has also been found in depression patients (Galecki et al., 2012). However, the effect of acupuncture on the inflammatory mediators involved in depression remains unclear.

The hippocampus and prefrontal cortex have been suggested to be the important brain regions associated with the mood regulation, cognitive function and memory. Clinical studies have indicated their functional and structural abnormalities in depression (Veeraiah et al., 2014; Müller et al., 2011; Mizoguchi et al., 2003). Therefore, in this study, we investigated the effect of acupuncture on inflammatory response in hippocampus and prefrontal cortex in a chronic unpredictable mild stress (CUMS) rat model of depression. Our results showed that acupuncture could attenuate inflammatory response in depression by inhibiting the key inflammation mediators via modulation of NF-κB activation in the brain regions.

## 2. Materials and methods

### 2.1. Animals

Male Sprague-Dawley rats (180–200 g) were obtained from Beijing Vital River Laboratories. Rats were kept in an air-conditioned room with a 12 h light/dark cycle with free access to food and water except when animals were subjected to deprivation stressors as described in stress. The experiment procedures were approved by the Animal Care and Use Committee at Beijing University of Chinese Medicine.

### 2.2. Groups and treatment

The rats were randomly divided into five groups (eight rats in each group): the control group was given no stress except general handling for 4 weeks; the CUMS group was exposed to CUMS for 4 weeks; the CUMS + Acu(Acu) group received acupuncture treatment once every other day during the 4-week stress period; the CUMS + Fluoxetine (Flu) group, used as a positive comparator for an antidepressant effect, was given Fluoxetine during the 4-week stress period. Fluoxetine was diluted in distilled water and orally given one hour before the stress exposure.

### 2.3. Chronic unpredictable mild stress procedure

Rats in stressed groups were exposed to CUMS after 1 week of acclimatization period under the housing conditions. The CUMS model was modified from the methods previously described (Willner et al., 1987; Slattery et al., 2007). The rats were randomly exposed to various stressors for 4 weeks, and each stressor was administered once a week. The stressors applied included: deprivation of food (24 h, F), deprivation of water (24 h, W), cold swimming (4°C, 5 min, S), cage shaking (30 min, C), behavior restraint (3 h, R), tail pinch (2 min, T), and soiled bedding (24 h, B). The stress sequence was changed every week in order to make the stress procedure unpredictable (Fig. 1). The control group was housed in a separate room, with free access to food and water.

### 2.4. Acupuncture treatment and drug administration

During acupuncture administration, the rats were maintained within a cloth bag without anesthesia, with one forelimb taken out, similar to what we described previously (Lu et al., 2016). Two points were selected: Baihui (GV20) and Neiguan (PC6). GV20 is located above the apex auriculate, on the midline of the head. PC6 is located between the tendons of m. palmarislongus and m. flexor carpi radialis, proximal to the transverse crease of the wrist. Sterilized disposable stainless steel needles (0.3\*25 mm, HuanQiu brand, Suzhou, China) were inserted obliquely as deep as 2–3 mm at Baihui (GV20) and Neiguan (PC6). The acupuncture treatment was

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