Journal of Ethnopharmacology 209 (2017) 219–229

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Banxia-houpu decoction restores glucose intolerance in CUMS rats through improvement of insulin signaling and suppression of NLRP3 inflammasome activation in liver and brain

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ARTICLE INFO

Keywords:
Banxia-houpu decoction
Depression
Glucose tolerance
Insulin signaling
NLRP3 inflammasome

ABSTRACT

Ethnopharmacological relevance: Banxia-houpu decoction is a famous formula in traditional Chinese medicine (TCM) with the powerful anti-depressant activity.

Aim of the study: This study aimed to investigate the effect of Banxia-houpu decoction on glucose intolerance associated with anhedonia in chronic unpredictable mild stress (CUMS) rats, then to explore its underlying pharmacological mechanisms.

Materials and methods: After 6-week CUMS procedure, male Wistar rats were given Banxia-houpu decoction (3.29 and 6.58 g/kg, intragastrically) for 6 weeks. Sucrose solution consumption test was employed to evaluate the anhedonia behavior. Oral glucose tolerance test (OGTT) was used to determine glucose tolerance. Serum levels of corticosterone, corticotropin-releasing factor (CRF), insulin and interleukin-1 beta (IL-1β) were measured by commercial enzyme-linked immunosorbent assay kits, respectively. Furthermore, the key proteins for insulin signaling, as well as nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, were analyzed by Western blot in periphery liver and brain regions hypothalamus, hippocampus and prefrontal cortex, respectively.

Results: Banxia-houpu decoction significantly increased sucrose solution consumption and decreased serum corticosterone and CRF levels in CUMS rats, further demonstrating its antidepressant activity. More importantly, Banxia-houpu decoction improved glucose tolerance in OGTT in this animal model. Furthermore, it protected against CUMS-induced insulin signaling impairment in the liver, as well as hypothalamus and prefrontal cortex in rats. Although without significant effect on serum IL-1β levels, Banxia-houpu decoction inhibited NLRP3 inflammasome activation in the liver, hypothalamus, hippocampus and prefrontal cortex of CUMS rats, respectively.

Conclusions: The present study demonstrates that Banxia-houpu decoction suppresses NLRP3 inflammasome activation and improves insulin signaling impairment in both periphery liver and brain regions in CUMS rats, possibly contributing to its anti-depressive effect with glucose tolerance improvement. These results may provide the evidence that Banxia-houpu decoction is a potential antidepressant with the advantage to reduce the risk of comorbid depression with type 2 diabetes mellitus.

1. Introduction

Depression is a common illness with the leading cause of disability worldwide. Seriously, depression increases the risk of insulin resistance and developing type 2 diabetes mellitus (T2DM) (Vancampfort et al., 2016, 2015; Winokur et al., 1988), and mortality among diabetic individuals (Park et al., 2013). It has been hypothesized that some physiopathological changes, such as the activation of hypothalamic-

Abbreviations: CUMS, chronic unpredictable mild stress; OGTT, oral glucose tolerance test; HPA axis, hypothalamic-pituitary-adrenal axis; CRF, corticotropin-releasing factor; IL-1β, interleukin-1 beta; NLRP3, nod-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing CARD; Caspase-1, cysteinyl aspartate specific proteinase-1; IR, insulin receptor; IRS1, insulin receptor substrate 1; Akt, protein kinase B; p-IR, phosphorylated insulin receptor; p-IRS1$^{(Y896)}$, phosphorylated insulin receptor substrate 1 at the site of tyrosine 896; p-IRS1$^{(S307)}$, phosphorylated insulin receptor substrate 1 at the site of serine 307; p-Akt, phosphorylated protein kinase B

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http://dx.doi.org/10.1016/j.jep.2017.08.004
Received 7 September 2016; Received in revised form 29 July 2017; Accepted 3 August 2017
Available online 04 August 2017
0378-8741/

pituitary-adrenocortical (HPA) axis with signaling pathway of glucocorticoids (cortisol or corticosterone) and corticotropin-releasing factor (CRF), induce comorbidity of depression and T2DM (Gragnoli, 2012, 2014; Pan et al., 2013). However, the mechanisms underlying are still unclear and warrant further investigation.

Chronic unpredictable mild stress (CUMS) model is a commonly recognized and widely used model to mimic clinical depression, showing the depressive-like behavior (anhedonia) in animals (Pan et al., 2014; Willner, 1997). Our previous study observed that CUMS procedure induced glucose intolerance in rats, supporting an increased risk of comorbid T2DM in depressed animals (Pan et al., 2013). Similar results in chronic unpredictable stress rats and mice are also reported by others (d'Audiffret et al., 2010; Patel et al., 2016). Thus, this animal model of depression is suitable to investigate the effect of drugs on depression comorbid T2DM.

Perturbation in insulin signaling pathway, as impaired signaling cascade of phosphorylation of insulin receptor (IR), insulin receptor substrate 1 (IRS1) and downstream serine/threonine kinase (Akt), promotes insulin resistance in periphery as well as in brain (Ramnanan et al., 2011; Saltiel and Kahn, 2001; Tanti and Jager, 2009). Inflammation induced by pro-inflammatory cytokine interleukin-1 beta (IL-1β), is a most common cause for insulin signaling impairment (Tack et al., 2012; Wen et al., 2011). Actually, inflammation or pro-inflammatory cytokine hypothesis is prevalent in depression, supported by previous studies in CUMS animals (Kubera et al., 2011; Pan et al., 2014). Recently, Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, modulating IL-1β maturation and secretion, is observed in periphery and brain of CUMS animals, possibly being critical in pathophysiology of depression and pharmacology of antidepressants (Alcocer-Gomez et al., 2014; Du et al., 2016; Iwata et al., 2013; Pan et al., 2014; Zhang et al., 2015). Of note, some antidepressants produce the mixed or even negative effects on glycemic control (Goodnick et al., 1995; van Reedt Dortland et al., 2010). For example, tricyclic antidepressant may lead to hyperglycemia or metabolic syndrome (Sugimoto et al., 2003). These observations strongly argue for the importance to find new effective drugs for comorbid depression with T2DM.

