



Behavioral and molecular responses to electroconvulsive shock differ between genetic and environmental rat models of depression



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ARTICLE INFO

Article history:

Received 13 April 2014

Received in revised form

9 December 2014

Accepted 18 December 2014

Available online 28 January 2015

Keywords:

Animal models

Antidepressant treatment

BDNF

CREB

ABSTRACT

Depression's causes play a role in individuals' different responses to antidepressant treatments, which require advancements. We investigated the mechanisms behind and responses to a highly effective antidepressant treatment, electroconvulsive therapy (ECT), in rat models with different (genetic or environmental) depression causes. Wistar Kyoto (WKY) rats and Wistar rats treated with chronic unpredictable mild stresses (CUMS) were used as genetic and environmental rat models of depression, respectively. The rats underwent electroconvulsive shock (ECS, the animal analog of ECT) or sham ECS. We performed a sucrose preference test, open field test, and Morris water maze to assess behavior. Hippocampal neuron numbers were measured with Nissl stain. Hippocampal BDNF, CREB, and p-CREB proteins were assayed with ELISA or western blotting. The main results showed that ECS impaired WKY rats' memories but improved CUMS rats' memories. It elevated hippocampal BDNF and CREB proteins only in CUMS rats, while it improved depressive behavior and hippocampal p-CREB protein levels in both rats, with more effective regulations in the CUMS rats. ECS did not change the hippocampal neuron number in both rats. These findings suggest that ECS exerted up-regulating effects on hippocampal BDNF and CREB (and its phosphorylation) in depressed rats, and the environmental model responded better.

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1. Introduction

Depression is responsible for a substantial proportion of worldwide disease burden, but clinical response to antidepressant treatments is still not satisfactory. Although pharmacotherapy has been the first-line treatment for depression, response to antidepressants varies between individuals (Keers and Uher, 2012), and more than half of patients fail to respond adequately to the first antidepressant they are prescribed (Trivedi et al., 2006). As a somatic treatment, electroconvulsive therapy (ECT) is known to be quicker and more effective than common antidepressants, but it is still not effective for up to 30% of patients with depression (Medda et al., 2009). Efficacy enhancements include exploring novel drugs and treatments, but there have been no significant advancements and robust response predictors to antidepressant treatments. ECT's mechanisms are complicated, and the cause of different individual responses to ECT for depression in terms of genes, environment, and their interaction are even more obscure.

Individual factors, especially depression's causes, play an essential role in different responses to antidepressant treatments (Uher, 2008; Keers and Aitchison, 2011; Klengel and Binder, 2013). Depression results from an interaction between genes and environments. The mainstream "diathesis-stress" hypothesis for depression's etiopathogenesis of depression shows that the genetic or environmental factors can lead to the occurrence and development of different depression subtypes. Previous studies indicated that those with "endogenous" depression (occurring in the absence of a prior stressor) and those with "reactive" depression (occurring in response to a stressor) responded totally differently to somatic treatments, antidepressants, or psychotherapies (Keers and Uher, 2012).

The "neurotrophic hypothesis" suggests that reduced neurotrophins, including brain-derived neurotrophic factor (BDNF), result in decreased hippocampal function and ultimately depression. Neurogenesis-related genes, including BDNF, cyclic adenosine monophosphate response element-binding protein (CREB), and the pathway are essential in gene-cognition-environment interactions in depression's mechanism (Juhász et al., 2011).

In the present study, we compared behavioral and molecular responses to electroconvulsive shock (ECS, the animal analog of ECT) between a genetic [Wistar Kyoto (WKY) rats, which are

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genetically hypersensitive to stressors, demonstrate depressive behaviors such as anhedonia, and are deemed a valid rat model of “endogenous” depression (Tejani-Butt et al., 2003)] and environmental [rats treated with chronic unpredictable mild stress (CUMS), which have similarities to patients with depression caused by chronic, low-level stresses, and are considered to simulate patients with “reactive” depression with good predictive, face, and construct validity] rat model of depression. We wished to reveal the profile and possible mechanism of different responses to ECT in rats with different depression causes.

2. Methods

2.1. Animals

Healthy adult male Wistar rats and WKY rats (weighing 200–240 g, from the Laboratory Animal Centre of Chongqing Medical University) were used. They were maintained in a standardized environment with free access to food and water for one-week acclimatization before the experiments. All procedures were approved by the Ethical Committee of Chongqing Medical University and carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

2.2. Groups and general procedures

Rats were randomly divided into six groups: groups S, K, C, SE, KE, and CE ($n=12$ in each group). WKY rats (in groups K and KE) and some Wistar rats (in groups S and SE) were normally bred for 28 days, and the rest of the Wistar rats (in groups C and CE) were treated with CUMS. After that, Wistar rats in group S were treated with sham ECS, Wistar rats in group SE treated with ECS, CUMS-treated Wistar rats (CUMS rats for short) in group C were treated with sham ECS, CUMS rats in group CE were treated with ECS, WKY rats in group K were treated with sham ECS, and WKY rats in group KE were treated with ECS. After the CUMS procedures (i.e., on the 29th day from the beginning of experiments), all the rats were tested with behavioral tests. The sucrose preference test (SPT), open field test (OFT), and Morris water maze (MWM) test were performed separately on the 29th, 30th, and 31st to 36th days, respectively. From the 37th day to the 43rd day, rats received ECS (or sham ECS). After that, rats were again subjected to behavioral tests: SPT on the 44th day, OFT on the 45th day, and MWM from the 46th day to 51st day. On the 52nd day, half the rats in each group of depressive rats (in group K, C, KE, and CE) were decapitated for hippocampi Nissl stain, while the remaining rats in these groups were decapitated, the hippocampi of which were used for enzyme linked immunosorbent assay (ELISA) and western blotting assay. The four depressive rat groups were assigned to treatments according to a (2×2) factorial design, with causes of depression (genetic or environmental) and antidepressant treatments (ECS or sham ECS) as the two factors.

