

Available online at www.sciencedirect.com



PHARMACOLOGY BIOCHEMISTRY ^{AND} BEHAVIOR

Pharmacology, Biochemistry and Behavior 87 (2007) 130-140

www.elsevier.com/locate/pharmbiochembeh

Icariin from *Epimedium brevicornum* attenuates chronic mild stress-induced behavioral and neuroendocrinological alterations in male Wistar rats

Ying Pan^a, Ling-Dong Kong^{a,*}, Yu-Cheng Li^a, Xing Xia^a, Hsiang-Fu Kung^b, Fu-Xing Jiang^a

^a State Key Laboratory of Pharmaceutical Biotechnology, Institute of Functional Biomolecules, School of Life Sciences,

Nanjing University, Nanjing 210093, People's Republic of China

^b Center for Emerging Infectious Diseases, Faculty of Medicine, The Chinese University of Hong Kong, Shatin,

N. T. Hong Kong, People's Republic of China

Received 12 June 2006; received in revised form 31 March 2007; accepted 10 April 2007 Available online 19 April 2007

Abstract

Chronic mild stress (CMS) is suggested to produce abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis and hypothalamus– pituitary–thyroid (HPT) axis. Therefore, compound that attenuates the neuroendocrinological alterations may have potential as antidepressant. The behavioral and neuroendocrinological effects of icariin, a major constituent of flavonoids isolated from *Epimedium brevicornum*, were investigated in the CMS model of depression in male Wistar rats. CMS procedure caused an anhedonic state in rats resulted in increased corticotropin-releasing factor (CRF) concentrations in dissected brain regions and serum, decreased total triiodothyronine (tT_3) in serum with no significant changes in serum adrenocorticotrophic hormone (ACTH) and thyroxine (tT_4). Administration of icariin reversed CMS-induced sucrose intake reduction and CRF elevation. These results suggested that icariin possessed potent antidepressant-like activities which were at least in part mediated by improving the abnormalities in the HPA axis functions. However, we did not find a clear correlation between the HPT axis and icariin treatment in the CMS-treated rats.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Icariin; Chronic mild stress; Hypothalamic-pituitary-adrenal axis; Hypothalamus-pituitary-thyroid axis

1. Introduction

Depression involves pathophysiological changes in neuroendocrinological function (Musselman and Nemeroff, 1996; Helmreich et al., 2005; Tichomirowa et al., 2005). The most frequently occurring neuroendocrinological abnormality in depressed subjects is hyperactivity of the hypothalamic– pituitary–adrenal (HPA) axis characterized by hypersecretion of corticotropin-releasing factor (CRF), which stimulates adrenocorticotrophic hormone (ACTH) release (DeMoranville and Jackson, 1996; Tsigos and Chrousos, 2002; Barden, 2004). Although, in contrast to the HPA axis system, overt hypothalamus–pituitary–thyroid (HPT) dysfunction is not common in depression (Fountoulakis et al., 2004; Schule et al., 2005a,b), thyroid hormones have a profound influence on behavior and

* Corresponding author. Tel./fax: +86 25 83594691. E-mail address: kongld@nju.edu.cn (L.-D. Kong). appear to be capable of modulating the phenotypic expression of major affective illness (Musselman and Nemeroff, 1996; Bauer and Whybrow, 2001; Fountoulakis et al., 2004). Significant reduction in serum total triiodothyronine (tT_3) concentrations but not in total thyroxine (tT_4) concentrations was observed in depressed patients (Rubin et al., 1987; Sakaue, 1990). However, increased serum tT₃ and tT₄ levels were found in chronic mild stress-induced Sprague-Dawley and Wistar rats with no any change in plasma ACTH levels (Kioukia-Fougia et al., 2000). In addition, there was a close interrelationship between the HPA and the HPT axes in depression (Baumgartner et al., 1990; Helmreich et al., 2005). CRF suppressed thyroid functions (Tsigos and Chrousos, 2002), resulting in T₃ content reduction. Conversely, CRF release in the hypothalamus increased in hypothyroid animals (Tohei et al., 1998). Elimination of thyroid hormones caused a marked reduction in transcription of CRF gene in the paraventricular nucleus of male rats, suggesting that the hormones of the HPT axis had a major effect on the central

^{0091-3057/\$ -} see front matter @ 2007 Elsevier Inc. All rights reserved. doi:10.1016/j.pbb.2007.04.009

regulation of the HPA axis (Shi et al., 1994). It is important to note that the complex regulation of the HPA and HPT axes highlights organism's complicated adjustability to stressful situations (Helmreich et al., 2005). The neuroendocrinological abnormalities of the HPA and HPT axes, although not observed in all patients with depression (Fava et al., 1995; Watson et al., 2002; Fountoulakis et al., 2004), have been identified as a useful diagnostic tool. Clinical studies also provided evidence that normalization of the HPA axis or the HPT axis abnormalities preceded successful treatment with antidepressants (Joffe, 1992; Bschor et al., 2003; Young et al., 2004; Nikisch et al., 2005; Rao et al., 2005; Schule et al., 2005a,b), indicating that future antidepressants might target the neuroendocrinological systems by regulating either the HPA axis or the HPT axis.

