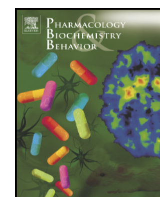
Pharmacology, Biochemistry and Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect
Pharmacology, Biochemistry and Behavior
journal homepage: www.elsevier.com/locate/pharmbiochembeh



Differential proteomic analysis of the anti-depressive effects of oleamide in a rat chronic mild stress model of depression

Lin Ge [a], Ming-ming Zhu [a], Jing-Yu Yang [a], Fang Wang [a], Rong Zhang [b], Jing-Hai Zhang [b], Jing Shen [c], Hui-Fang Tian [c], Chun-Fu Wu [a,*]

[a] Department of Pharmacology, Shenyang Pharmaceutical University, Shenyang 110016, PR China
[b] School of Life Science and Bio-pharmaceutics, Shenyang Pharmaceutical University, Shenyang 110016, PR China
[c] Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Central Laboratory, Beijing Cancer Hospital & Institute, Beijing 100142, PR China

ARTICLE INFO

Article history:
Received 21 February 2014
Received in revised form 20 January 2015
Accepted 23 January 2015
Available online xxxx

Keywords:
Chronic unpredictable mild stress
Hippocampus
Oleamide
Proteomics

ABSTRACT

Depression is a complex psychiatric disorder, and its etiology and pathophysiology are not completely understood. Depression involves changes in many biogenic amine, neuropeptide, and oxidative systems, as well as alterations in neuroendocrine function and immune-inflammatory pathways. Oleamide is a fatty amide which exhibits pharmacological effects leading to hypnosis, sedation, and anti-anxiety effects. In the present study, the chronic mild stress (CMS) model was used to investigate the antidepressant-like activity of oleamide. Rats were exposed to 10 weeks of CMS or control conditions and were then subsequently treated with 2 weeks of daily oleamide (5 mg/kg, i.p.), fluoxetine (10 mg/kg, i.p.), or vehicle. Protein extracts from the hippocampus were then collected, and hippocampal maps were generated by way of two-dimensional gel electrophoresis (2-DE). Altered proteins induced by CMS and oleamide were identified through mass spectrometry and database searches. Compared to the control group, the CMS rats exhibited significantly less body weight gain and decreased sucrose consumption. Treatment with oleamide caused a reversal of the CMS-induced deficit in sucrose consumption. In the proteomic analysis, 12 protein spots were selected and identified. CMS increased the levels of adenylate kinase isoenzyme 1 (AK1), nucleoside diphosphate kinase B (NDKB), histidine triad nucleotide-binding protein 1 (HINT1), acyl-protein thioesterase 2 (APT-2), and glutathione S-transferase A4 (GSTA4). Compared to the CMS samples, seven spots changed significantly following treatment with oleamide, including GSTA4, glutathione S-transferase A6 (GSTA6), GTP-binding nuclear protein Ran (Ran-GTP), ATP synthase subunit d, transgelin-3, small ubiquitin-related modifier 2 (SUMO2), and eukaryotic translation initiation factor 5A-1 (eIF5A1). Of these seven proteins, the level of eIF5A1 was up-regulated, whereas the remaining proteins were down-regulated. In conclusion, oleamide has antidepressant-like properties in the CMS rat model. The identification of proteins altered by CMS and oleamide treatment provides support for targeting these proteins in the development of novel therapies for depression.

© 2015 Published by Elsevier Inc.

1. Introduction

Oleamide (cis-9,10-octadecenoamide, OLE) belongs to the family of long chain primary fatty acid amides (Lees and Dougalis, 2004; Leggett et al., 2004). The compound was first identified in 1989 from normal human serum; it was then isolated from the cerebrospinal fluid of sleep-deprived cats and was shown to induce physiological sleep in rats (Arafat et al., 1989; Lerner et al., 1994; Cravatt et al., 1995, 1996; Boger et al., 1998a; Herrera-Solísa et al., 2010). To date, oleamide has been shown to have various pharmacological activities, including anti-anxiety effects, hypnosis, sedation, gap junction inhibition, vasorelaxation, and anti-inflammation (Boger et al., 1998b; Yang et al., 1999; Dougalis et al., 2004; Sudhahar et al., 2009; Oh et al., 2010). A number of studies have demonstrated that oleamide is an endogenous bioactive lipid signaling molecule which acts on endogenous cannabinoid, serotonergic, and GABAergic systems (Thomas et al., 1998; Boger et al., 1998c;