2.3. Chronic unpredictable mild stress procedure

For 4 weeks, rats received no stresses (in groups S, SE, K and KE) or daily stressor stimulus (in the other groups) (Luo, et al., 2010). One stressor stimuli was applied randomly to the rats in groups C and CE once daily: (1) swimming in cold water at 4 °C for 5 min; (2) pinching tail for 1 min; (3) food deprivation for 24 h; (4) water deprivation for 24 h; (5) social crowding (24 rats per cage) with cage being tilted to 30° horizontally for 24 h; (6) shake for 20 min (1 shake/s); (7) 24 h of continuous lighting; (8) housing in a soiled cage for 24 h; (9) hot stress in oven at 45 °C for 5 min; or (10) undesirable confinement for 2 h. Stressor stimuli were administered three times within the 4 weeks except for stressors one and two, which was applied two times each.

2.4. Electroconvulsive shock treatments

ECS or sham ECS were performed under anesthesia with propofol (FX061, AstraZeneca, UK; 10 mg/ml, 9 ml/kg, i.p.). ECS was delivered via ear clip electrodes using a Niviqure ECT system (Niviqure Meditech, Bangalore, India; bidirectional square wave pulses, 120 mC) once daily for 7 days (Luo, et al., 2012). Sham ECS was handled identically as ECS without currents. Oxygen was given and the blood oxygen saturation (SpO_2) was monitored and maintained. Only rats with a SpO_2 value no less than 95% were included.

2.5. Behavioral tests

2.5.1. Sucrose preference test

After a 23-h period of water and food deprivation, each rat was given free access to two pre-weighed bottles for 1 h (one filled with 1% (w/v) sucrose solution and the other with water). Both before and after 1 h drink, each bottle was weighed. The percentage of consumed sucrose solution occupied in the total liquid consumed indicated each rat's sucrose preference (Luo, et al., 2010). The sucrose preference percentage (SPP) was calculated as follows: $SPP (\%) = \text{sucrose solution consumption} / (\text{water consumption} + \text{sucrose solution consumption}) \times 100\%$. SPP is represented as an index of hedonic behavior, the loss of which indicates depressive disorder. $SPP \text{ increase rate } (\%) = [SPP \text{ after ECS (or sham ECS) treatment} - \text{baseline SPP}] / \text{baseline SPP} \times 100\%$.

2.5.2. Open field test

The test was performed as described previously with minor modification (Qi et al., 2008). The apparatus consisted of a black-painted circular arena, 150 cm in diameter with 60 cm walls, put in a dimly lit room. Each rat was placed at the centre of the arena and its activities observed for 5 min. Indices assessed were the horizontal ambulation (the total distance traveled, indicating locomotor behavior) and the number of rearing times (when a rat stood completely erecting on its hind legs, indicating exploratory behavior), which were recorded and analyzed with a SLY-WMS 2.0 system (Sunny Instruments, Beijing, China). The increased rate of distance (or rearing number) (%) = $[\text{distance (or rearing number) after ECS (or sham ECS) treatment} - \text{baseline distance (or rearing number)}] / \text{baseline distance (or rearing number)} \times 100\%$.

2.5.3. Morris water maze test

The test was performed as described previously with minor modification (Parihar, et al., 2011). Briefly, in the acquisition trials, each rat was subjected to four consecutive trials from each one of four quadrants in a pool (150 cm in diameter, 50 cm in height, colored with black ink) per day for 5 days and trained to find a hidden circular platform (10 cm in diameter, 2 cm underneath the water in the middle of the southwestern quadrant). Every rat was allowed a maximum of 60 s to reach the platform or was otherwise guided toward it. The rat was then left there for 15 s. On the 6th day, every rat was given a probe test for 60 s in the absence of the platform in the pool from the northeastern quadrant. The percentage of dwell time spent in the southwestern quadrant (i.e., time percentage in platform quarter, TPPQ) positively indicated the rats' spatial memory. The rats' activity data were recorded and analyzed with a SLY-WMS 2.0 system (Sunny Instruments, Beijing, China). The TPPQ calculation of is as follows: $TPPQ (\%) = \text{swimming time in platform quarter (s)} / \text{total swimming time (s)} \times 100\%$. $TPPQ \text{ increase rate } (\%) = [TPPQ \text{ after ECS (or sham ECS) treatment} - \text{baseline TPPQ}] / \text{baseline TPPQ} \times 100\%$. The description of procedures of MWM are illustrated in Table 1 and the supplemental document in more details.

2.6. Nissl stain

Rats were perfused with 4% paraformaldehyde after being anesthetized. The coronal brain sections were cut in a vibratome after the brains were postfixed in the same fixative. To ensure hippocampal sections were matched between groups, we used anatomical landmarks provided by the brain atlas. The selected brain sections were stained with 0.5% cresyl violet and examined with a TE2000-U

Table 1
Procedures in the Morris water maze test.

Procedures	Start location	Time of trial or test	Maximum time for a rat's swimming	Time to leave a rat on the platform	Indication
1. Acquisition trials	One of the four quadrants (northwestern, northeastern, southwestern, or southeastern)	Four trials (with the start location of one quadrant each) every day for five days	60 s	15 s	Learning process
2. Probe test	The quadrant opposite to the original position of the platform (i.e. the northeastern quadrant in this study)	Once on the 6th day	60 s	0 s (without a platform in the test)	Memory

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