Traditional Chinese medicine (TCM) and the active ingredients are therapeutically beneficial in chronic diseases including depression and T2DM (Yeung et al., 2014; Zhang and Jiang, 2012). Banxia-houpu decoction is a TCM formula consisted of Pinellia tuber, Magnolia cortex, Poria, Perilla leaf and Ginger rhizome. Banxia-houpu decoction is firstly recorded in TCM book, "Jin Gui Yao Lue" written by Zhong-Jing Zhang in the early 3rd century, and then has been applied with good efficiency in depressed patients (Naito et al., 2003). Our previous studies demonstrated the antidepressant-like activity of water- and ethanol-extracts and polysaccharides from Banxia-houpu decoction, with the regulatory effects on multiple biochemical systems related to neurotransmitters, the HPA axis and immune-inflammation (Guo et al., 2004; Li et al., 2003; Wang et al., 2005; Yi et al., 2009). However, there is little report of Banxia-houpu decoction on comorbid depression with metabolic diseases.

In the present study, the effect of Banxia-houpu decoction against glucose intolerance was investigated in depressed CUMS rats. Insulin signaling controls glucose homeostasis not only in periphery but also in brain (Ghasemi et al., 2013). Therefore, to explore the possible mechanisms underlying the impairment of glucose tolerance, IR/IRS1/Akt insulin signaling and the activation of NLRP3 inflammasome were detected in peripheral liver tissue, as well as in brain regions hypothalamus, hippocampus and prefrontal cortex in CUMS rats, respectively. More importantly, the ability of Banxia-houpu decoction to attenuate insulin signaling impairment and NLRP3 inflammasome activation was evaluated in depressed animals. These results may provide experimental evidence to strengthen our understanding about the pharmacological mechanisms by which Banxia-houpu decoction reduces the risk of comorbid depression with T2DM.

2. Materials and methods

2.1. Preparation and determination of Banxia-houpu decoction

2.1.1. Preparation of Banxia-houpu decoction

Banxia-houpu decoction was consisted of five herbs, Pinellia tuber, Magnolia cortex, Poria, Perilla leaf and Ginger rhizome (Table 1), and prepared according to our previous study (Li et al., 2003). All of these herbs were purchased from Medicinal Materials Company of Jiangsu Province (P.R. China). These herbs were immersed in 10 times volume of water for 0.5 h; then decocted at boiling temperature for 1 h and get the filtrate. The residues were added with 8 times volume of water and decocted for 40 min and get the filtrate. The filtrates were merged and centrifuged to obtain the supernatants, which were concentrated and then dried into powder in a vacuum oven. The yield of this powder was about 21.5%.

2.1.2. Determination of Banxia-houpu decoction

The qualitative analysis of components in water extract of Banxia-houpu decoction was employed by a LC-MS/MS method. 283 mg of Banxia-houpu decoction extract was dissolved in 10 mL 50% methanol (HPLC grade), then filtered through a 0.22 μm membrane filter, centrifuged at 16,000*g*, 4 °C for 5 min, finally collected the supernatant for analysis. The liquid chromatography equipment was a Shimadzu LC30AD pump and Shimadzu SPD-20A detector. Analysis was carried out on a common C_{18} column (150 mm × 4.6 mm, 5 μm) and the column temperature was maintained at 40 °C. The mobile phase was composed of A (0.1% formic acid in water, v/v) and B (acetonitrile) using a gradient elution of 5% B at 0–2 min; 5–70% B at 2–30 min; 70–90% B at 30–33 min; 90% B at 33–37 min; 90–5% B at 37–37.1 min. The flow rate was set at 0.4 mL/min. The injection volume was 5 μL. The accurate mass spectrometric experiment was operated in the ESI negative and positive-ion mode of a TripleTOF 4600 mass spectrometer system equipped with a DuoSpray ion source (AB Sciex, California, USA). The following operation parameters were used: ion source gas 1 and ion source gas 2, 55 psi; curtain gas, 35 psi; ion spray voltage floating, 4500 V; temperature, 550 °C; collision energy, 40 V; and collision energy spread, 20 V. Data was managed with PeakView 2.2 software (AB Sciex, California, USA). MS/MS fingerprints of components in Banxia-houpu decoction water extract were referred to some databases like Metlin, SDBS and MassBank for preliminary confirmation.

Quantitative analysis of the specific five components in Banxia-

Table 1
Prescription of Banxia-houpu decoction.

Local name	English name	Latin name	Part used	Origin (P.R. China)	Amount (g)
Ban Xia	Pinellia Tuber	*Pinellia ternata (Thunb.) Breit.*	Root	Gui Zhou	12
Hou Pu	Magnolia Cortex	*Magnolia officinalis Rehd.et Wils.*	Bark	Si Chuang	9
Fu Ling	Poria	*Poria cocos (Schw.) Wolf.*	Sclerotium	An Hui	12
Sheng Jiang	Ginger Rhizome	*Zingiber officinale Rosc.*	Rhizome	Jiang Su	9
Zi Su Ye	Perilla Leaf	*Perilla frutescens (L.)Britt.*	Leaf	Jiang Su	6