COGNITIVE FLEXIBILITY IMPAIRMENT AND REDUCED FRONTAL CORTEX BDNF EXPRESSION IN THE OUABAIN MODEL OF MANIA

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Abstract—Central infusion of the Na+/K+-ATPase inhibitor, ouabain in rats serves as an animal model of mania because it leads to hyperactivity, as well as reproduces ion dysregulation and reduced brain-derived neurotrophic factor (BDNF) levels similar to that observed in bipolar disorder. Bipolar disorder is also associated with cognitive inflexibility and working memory deficits. It is unknown whether ouabain treatment in rats leads to similar cognitive flexibility and working memory deficits. The present study examined the effects of an intracerebral ventricular infusion of ouabain in rats on spontaneous alternation, probabilistic reversal learning and BDNF expression levels in the frontal cortex. Ouabain treatment significantly increased locomotor activity, but did not affect alternation performance in a Y-maze. Ouabain treatment selectively impaired reversal learning in a spatial discrimination task using an 80/20 probabilistic reinforcement procedure. The reversal learning deficit in ouabain-treated rats resulted from an impaired ability to maintain a new choice pattern (increased regressive errors). Ouabain treatment also decreased sensitivity to negative feedback during the initial phase of reversal learning. Expression of BDNF mRNA and protein levels was downregulated in the frontal cortex which also negatively correlated with regressive errors. These findings suggest that the ouabain model of mania may be useful in understanding the neuropsychopathology that contributes to cognitive flexibility deficits and test potential treatments to alleviate cognitive deficits in bipolar disorder.

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Key words: bipolar disorder, ouabain, reversal learning, working memory, BDNF, frontal cortex.

INTRODUCTION

Bipolar disorder is a severe mood disorder that is accompanied by significant cognitive impairments that can include deficits in working memory and cognitive flexibility (McKirdy et al., 2009; Dickstein et al., 2010; Hill et al., 2015; Vrabie et al., 2015). These cognitive deficits are observed in individuals with either type I or type II bipolar disorder (Solé et al., 2011). The cognitive deficits in bipolar disorder are associated with poor work adjustment and reduced daily functioning (Wingo et al., 2009a; Bonnin et al., 2014). Moreover, euthymic bipolar disorder individuals can still exhibit cognitive deficits (Martinez-Arán et al., 2004; Torrent et al., 2012) and treatments effective in stabilizing mood can have very limited effects in reducing cognitive deficits or may even, in certain cases, exacerbate existing impairments (Wingo et al., 2009b; Kozicky et al., 2012). At present, there are no approved treatments to alleviate cognitive deficits in bipolar disorder.

Animal models offer an opportunity to better understand the neuropsychopathology associated with cognitive deficits and test novel treatments to alleviate cognitive deficits in bipolar disorder. The ouabain model of mania is increasingly employed to further understand the neuropsychopathology of bipolar disorder (Decker et al., 2000; Herman et al., 2007; Kim et al., 2008, 2013; Souza et al., 2014; Sui et al., 2013; Toniin et al., 2014; Valvassori et al., 2015; Yu et al., 2010, 2011) and examine treatments that may alleviate defining symptoms in the disorder (Brocardo et al., 2010; Gao et al., 2011; Jomada et al., 2011; Brüning et al., 2012; Wang et al., 2013; Souza et al., 2014; Valvassori et al., 2016). Ouabain principally acts as a Na+/K+-ATPase inhibitor and is meant to model reduced Na+/K+-ATPase activity observed in bipolar disorder individuals (Goldstein et al., 2009; Huff et al., 2010; Banerjee et al., 2012). Consistent with ouabain treatment serving as a model of mania, an intracerebroventricular (ICV) injection of ouabain increases locomotor activity in rats (Decker et al., 2000; Herman et al., 2007; Brocardo et al., 2010; Souza et al., 2014; Varela et al., 2015). However, few studies have examined whether the ouabain model of mania leads to cognitive deficits (Wang et al., 2013, 2014) and even less is known about whether ICV ouabain treatment leads to impairments in working memory and cognitive flexibility.

An examination of working memory and cognitive flexibility in the ouabain model of mania is of further interest to understand how ouabain-induced changes in brain trophic factors may relate to changes in cognitive...
function. More specifically, there is accumulating evidence that decreased brain-derived neurotrophic factor (BDNF) is related to bipolar disorder (Cunha et al., 2006; Palomino et al., 2006; Pandey et al., 2008; Fernandes et al., 2015; Nassan et al., 2015). In a comparable fashion, recent studies with ICV treatment of ouabain in rats found reduced BDNF levels in the frontal cortex (Varela et al., 2015; Valvassori et al., 2016). In addition, other experiments in rodents report that BDNF in the frontal cortex is important for both reversal learning (Kanoski et al., 2007; Graybeal et al., 2011; Xue et al., 2007; Weiler et al., 2009; Dickstein et al., 2010; D'Cruz et al., 2011; Wang et al., 2014; Varela et al., 2015). To understand whether ouabain treatment affects discrimination learning and/or cognitive flexibility, rats were also tested in a two-choice spatial discrimination using 80/20 probabilistic reinforcement. A probabilistic learning and reversal learning test was used because past studies demonstrated that individuals with bipolar disorder or other psychiatric disorders exhibit probabilistic reversal learning deficits (Waltz and Gold, 2007; Weiler et al., 2009; Dickstein et al., 2010; D'Cruz et al., 2013). This study further determined whether ouabain treatment affected BDNF expression in the frontal cortex and was related to behavioral performance.

