

## RESEARCH ARTICLE

# Effects of Acupuncture at Zu-San-Li (ST36) on the Activity of the Hypothalamic–Pituitary–Adrenal Axis during Ethanol Withdrawal in Rats



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ethanol

## Abstract

The current study investigated the effects of acupuncture at Zu-San-Li (ST36) on the hypothalamic–pituitary–adrenal axis during ethanol withdrawal in rats. Rats were intraperitoneally treated with 3 g/kg/day of ethanol or saline for 28 days. Following 24 hours of ethanol withdrawal, acupuncture was applied at bilateral ST36 points or non-acupoints (tail) for 1 minute. Plasma levels of corticosterone (CORT) and adrenocorticotrophic hormone (ACTH) were measured by radioimmunoassay (RIA), and the corticotropin-releasing factor (CRF) protein levels in the paraventricular nucleus of the hypothalamus were also examined by RIA 20 minutes after the acupuncture treatment. RIA showed significantly increased plasma levels of CORT and ACTH in the ethanol-withdrawn rats compared with the saline-treated rats, which were inhibited significantly by the acupuncture at the acupoint ST36 but not at the non-acupoint. Additionally, ethanol withdrawal promoted CRF protein expressions in the paraventricular nucleus of the hypothalamus, which were also blocked by the acupuncture at ST36. These findings suggest that acupuncture at the

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specific acupoint ST36 can inhibit ethanol withdrawal-induced hyperactivation of hypothalamic–pituitary–adrenal axis, and it may be mediated via the modulation of hypothalamic CRF.

## 1. Introduction

Converging evidence from preclinical and clinical studies has demonstrated that in both rodents and humans, negative emotion associated with ethanol withdrawal promotes a relapse in drinking [1,2]. Numerous studies have also shown that the damage of the central nervous system, one of the most serious consequences of alcohol abuse and dependence, is markedly exacerbated by ethanol withdrawal [3], highlighting the critical role of withdrawal in the development of ethanol dependence and pathology. The hypothalamic–pituitary–adrenal (HPA) axis is a major component of the neuroendocrine system that controls reactions to stress. Ethanol withdrawal can be a stressful event and produces hyperactivation of the HPA axis. People undergoing acute ethanol withdrawal have higher levels of cortisol, and the magnitude of the increased cortisol response appears to be proportional to the severity of the withdrawal syndrome [4]. Animal experiments also revealed that high levels of corticotropin-releasing factor (CRF) could influence the severity of withdrawal. For instance, intracerebroventricular infusion of a CRF antagonist blocked the enhanced stress sensitivity induced by ethanol withdrawal [5], and plasma corticosterone (CORT) levels increased during ethanol withdrawal in rats [6]. Excessive HPA axis activation during ethanol withdrawal underlies some of the clinical complications of alcoholism [7,8]. Considering that biochemical disorders precede pathological changes, it is conceivable that medical inhibition of the hyperactivated HPA axis during ethanol withdrawal may be a promising means of avoiding the emergence of withdrawal syndrome, further to treating alcoholism.

Acupuncture, a widely known alternative medicine therapy, has been used in Eastern countries for the treatment of several mental disorders, including drug abuse withdrawal syndrome [9]. Although the biological mechanisms of acupuncture are not yet clear, several lines of evidence suggest that acupuncture can contribute to the maintenance of biochemical balance in the central nervous system and recovery of homeostasis in the body [10,11]. Previously, we reported that acupuncture at the specific acupoint Shen Men (HT7) improved ethanol withdrawal-induced anxiety-like behavior and reduced plasma CORT levels by normalizing amygdaloid catecholamines [6]. More recently, we also demonstrated that the anxiolytic effect of acupuncture at HT7 is mediated by the modulation of amygdaloid CRF during ethanol withdrawal [12]. In traditional Chinese medicine (TCM), similar to HT7, the ST36 acupoint is used extensively to treat mental disorders, and modulation of HPA axis is one of the mechanisms [13]. Therefore, in the present study, we investigated the effect of acupuncture at ST36 on the activity of HPA axis during ethanol withdrawal, to elucidate its possible therapeutic effect on alcoholism.

## 2. Materials and methods

### 2.1. Animals and experimental design

Adult male Sprague–Dawley rats (250–270 g) were obtained from the Laboratory Animal Center at the Medical College of Yanbian University (Yanji, China). The rats were given food and water *ad libitum* and maintained on a 12-hour light, 12-hour dark cycle throughout the course of the study. All animal procedures were conducted in accordance with the National Institutes of Health guidelines on the care and use of laboratory animals and approved by the Animal Care and Use Committee of Yanbian University.

The rats were treated with 3 g/kg/day ethanol (20% w/v) or saline by intraperitoneal injection for 28 days. After the last dose of ethanol, the rats underwent ethanol withdrawal for 24 hours. The acupuncture groups were subjected to acupuncture at either acupoint ST36 or non-acupoints (tail; Fig. 1) for 1 minute.

For acupuncture stimulation, stainless-steel needles (0.2 mm in diameter) were inserted into two identical ST36 acupoints (or tail non-acupoints) located on the left and right sides of the animal (depth of 2–3 mm). The acupuncture stimulation process was divided into two parts: reduction and reinforcement. In the reduction session (the first session), the needles were twisted significantly ( $>360^\circ$ ) twice per second for 30 seconds; in the reinforcement session (the second session), the needles were twisted ( $<180^\circ$ ) gently once per second for another 30 seconds. Anatomical locations of the stimulated acupuncture points in rats were equivalent to the acupoints in humans, as described by Stux and Pomeranz [14] and in the animal acupuncture atlas [15]. Two groups of rats treated

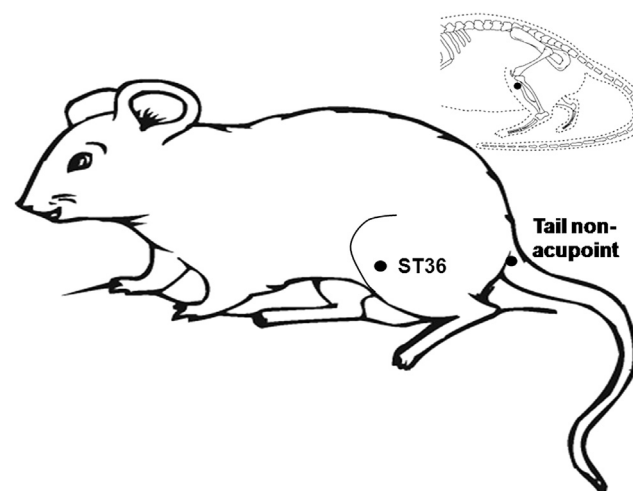


Figure 1 Diagram of the acupoint ST36 and the non-acupoint located in the tail in a rat.

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