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Effects of lithium and carbamazepine on spatial learning and depressive behavior in a rat model of bipolar disorder induced by ouabain ☆

Ying-Chou Wang [a,1], En-Nan Wang [a,b,c,1], Chia-Chuan Wang [d], Chung-Lei Huang [e], Andrew Chih Wei Huang [e,*]

[a] Department of Clinical Psychology, Fu Jen Catholic University, New Taipei City 24205, Taiwan
[b] Department of Psychiatry, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[c] Graduate Institute of Humanities in Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[d] School of Medicine, Fu Jen Catholic University, New Taipei City 24205, Taiwan
[e] Department of Psychology, Fo Guang University, Yilan County 26247, Taiwan

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ABSTRACT

Lithium (LiCl) and carbamazepine (CBZ), the common mood stabilizers, are thought to be effective treatments for bipolar disorder. The aim of the present study was to investigate whether LiCl as well as CBZ has similar effects on the bipolar disorder-associated cognitive dysfunctions in rats, particularly the spatial learning and depressive responses. Adult male Wistar rats were administered intracerebroventricularly with 5 μl of 10^{-3} M ouabain on session 1, and then received an intraperitoneal injection of LiCl or CBZ for 4 sessions (1 session/2 days). For the behavioral tests, all rats were subjected to the water maze 15 min for spatial learning and the forced swimming test 5 min for depression on each session. The present results showed that ouabain resulted in increased latency and longer distance traveled to reach the hidden platform in the water maze, indicating that ouabain impaired the spatial learning. However, ouabain did not affect swimming velocity in the water maze and depressive responses in the forced swimming test. LiCl treatment decreased the ouabain-enhanced latency and the total distance, but not the velocity, swam to reach the hidden platform in the water maze task. Additionally, LiCl did not result in changes of any depressive indices, such as struggling behavior, swimming behavior, and floating behavior. Likewise, CBZ did not affect any behavioral indices of spatial learning and depression. A linear regression analysis suggested that LiCl, but not CBZ, could predict the decreased latency and total distance traveled except the velocity of swimming in the water maze and depressive behaviors. In summary, the present results suggested that lithium provided a better therapeutic effect than CBZ for ouabain-caused dysfunctions of spatial learning in a rat model of bipolar disorder.

1. Introduction

Lithium has been introduced for over 60 years to treat bipolar disorder in humans (Cade, 1949), and is still considered as a first-line, available medication. Particularly, its major pharmacological action is to decrease the manic episode of bipolar disorders, and thereby alleviates the depressive symptoms (Soares and Gershon, 1998). Despite the fact that an estimated 70–80% of patients with bipolar disorder appear better after taking lithium for one or two weeks (Price and Heninger, 1994; Prien and Potter, 1990), there are some limitations. For example, some patients with bipolar disorder might have adverse side effects, including limb tremors, thirst, excessive urine production, and weight gain while taking lithium (Findling, 2009; Suraya and Yoong, 2001). Because 30–40% of bipolar disorder patients cannot develop lithium tolerance, carbamazepine (CBZ), an anticonvulsant drug, would be considered as an alternative treatment for this subgroup of patients (Okuma, 1993; Vasudev et al., 2000).

Despite the fact that CBZ is suggested to be an alternative drug for treating bipolar disorder, therapeutic effects of lithium and CBZ were inconsistent in clinics and they have different actions in the neural mechanism (Berns et al., 2002; Elphick, 1989; Okuma, 1993; Vasudev et al., 2000). For example, some clinical studies have shown that lithium may be more effective than CBZ in treating patients with bipolar disorder (Davanzo et al., 2003). CBZ is often used in the treatment of seizure and served as an anticonvulsant drug and it is an available treatment to partial or focal seizures (Liu et al., 2006). However, lithium is not related to anticonvulsants, and instead, it is used as a mood stabilizer in clinics (Davanzo et al., 2003). The mechanism of pharmacological action of lithium is not certain until now (Lee et al., 1999; Manji et al., 2001; Soares and Gershon, 1998). Lithium may be possibly involved in a variety of neurotransmitter systems, such as GABA (Hetmar and Nielsen, 1988),

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* Corresponding author at: Department of Psychology, Fo Guang University, No. 160, Linwei Road, Jiaosi Shiang, Yilan County 26247, Taiwan. Tel.: +886 3 9871000x27114; fax: +886 3 9875530.
E-mail address: chweihuang@mail.fgu.edu.tw (A.C.W. Huang).

