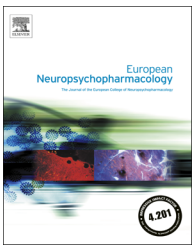
European Neuropsychopharmacology (2014) 24, 172–180



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Orcinol glucoside produces antidepressant effects by blocking the behavioural and neuronal deficits caused by chronic stress

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Received 9 January 2013; received in revised form 18 May 2013; accepted 24 May 2013

KEYWORDS
Orcinol glucoside;
Antidepressant;
Hypothalamic-pituitary-adrenal (HPA) axis;
Brain-derived neurotrophic factor (BDNF);
Extracellular signal-regulated kinase (ERK)

Abstract
This study focused on the antidepressant potential of orcinol glucoside (OG) and its possible mechanisms of action. We established a depressed rat model using 3 consecutive weeks of chronic unpredictable mild stress (CUMS). The antidepressant-like effect of OG was revealed using the sucrose preference test, the open field test, the forced swimming test (FST), and the tail suspension test (TST). The activity of the hypothalamic-pituitary-adrenal (HPA) axis was evaluated by detecting the serum corticosterone (CORT) concentrations and mRNA expression of corticotrophin-releasing hormone (CRH) in the hypothalamus. The protein expression levels of brain-derived neurotrophic factor (BDNF) and total phosphorylated-ERK1/2 were detected by western blot. The results showed that OG treatment (1.5, 3, or 6 mg/kg) alleviated the depression-like behaviour of rats under CUMS, as indicated by the increased sucrose preference and the decreased immobility in both the FST and TST, although the rearing frequency in the open field test increased only in the group that received the lowest dose (1.5 mg/kg OG). Rats that received OG treatment exhibited reduced serum CORT levels and CRH mRNA expression in the hypothalamus, suggesting that the hyperactivity of the HPA axis in CUMS rats was reversed by OG treatment. Moreover, OG treatment upregulated the protein levels of BDNF and phosphorylated-ERK1/2 in the hippocampus, even above control levels. Our findings suggest that OG improved depressive behaviour in CUMS rats by downregulating HPA axis hyperactivity and increasing BDNF expression and ERK1/2 phosphorylation in the hippocampus.

1. Introduction

Depression is a serious mental disorder that affects approximately 16% of the population and is one of the three most

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0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2013.05.007

widespread and debilitating illnesses worldwide (Kessler et al., 2003). Based on the monoaminergic hypothesis of depression (Baldessarini, 1975), raising monoamine levels in synaptic clefts has been a major strategy for treating depression over the past 50 years. Unfortunately, not all depressed patients respond to existing antidepressants, and months of treatment are usually required to produce a response (Cassano and Fava, 2004; Trivedi et al., 2006; Ioannidis, 2008), suggesting that monoamine depletion might not be the only pathogenic process of depression. Thus, a deeper understanding of the pathogenesis of depression and better antidepressants are needed to improve the efficacy and safety of depression treatment.

Stressful life events and the resulting hypothalamic-pituitary-adrenal (HPA) axis hyperactivity are proposed to be among the most potent factors triggering depressive episodes (Swaab et al., 2005; Wang et al., 2010). Animal models and human studies have shown that chronic stress can result in depression-like behaviour accompanied by HPA axis hyperactivity (Evans et al., 2012; Garza et al., 2012), indicated by elevated serum glucocorticoid concentrations and hypothalamic corticotrophin-releasing hormone (CRH) expression (Chen et al., 2009; Wang et al., 2010). Chronic mild unpredictable stress (CUMS) has been long used in animal research of depression as it reproduces the role of the chronic exposure to socio-environmental stressors to induce depression and mimics several aspects of depressive-related syndrome and highlights (Willner et al., 1987).

It has also been suggested that reduced levels of brain-derived neurotrophic factor (BDNF) in the hippocampus cause the decreased proliferation of hippocampal neurons and consequently result in depression (Bai et al., 2012; Cieslik et al., 2011; Elfving et al., 2010; Paizanis et al., 2010). Chronic stress and glucocorticoid administration may induce depressive effects in rats by lowering hippocampal BDNF levels (Smith et al., 1995; Hansson et al., 2003), whereas some antidepressants are reported to achieve their efficacy by increasing BDNF in the hippocampus (Li et al., 2011; Takano et al., 2012; Zhang et al., 2012). Although the underlying mechanisms remain unidentified, it has been reported that glucocorticoids can prevent synaptic function maturation through suppression of the BDNF-stimulated MAPK/ERK pathway (Kumamaru et al., 2011, 2008).