Icariin (Fig. 1) is a major constituent of flavonoids isolated from Epimedium brevicornum Maxim (Berberidaceae), which is used in traditional Chinese medicine to nourish the kidney and reinforce yang. Clinical evidences suggested that E. brevicornum and its decoction could improve depressive symptoms after stroke (Lai, 2001; Ma, 2003). E. brevicornum decreased plasma ACTH and corticosterone concentrations and possessed protective effects on hypothalamus-pituitary-adrenal-thymus axis induced by exogenous glucocorticoid in clinical and experiments (Cai et al., 1998). The total flavonoids reversed the attenuations of monoamine neurotransmitters and regulated neuroendocrine-immunological network in hypothalamus of the old rats (Shen et al., 2004). Recently, our laboratory demonstrated antidepressant actions of total flavonoid extracts and icariin from E. brevicornum in the forced swimming test (FST) and the tail suspension test (TST) in mice (Pan et al., 2005; Zhong et al., 2005). Subsequent study exhibited that icariin administration attenuated the swim stress-induced elevation in serum CRF concentrations (Pan et al., 2005). Thus, these findings might provide some supports for the hypothesis that icariin could modulate abnormal neuroendocrinological function in depressed animals.

Chronic mild stress (CMS) model of depression in animal is accepted as a valuable method for predicting potential antidepressant actions of compounds in humans. The CMS regimen altered behavioral parameters consistent with a loss of responsiveness to reward, such as decreased sucrose consumption, a specific hedonic deficit (Willner et al., 1987; Willner, 1997, 2005). The stress-induced anhedonic-like state in rats



Fig. 1. Structure of icariin.

gradually developed over several weeks and could be prevented or reversed by chronic administration of antidepressant drugs (Griebel et al., 2002; Papp et al., 2003; Willner, 2005). In addition, the CMS produced several neurohormonal changes in rodents that are similar to those found in human depression (Azpiroz et al., 1999; Bratt et al., 2001; Kioukia-Fougia et al., 2002; Grippo et al., 2005a). However, few studies have simultaneously examined behavioral and neuroendocrinological changes in the HPA and the HPT axes during the CMS exposure in rats. The present study explores the possible relationship of the HPA axis and the HPT axis in the CMS model of depression in male Wistar rats, and simultaneously examines the effects of icariin and known antidepressant fluoxetine on neurohormonal mediators of the HPA axis (circulating CRF and ACTH), as well as the central nervous system (CRF in the dissected brain) and the HPT axis (circulating tT_3 and tT_4). These results firstly demonstrate that the CMS induces a profile of the two axes alterations in rats and provide a basis for examining the neurohormonal pathways directly and interactions that underlie the link between depression and icariin treatment

2. Materials and methods

2.1. Animals

Male Wistar rats (Laboratory Animal Center, Jiangsu Province, China), weighing 220–250 g, were brought into the laboratory 3 weeks before the experiment started. The animals were individually housed, with food and water freely available, and maintained on a 12 h dark–light cycle (with the lights on at 07:00 h locate time) under regulated temperature conditions ($22\pm$ 2 °C), except as described below. The study was approved by the institutional Animal Care Committee at the Nanjing University, or the China council on Animal Care at Nanjing University.

2.2. Drugs

Icariin was purchased from Bio-sep Bio-technique Stock Co., Ltd. Xi'an Jiaotong University (P. R. China). The purity of icariin was checked by high-performance liquid chromatography to be at least 98% pure (Wang et al., 2003). Fluoxetine hydrochloride was from Changzhou Siyao Pharmaceuticals Co., Ltd. (P. R. China). Other reagents were analytical grades made in P. R. China.

2.3. Chronic mild stress (CMS)

Before CMS procedure, rats were trained to consume a 1% sucrose solution. Training consisted of initial 72 h sucrose solution exposure without any food or water available. After the period of adaptation, animals were distributed into two subgroups and sucrose solution intake baseline tests were performed 6 times over 14 days for all subjects. Sucrose intake tests took place once a week at regular times. The intake was expressed in relation to the animal's body weight (g/kg).These tests involved a 14-h period of food and water deprivation

Download English Version:

https://daneshyari.com/en/article/2014351

Download Persian Version:

https://daneshyari.com/article/2014351

Daneshyari.com