[1] The first and second authors contributed equally to this article.

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5-HT (Jitsuiki et al., 2000), and dopamine (Montezinho et al., 2007). In contrast to lithium, CBZ, an anticonvulsant drug, exerts its actions through a distinct mechanism for treating bipolar disorder (Okuma, 1993; Waldmeier, 1987). Moreover, CBZ can antagonize A_1-adenosine receptors in hippocampus membranes (Gasser et al., 1988). Additionally, CBZ has been shown to reduce sodium currents (Willow et al., 1985) and calcium fluxes (Gasser et al., 1988; Schirrmacher et al., 1995) crossing neural membranes and, subsequently, to decrease membrane depolarization. An early in vitro cultured study showed that CBZ could potentiate the activation of $GABA_A$ receptor to induce chloride ion currents, and therefore elicit an inhibitory postsynaptic potential (Granger et al., 1995). In summary, these results suggested that the mechanism of action of CBZ is different from that of lithium.

Growing evidence has demonstrated that intracerebroventricular administration of ouabain, a Na^+–K^+ ATPase inhibitor, could result in a mania-like hyperactivity in an animal model of bipolar disorder (Decker et al., 2000; El-Mallakh et al., 1995, 2003; Ruktanonchai et al., 1998). Moreover, recent studies have manifested that debilitating Na^+–K^+ ATPase functions may exhibit cognitive impairment (Moseley et al., 2007; Schaefer et al., 2011; Zhan et al., 2004). Whether ouabain can result in cognitive dysfunction and bipolar-associated depression remains to be scrutinized.

To address the above questions, the present study was designed to examine whether ouabain can result in dysfunctions in spatial learning and depressive behaviors in an animal model of bipolar disorder, using the Morris water maze and the forced swimming tests. Further, we would like to compare the effects of lithium and CBZ on the ouabain-caused bipolar disorder.

2. General method

2.1. Animals

Seventy-six adult male Wistar rats (purchased from the BioLASCO Taiwan Co., Ltd) weighing 220–350 g at the beginning of the experiments were used. Rats were group-housed, two per cage, and maintained at 22 ± 2 °C with free access to food and water available on a 12/12 h light–dark cycle (lights on 06:00–18:00). After acclimation for 7 days, experimental manipulations were performed between 09:00 and 15:00 h. All experimental procedures in the present study were performed in compliance with the Animal Scientific Procedures Act of 1986 and received local ethics committee approval.

2.2. Drug preparation and administration

All chemicals, including ouabain, sodium chloride, lithium chloride (LiCl), and carbamazepine (CBZ), were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Ouabain was dissolved in artificial cerebrospinal fluid (aCSF) at a concentration of 10^{-3} M. Ouabain and aCSF were administered in a volume of 5 μl through an intracerebroventricular (i.c.v.) cannula as previously described (El-Mallakh et al., 2006; Herman et al., 2007; Li et al., 1997; McGrath et al., 2007). Sodium chloride (0.15 M) and LiCl (0.15 M) were dissolved in distilled water. Carbamazepine (CBZ) was dissolved in its vehicle, a mixture of DMSO/propylene glycol/ethanol (42.5:42.5:15). The lithium dosages used in this study were 1 ml/kg and 4 ml/kg of 0.15 M LiCl, and the doses of CBZ were 20, 30, and 40 mg/kg. Rats in control group were injected intraperitoneally with a volume of 1 ml/kg of vehicle.

