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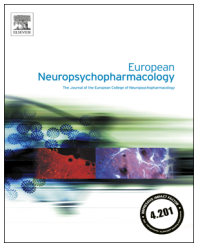

Antidepressant-like effect of geniposide on chronic unpredictable mild stress-induced depressive rats by regulating the hypothalamus-pituitary-adrenal axis

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Abstract
Geniposide as the major active component of *Gardenia jasminoides Ellis* has neuroprotective activity. This study elucidated the potential antidepressant-like effect of geniposide and its related mechanisms using a depression rat model induced by 3 consecutive weeks of chronic unpredictable mild stress (CUMS). Sucrose preference test, open field test (OFT) and forced swimming test (FST) were applied to evaluate the antidepressant effect of geniposide. Adrenocorticotropic hormone (ACTH) and corticosterone (CORT) serum levels, adrenal gland index and hypothalamic corticotrophin-releasing hormone (CRH) mRNA expression were measured to assess the activity of hypothalamus-pituitary-adrenal (HPA) axis. Hypothalamic glucocorticoid receptor α (GRα) mRNA expression and GRα protein expression in hypothalamic paraventricular nucleus (PVN) were also determined by real-time PCR and immunohistochemistry, respectively. We found that geniposide (25, 50, 100 mg/kg) treatment reversed the CUMS-induced behavioral abnormalities, as suggested by increased sucrose intake, improved crossing and rearing behavior in OFT, shortened immobility and prolonged swimming time in FST. Additionally, geniposide treatment normalized the CUMS-induced hyperactivity of HPA axis, as evidenced by reduced CORT serum level, adrenal gland index and hypothalamic CRH mRNA expression, with no significant effect on ACTH serum level. Moreover, geniposide treatment upregulated the hypothalamic GRα mRNA level and GRα protein expression in PVN, suggesting geniposide could recover the impaired GRα negative feedback on CRH expression and HPA axis. These aforementioned therapeutic effects of geniposide were essentially similar to fluoxetine.

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Our results indicated that geniposide possessed potent antidepressant-like properties that may be mediated by its effects on the HPA axis.

1. Introduction

Depression is a common and serious mental disorder characterized by feelings of sadness. It is a major cause of disability, and imposes a substantial health threat to the modern society (Kessler, 2012). Although the pathogenic process of depression development is very complex and still elusive, the pathological role of chronic stress and the consequent hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis have been verified in the pathogenesis and neurobiology of depression (Swaab et al., 2005).

The hyperactive HPA axis in patients with depressive and anxiety disorders, indicated by increased levels of cortisol (corticosterone in rodents, CORT) (Holsboer, 2001), hypertrophy of pituitary and adrenal cortex (Modell et al., 1997) and over-expressed hypothalamic corticotrophin-releasing hormone (CRH) (Wang et al., 2008), has mostly been ascribed to impaired feedback regulation of the HPA axis, possibly caused by altered function of the glucocorticoid receptor (GR) (Anacker et al., 2011). In turn, antidepressants ameliorate many of the neurobiological disturbances in depression including HPA axis hyperactivity, partly by restoring GR function, and thereby alleviate depressive symptoms (Mason and Pariante, 2006). Similarly, the HPA axis in depressive animal models is also modified by chronic stress and normalized by antidepressants (Raone et al., 2007). These findings indicate that the HPA axis and GR feedback may be an important target of antidepressant action.

However, many current clinical antidepressants (mainly aimed at modulating monoamine neurotransmission) have only 60–70% effective response rates on patients (Rush et al., 2006; Willner et al., 2013), and long-term medication always causes significant side effects including cardiotoxicity, sexual dysfunction and sleep disorder (Sarko, 2000). Therefore, it is necessary to explore and develop more effective and reliable new antidepressants. With advantages in terms of safety, tolerability and patient compliance (Meeks et al., 2007), herbal therapies currently have been introduced for the treatment of depression and provide prospective alternative/complementary strategies (Thachil et al., 2007). Particularly, clinical trials revealed that compared with synthetic antidepressants, the extract of St John's wort (*Hypericum perforatum*) had much lower incidence of adverse reaction and its safety might be considered more favorable (Schulz, 2006; Woelk, 2000). The extracts and isolated compounds of medicinal plants in drug discovery and development have attracted increasing attentions of many scholars. In fact, in China and other oriental countries, numerous plant-derived compounds including peoniflorin, glycyrrhizin, rosmarinic acid, and hypericin with apparent antidepressant effects and high safety margins have become a novel pharmacotherapy in the treatment of affective disorders (Zhang, 2004).

Geniposide, an iridoid glycoside compound, is the main bioactive component of *Gardenia jasminoides Ellis* (called Zhi-Zi in Chinese pharmacopoeias) and possesses diverse beneficial biological and pharmacological activities, including antioxidant, anti-inflammatory and anti-arthritic properties, with little toxicity and adverse effects (Wang et al., 2014). Interestingly, the medicinal plant Zhi-Zi is included in many traditional medicine formulations such as "Yueju Wan" and "Zhi-Zi-Hou-Pu Tang" for treatment of psychiatric illnesses including depression, anxiety and irritability (Wei et al., 2008; Yao et al., 2013). The Zhi-Zi extraction and geniposide increased the social interaction time of mice through an anxiolytic-like effect (Toriizuka et al., 2005). Additionally, several recent studies reported that geniposide could improve the ability of learning and memory in Alzheimer-like rat model (Gao et al., 2014), reduce amyloid β peptide-induced toxicity (Yin et al., 2012) and promote neurite outgrowth (Liu et al., 2009), indicating the neuroprotective effects of this compound. However, detailed analysis on the antidepressant effect of geniposide and its relationship with the HPA axis remains poorly understood.

The present study focused on the antidepressant effect of geniposide using a classic depression rat model induced by chronic unpredictable mild stress (CUMS) (Willner, 1997; Willner et al., 1987), as evaluated by sucrose preference test, open field test (OFT) and forced swim test (FST). Additionally, adrenocorticotropic hormone (ACTH) and CORT serum levels, adrenal gland index, hypothalamic CRH and GRα mRNA levels, and GRα protein expression in the paraventricular nucleus (PVN) were assessed to explore the regulatory effect of geniposide on the HPA axis and its possible action mechanisms.

2. Experimental procedures

2.1. Drugs and reagents

Geniposide was isolated from *Gardenia jasminoides Ellis* and provided by Prof. Wen-jian Tang (School of Pharmacy, Anhui Medical University, Hefei, China), with a purity of 99% (HPLC). The structure of geniposide was shown in Figure 1. Fluoxetine hydrochloride (Prozac) as a positive control drug was obtained from Eli Lilly Pharmaceuticals (Suzhou, China). ACTH and CORT enzyme-linked immunosorbent assay (ELISA) kits were purchased from RapidBio Lab (California, USA). GR antibody was obtained from Santa Cruz Biotechnology (California, USA). All PCR primers were produced by Sangon Biotech Company (Shanghai, China).

2.2. Animals and drug administration

Sixty male Sprague-Dawley rats weighing 140–160 g were obtained from the Experimental Animal Center of Anhui Medical University. After 7-day acclimatization, rats were randomly divided into six groups (10 rats per group): normal control group, CUMS group, three geniposide-treated groups (25, 50, 100 mg/kg geniposide+CUMS)

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