Abbreviations: CMS, chronic mild stress; 2-DE, two-dimensional gel electrophoresis; AK1, adenylate kinase isoenzyme 1; NDKB, nucleoside diphosphate kinase B; HINT1, histidine triad nucleotide-binding protein 1; APT-2, acyl-protein thioesterase 2; GST, glutathione S-transferase; GSTA4, glutathione S-transferase A4; GSTA6, glutathione S-transferase A6; Ran-GTP, GTP-binding nuclear protein Ran; SUMO2, small ubiquitin-related modifier 2; eIF5A1, eukaryotic translation initiation factor 5A-1; OLE, oleamide; MDD, major depressive disorder; HPA, hypothalamic–pituitary–adrenal; MS, mass spectrometry; FLX, fluoxetine; MW, molecular weight; EC, endogenous cannabinoid; SSRI, selective serotonin reuptake inhibitor; dF1F0, d subunit of mitochondrial F1Fo ATP synthase; BD, bipolar disorder; SCZ, schizophrenia; CNS, central nervous system; NDPK, nucleoside diphosphate kinase; NDP, nucleoside diphosphate; NTP, nucleoside triphosphate; NDKA, nucleoside diphosphate kinase A; NDKB, nucleoside diphosphate kinase B; Ran, Ras-related nuclear protein; RanGAP1, Ran GTPase-activating protein 1; RCC1, chromosome condensation 1.

* Corresponding author. Tel./fax: +86 24 23843567.
E-mail address: chunfuw@gmail.com (C.-F. Wu).

http://dx.doi.org/10.1016/j.pbb.2015.01.017
0091-3057/© 2015 Published by Elsevier Inc.

Cheer et al., 1999; Leggett et al., 2004; Lees and Dougalis, 2004; Oh et al., 2010). Some evidence suggests that oleamide can significantly decrease the immobility time in a forced swimming test in rats and mice, indicating that it may be a potential antidepressant agent (Hill and Gorzalka, 2005; Akanmu et al., 2007).

Major depressive disorder (MDD) is a severe, life-threatening, and highly heterogeneous psychiatric disease characterized by depressed mood, anhedonia (loss of interest in rewarding stimuli), and extreme alterations in vegetative function (i.e., decreases or increases in appetite) (Hill and Gorzalka, 2005; Mill and Petronis, 2007; Ashwani and Preeti, 2012). Despite extensive research, the exact mechanisms of MDD have not been identified. Recently, a new hypothesis suggests that the activation of inflammatory and oxidative pathways is a key pathophysiological factor in MDD (Maes et al., 2011, 2012). The chronic mild stress (CMS) model is a wildly used animal model of MDD, with a protracted time course very suitable for investigating the effects of chronic drug treatments (Willer et al., 1992; Willner, 2005). In our research, the CMS model in rats was used to evaluate the antidepressant effects of chronic oleamide administration.

The hippocampus plays an important role in memory, emotional expression, and navigation (Warner-Schmidt and Duman, 2006). It is also a key structure for studying the neurobiological substrates of depression due to its involvement in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis and the high number of corticosteroid and 5-HT receptors in this region. In addition, a number of studies have demonstrated that stress and depression lead to reductions in the total volume of the hippocampus, as well as atrophy and loss of neurons in this structure (Rajkowska, 2003; Warner-Schmidt and Duman, 2006; Ashwani and Preeti, 2012).

In our research, two-dimensional gel electrophoresis (2-DE) and mass spectrometry (MS) techniques were used to identify proteins that are altered by CMS and oleamide treatment in the hippocampal regions. Because of its ability to determine which proteins are changed by the cell, tissue, or organism's response to internal states, external stimulations, or developmental changes, proteomics technology provides a globally sensitive tool to elucidate complex biological mechanisms. Additionally, it also provides a mechanism to profile differential protein expression. Protein expression analysis of the rat hippocampus following CMS and oleamide treatment thus provided a better understanding of the biochemical changes that occur during the development of depression and treatment.

The aims of the current study were as follows: 1) to investigate the anti-depressive effects of oleamide in the CMS model, and 2) to use a proteomic approach to identify affected proteins in the hippocampi of animals following CMS and oleamide treatment.