EXPERIMENTAL PROCEDURES

Subjects

Adult male Long–Evans rats weighing 320–380 g served as the subjects for this study. The rats were individually housed in plastic cages (26.5 × 50 × 20 cm) in a temperature-controlled room at 21–23 °C and humidity 30%. Rats were on a 12-h light/dark cycle. The animals were food restricted to 85–90% of their body weight during the experiment. A total of 24 rats were used in this experiment. Animal care and use was in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was approved by the Institutional Laboratory Animal Care and Use Committee at the University of Illinois at Chicago.

The specific timeline for the procedures described below is illustrated in Fig. 1.

**Experimental Methods Timeline**

<table>
<thead>
<tr>
<th>Day</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Surgery</td>
</tr>
<tr>
<td>7</td>
<td>Maze Training (4-6 daily sessions)</td>
</tr>
<tr>
<td>14</td>
<td>ICV Ouabain Injection</td>
</tr>
<tr>
<td>18</td>
<td>Maze Training</td>
</tr>
<tr>
<td>19</td>
<td>Maze Training</td>
</tr>
<tr>
<td>20</td>
<td>Spontaneous Alternation and Spatial Acquisition</td>
</tr>
<tr>
<td>21</td>
<td>Spatial Reversal Learning</td>
</tr>
<tr>
<td>22</td>
<td>Rat Sacrificed and Brain Removed</td>
</tr>
<tr>
<td>≥23</td>
<td>Histology and BDNF Assays</td>
</tr>
</tbody>
</table>

**Surgical procedure**

Stereotaxic surgery was conducted during the light phase of the light/dark cycle. All rats were anesthetized with xylazine (10 mg/kg) and ketamine (100 mg/kg). Each rat received unilateral implantation of a guide cannula (22 gauge, Plastics One) aimed at the left lateral ventricle. The stereotaxic coordinates were as follows: anterior-posterior = −0.4 mm from bregma; medial-lateral = −1.5 mm from the midline and ventral = 4.0 mm from skull. The coordinates were based on the stereotaxic atlas by Paxinos and Watson (1998). Four jeweler screws were positioned in the skull surrounding the cannula and secured with dental acrylic. A stylet was placed into the guide cannula to prevent clogging. After surgery, rats received a 1-mg/kg injection of meloxicam to reduce any pain from the surgery. Rats were allowed to recover for 14 d after surgery. For 5 d after surgery, rats were fed *ad libitum* and left undisturbed. After recovery rats were food restricted as described above and handled 10 min/d.

**Microinfusion procedure**

Two weeks following surgery each rat received an ICV injection of ouabain (1 mM) dissolved in saline or saline alone in a 5 μl volume. The dose was based on past studies using the same concentration of ouabain (Gao et al., 2011; Wang et al., 2014; Varela et al., 2015). To execute the microinfusion procedure the stylet was first removed from the guide cannula while a rat was restrained. Subsequently, an injection cannula (28 gauge) was inserted into the guide cannula that extended 1 mm below the guide cannula. The injection cannula was connected by polyethylene tubing to a 10 μl syringe (Hamilton Company, Reno, NV, USA). Each treatment was infused at a rate 1 μl/1.5 min by a microinfusion pump (74900 Series; Cole Palmer). A rat was allowed to freely roam in its home cage as the infusion was occurring. The injection cannula was left in place for 1 min after injection to allow for diffusion.

**Apparatuses**

For the spontaneous alternation test, rats were tested in a Y-shaped maze. Each maze arm contained a base (10 × 55 cm), two side walls (15 × 55 cm), and a back wall (8 × 15 cm). A triangular center connected all three arms together. The maze was elevated 72 cm above the floor in a room with various extra maze cues. For the spatial discrimination test, training and testing occurred in a four-arm maze made from black acrylic. The maze was located in a different room than the Y-maze. The maze had a center square base (10 × 10 cm) that connected all four arms. Each maze arm contained a base (10 × 55 cm), two side walls (15 × 55 cm) and a back wall (8 × 15 cm). There was a circular food well (3.2 cm in diameter and 1.6 cm deep) that was placed 3 cm away from the back wall. The maze was placed on a table that had a height of 72 cm. The maze was located in a room that had various extramaze cues that could be used to spatially navigate in the maze.
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