2.3. Experimental groups and procedures

The present study consisted of two experiments. Experiment 1 was done to examine whether lithium has effects on spatial learning and depressive tests in bipolar disorder rats. Rats were randomly assigned to aCSF + 1 ml/kg of Saline (n = 8), Ouabain + 1 mg/kg of Saline (n = 7), Ouabain + 1 ml/kg of LiCl (n = 8), and Ouabain + 4 ml/kg of LiCl (n = 8) groups. Experiment 2 was done to investigate effects of CBZ on spatial learning and depressive responses in bipolar disorder rats. Rats were randomly divided into aCSF + VEH (n = 10), Ouabain + VEH (n = 9), Ouabain + 20 mg/kg CBZ (n = 9), Ouabain + 30 mg/kg CBZ (n = 9), and Ouabain + 40 mg/kg CBZ (n = 8) groups.

As shown in Fig. 1A, the experimental procedures consisted of three stages: stereotaxic surgery stage (day 0), recovery stage (days 1–7), and behavioral testing stage (days 8, 10, 12 and 14). On day 0, rats received an i.c.v. cannulation and then waited for a 7-day surgery recovery period (days 1–7). The behavioral testing stages contained 4 sessions, one session every other day. For drug administration, ouabain was only injected on day 8 (session 1) and LiCl, CBZ, or vehicles were treated on days 8, 10, 12 and 14 (sessions 1–4). Briefly, on day 8 (session 1 of behavioral testing stage), rats were i.c.v. injected with 5 μl of aCSF or 10^{-3} M ouabain and then received treatment (intraperitoneal injection) either with LiCl, CBZ, or their respective vehicles before the behavioral tests (Fig. 1B). On days 10, 12 and 14 (session 2–4), rats in Experiment 1 received saline or LiCl treatment 4 h before behavioral tests were conducted, whereas behavioral tests in Experiment 2 were performed 100 min after CBZ or vehicle was injected intraperitoneally (Fig. 1C). In the behavioral tests, all rats received the water maze test for 15 min and the forced swimming test for 5 min. To avoid the temporal bias, the water maze and forced swimming tests were given in a randomly counterbalanced way.

2.4. Intracerebroventricular cannulation

All rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneally). After animals were placed on a stereotaxic apparatus and an incision was made in the scalp, a small hole was drilled followed by insertion of a guide cannula into the left lateral ventricle (1 mm caudal to bregma, 2.5 mm lateral to midline, and 3.5 mm in depth), according to the rat brain atlas (Paxinos and Watson, 2007). The cannula was secured with dental cement and anchored to the skull with stainless steel screws. Then, animals were returned to their home cages for recovery for 7 days before experiments.

2.5. Apparatus

2.5.1. Morris water maze: spatial learning and memory

The Morris water maze consisted of a round plastic pool (200 cm diameter, 50 cm height) filled with water (30 cm depth) at 25 ± 1 °C and virtually divided into four equivalent quadrants: northeast, northwest, southeast, and southwest. A hidden platform (10 cm diameter, 20 cm height) was placed in the northwest quadrant of the pool and submerged 2 cm below the water surface. Each rat received four trials per session. For each trial, rats were randomly placed into one of the quadrants and then allowed to swim freely until they found and climb onto the hidden platform. When successfully reaching the hidden platform, the rat was allowed to rest on the platform for 30 s. In contrast, when unsuccessful, the cutoff time for each trial was 120 s. The inter-trial interval of the Morris water maze test was 1 min. Animal behaviors were recorded by a video camera. The latency to reach the platform, total distance traveled, and swimming velocity for each trial were analyzed using the video tracking software (Video Tracking Record System Version 1.17, SINGA Technology Corporation, Taipei, Taiwan).

2.5.2. Forced swimming test: depressive responses

Rats were individually placed in a plastic cylinder (33 cm diameter × 40 cm high) containing water (25 ± 1 °C) with a depth of 25 cm. For each trial, each rat was put into water and forced to swim for 5 min. The time spent in floating, swimming and struggling was recorded. Floating behavior is defined as immobility with the exception of movements necessary to keep the head above the water. Swimming behavior is the forward motion through the water and forepaws kept on the water surface. Struggling behavior is an upright position in the water and forepaws breaking the