2. Materials and methods

2.1. Animals

Thirty-two male Sprague–Dawley rats (supplied by the Experimental Animal Center of Shenyang Pharmaceutical University), weighting 180–220 g, were used in the present study. Rats were allowed 3 days to acclimate prior to beginning the experiment. Food and tap water were available ad libitum throughout the experiments, except when the CMS procedure required deprivation. The room temperature was maintained at 20 ± 2 °C. Animals were maintained on a 12 h/12 h light/dark cycle (lights on at 8:00 am) unless otherwise noted (Gronli et al., 2005). All experiments and procedures were carried out according to the Regulations of Experimental Animal Administration issued by the State Committee of Science and Technology of China.

2.2. Drugs

Oleamide (OLE, purity > 98%) was supplied by Shenyang Pharmacology University and was dissolved in olive oil. Fluoxetine (FLX) was supplied by the China Shanghai Zhongxi Pharmaceutical Factory and was dissolved in saline. OLE and FLX were administered via an intraperitoneal (i.p.) injection at a volume of 0.1 ml/10 g.

2.3. General experimental procedure

Following adaptation to the experimental environment, baseline body weight, food intake, and sucrose intake were determined for 3 weeks. Animals were then randomly divided into four groups: a control group (n = 8), a CMS group (n = 8), a CMS + OLE group (n = 8), and a CMS + FLX group (n = 8). Animals in the CMS groups were subjected to CMS for 10 weeks, after which drugs were administered for 2 weeks in the absence of the stressors. The dose of OLE was 5 mg/kg/day and FLX was 10 mg/kg/day (Papp et al., 2003). In a previous study, we used the forced swim test to determine the optimal dose of OLE, and the results showed that both 5 mg/kg/day and 10 mg/kg/day OLE had anti-depressive activity (unpublished). We therefore chose the 5 mg/kg/day as the optimal dose in this study, in order to examine the effects of the lowest but still effective dose of OLE. Animals in the control and CMS groups received the same volume of olive oil as the CMS + OLE and CMS + FLX groups.

Body weight, food intake and sucrose solution consumption were determined weekly. The animals were euthanized after 12 weeks, and their brain tissues were dissected on ice and stored at −80 °C. The protein from hippocampal tissues obtained from the four groups was subsequently extracted for two dimensional gel electrophoresis (2-DE).

2.4. Chronic mild stress

During experimental procedures, rats in the control group were housed in two cages (4 rats per cage) and the remaining animals (the CMS, CMS + OLE, and CMS + FLX groups) exposed to chronic mild stress were housed individually. The stressors in this study included: one period of water and food deprivation (20 h, immediately prior to the sucrose solution consumption test); one period of water deprivation (17 h) immediately followed by 1 h exposure to an empty bottle; one period of food deprivation (18 h; no food supplied) or food restriction (18 h; 1–2 g food supplied); two periods of 45° cage tilt (8 h and 18 h); two periods of housing in a soiled cage (200 ml of water in sawdust bedding per individual cage) (7 h and 17 h); one period of white noise (12 h, 85 dB); one period of paired housing (17 h); one period of overnight light (12 h); one period of behavior restrictions (16 h; each rat was restricted to a 25 ∗ 16 cm box). The animals were exposed to each stressor one time per week in a random order for a total of 10 weeks.

The control group was exposed to water and food deprivation prior to the sucrose intake tests. In all other cases, food and water were freely available in their home cages (Willer et al., 1992; Gronli et al., 2005). Q8

2.5. Body weight gain and food intake

Body weight was measured and body weight gain was calculated at weekly intervals. Food intake was measured every Monday morning. Food consumption was measured by comparing the food weight before and after a 24-h period.

2.6. Sucrose solution consumption tests

The animals were first trained to consume a 1% sucrose solution for 3 weeks (two times per week) before the tests. During the training period, all animals were exposed to a 1% sucrose solution for 1 h following a 20 h period of food and water deprivation. The sucrose intake was measured by weighing previously weighed bottles containing 1% sucrose solution at the end of the test. The baseline of sucrose intake was the average of two values measured during the 3rd week. Throughout the entire experiment, sucrose intake was measured at weekly intervals (Willer et al., 1992; Papp et al., 2002; Henningsen et al., 2012). Q9

UNCORRECTED PROOF

Please cite this article as: Ge L, et al, Differential proteomic analysis of the anti-depressive effects of oleamide in a rat chronic mild stress model of depression, Pharmacol Biochem Behav (2015), http://dx.doi.org/10.1016/j.pbb.2015.01.017

Download English Version:

https://daneshyari.com/en/article/8350676

Download Persian Version:

https://daneshyari.com/article/8350676

Daneshyari.com