Herbal medicines with antidepressant effects and high safety margins represent a novel pharmacotherapy in the treatment of depression (van der Watt et al., 2008; Zhang et al., 2012). Orcinol glucoside (OG) is an active constituent isolated from the rhizomes of *Curculigo orchioides* Gaertn. (Li et al., 2003), which is a common traditional Chinese medicine with diverse beneficial biological and pharmacological activities, including immunomodulatory activity (Bafna and Mishra, 2006) and antioxidant effects (Wu et al., 2005). Recently, a number of studies have focused on the neuroprotective effects of curculigoside, another major component from *C. orchioides* (Tian et al., 2012; Wu et al., 2012). These studies demonstrated that this compound could protect against N-methyl-D-aspartate (NMDA)-induced neuronal excitotoxicity (Tian et al., 2012), attenuate cerebral ischaemia injury (Jiang et al., 2011), and promote learning and memory in aged rats (Wu et al., 2012). However, little is known about the biological activity of OG.

In this study, we established a rat depression model using chronic unpredictable mild stress (CUMS) and explored the effects of OG on depression-like behaviour. The behaviour tests used to probe the effects of OG included the open field test, the sucrose preference test, the tail suspension test (TST), and the forced-swimming test (FST). Moreover, we investigated whether this compound was capable of down-regulating HPA hyperactivity and upregulating the expression of BDNF and phosphorylated extracellular signal-regulated kinase (p-ERK) in the hippocampus of CUMS rats.

2. Experimental procedures

2.1. Drugs

Orcinol glucoside (OG) was isolated by Anhui Key Laboratory of Bioactivity of Natural Products (Hefei, Anhui, China), with a purity of 99%. The structure of OG is shown in Figure 1. Fluoxetine hydrochloride (Prozac) was provided by Eli Lilly Pharmaceuticals.

2.2. Animals

After 7 days of adapting to their housing 54 male adult Sprague-Dawley rats were randomly assigned to 6 groups, including an unhandled control group (control), a chronic unpredictable mild stress group (CUMS), 3 OG treatment groups (1.5 mg/kg/day OG +CUMS; 3 mg/kg/day OG+CUMS; 6 mg/kg/day OG+CUMS), and a fluoxetine-treated CUMS group (2 mg/kg/day fluoxetine hydrochloride+CUMS). Rats were raised under a 12-h light-dark cycle (lights on 0730-1930), and the ambient temperature was maintained at 21-22 °C with 50-60% relative humidity. Rats in the control group were housed 4 per cage with ad libitum access to a standard rodent diet and water. Rats in the other 5 groups were singly housed and were stressed according to the CUMS procedure described below. All experimental procedures were approved by the Animal Care and Use Committee at Anhui Medical University and complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1985).

2.3. Chronic unpredictable mild stress procedure

The CUMS procedure was performed according to the method described previously (Wu et al., 2007) with minor modifications. Briefly, for 3 consecutive weeks, stressors were administered once daily between 0830 and 1030, with the exception of the 24-h duration stressors. Stressors included (1) 24 h of social crowding (24 rats per cage); (2) a 1-h warm swim at 30 °C (after which the rats were towelled dry); (3) 24 h in a tilt cage at 30° from the horizontal; (4) a 5-min cold swim at 8-10 °C (after which the rats were towelled dry); (5) 24 h in a wet cage; (6) a 1-min tail pinch; and (7) 24 h of food and water deprivation. The different stressors were randomly distributed, with an interval of 7 days between repetitions. All stressors were administered 3 times within 21 days. Rats in the treatment group received OG or fluoxetine on days 14-21; the control and CUMS rats were given a vehicle-only equivalent to the drug treatment. The schedule of the experimental design is shown in Figure 2.

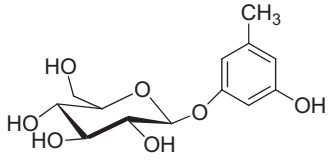

Figure 1 The structure of orcinol glucoside (OG).