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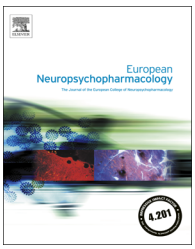

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Effects of lithium and aripiprazole on brain stimulation reward and neuroplasticity markers in the limbic forebrain

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Abstract
Bipolar disorder (BD) is a severe pathological condition with impaired reward-related processing. The present study was designed to assess the effects of two commonly used BD medications, the mood stabilizer lithium chloride (LiCl) and the atypical antipsychotic and antimanic agent aripiprazole, in an animal model of reward and motivation and on markers of neuroplasticity in the limbic forebrain in rats. We utilized intracranial self-simulation (ICSS) to assess the effects of acute and chronic administration of LiCl and aripiprazole on brain stimulation reward, and phosphorylation studies to determine their effects on specific cellular neuroplasticity markers, i.e., the phosphorylation of CREB and crucial phosphorylation sites on the GluA1 subunit of AMPA receptors and the NA1 and NA2B subunits of NMDA receptors, in the limbic forebrain. Chronic LiCl induced tolerance to the anhedonic effect of the drug observed after acute administration, while chronic aripiprazole induced a sustained anhedonic effect. These distinct behavioral responses might be related to differences in molecular markers of neuroplasticity. Accordingly, we demonstrated that chronic LiCl, but not aripiprazole, decreased phosphorylation of CREB at the Ser133 site and NA1 at the Ser896 site in the prefrontal cortex and GluA1 at the Ser831 site and NA2B at the Ser1303 site in the ventral striatum. The present study provides evidence for BD medication-evoked changes in reward and motivation processes and in specific markers of neuronal plasticity in the limbic forebrain, promoting the notion that these drugs may blunt dysregulated reward processes in BD by counteracting neuronal plasticity deficits.

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1. Introduction

Bipolar disorder (BD) is a chronic, severe neuropsychiatric disorder characterized by alternating episodes of depression and mania (Belmaker, 2004). Current theories contend that BD could be better conceptualized in the general context of disorders of neuroplasticity (Manji and Chen, 2002; Schloesser et al., 2008; Szabo et al., 2009).

BD is characterized by heterogeneity in symptomatology, with patients often demonstrating dysregulated reward and motivation, which varies from anhedonia, during the depressive phase, to increased euphoria and searching for hedonic stimuli, during the manic phase (Abler et al., 2008; Diekhof et al., 2008). Several recent clinical studies utilizing functional neuroimaging techniques, demonstrated dysfunction of the brain reward circuitry that consists of structures innervated by the mesocorticolimbic dopaminergic system in bipolar patients (Abler et al., 2008; Diekhof et al., 2008).

Intracranial self-stimulation (ICSS) is a behavioral paradigm based on the discovery of Olds and Milner that rats will repeatedly press a lever to stimulate specific components of their brain reward circuit. The validity of this animal model has been corroborated by a number of different studies for the assessment of both rewarding and anhedonic effects of drugs or other physiological and pharmacological manipulations (Carlezon and Chartoff, 2007). Thus, ICSS has been used to study preclinically the elation and increased hedonistic drive endophenotype of BD (Mavrikaki et al., 2009). Indeed, the ICSS paradigm has previously been used to assess the acute effects of mood stabilizers on brain reward processes (Beguin et al., 2012; Cassens and Mills, 1973; Mavrikaki et al., 2009, 2010; Takigawa et al., 1994; Tomasiewicz et al., 2006).

Although there has been significant progress in research, especially in genetics, the exact neurobiological substrate of BD and the therapeutic mechanism of action of medications that are commonly used in the clinic, such as the mood stabilizer lithium chloride (LiCl) and the atypical antipsychotic and antimanic agent aripiprazole, have not been clearly defined (Derry and Moore, 2007; Leng et al., 2008; Newberg et al., 2008). Lithium affects multiple intracellular targets, either directly or indirectly, including inhibition of protein kinase A (PKA) and protein kinase C (PKC) (Du et al., 2004a; Quiroz et al., 2004; Szabo et al., 2009). In contrast, aripiprazole acts as a partial D_2/D_3 and 5-HT_{1A} receptor agonist, and 5-HT_2 receptor antagonist (Fleischhacker, 2005; Shapiro et al., 2003). Despite their different mechanism of action, both drugs have been shown to be efficient antimanic agents. Thus, the comparative study of their effects in a behavioral model of brain reward and on related intracellular targets may delineate unknown aspects of their therapeutic mechanism of action as mood stabilizing and antimanic drugs.

The cyclic AMP-responsive element binding protein (CREB) is a post-translationally activated transcription factor, following phosphorylation in Ser133 that has been implicated in numerous brain functions, including the neuronal adaptation to chronic administration of psychotropic compounds (Liang et al., 2008; Sakamoto et al., 2011). The glutamatergic system plays a pivotal role in synaptic plasticity and associated phenomena, such as the induction of long-term potentiation (LTP) and long-term depression (LTD) (Lee, 2006; Zhuo, 2009). Furthermore, it has been demonstrated that disruption of the bidirectional pathway of neuronal activity in relation to trafficking of the ionotropic glutamatergic receptors, AMPA and NMDA, could be associated with neuropsychiatric disorders (Gao and Wolf, 2008). Recent research is focused on post-translational modifications of the AMPA/NMDA receptor subunits (Mao et al., 2011). Thus, AMPA receptor trafficking requires phosphorylation of GluA1 subunit at the Ser845 site by PKA (Du et al., 2004a). This phosphorylation is required for the insertion of new AMPA receptors in the synapse (Du et al., 2004a), while activity-dependent insertion of new AMPA receptors also demands phosphorylation of the GluA1 subunit at the Ser831 site by PKC and calmodulin-dependent protein kinase II (CaMKII) (Du et al., 2007; D. Liao et al., 2001). Dephosphorylation of GluA1 at the Ser845 site leads to clathrin-coated dependent endocytosis of synaptic AMPA receptors (Kameyama et al., 1998; Lee et al., 2000, 1998). The insertion of new NMDA receptors in the synapse requires phosphorylation of the NA1 subunit at the Ser890 and Ser896 sites by PKC and the Ser897 site by PKA (Lau and Zukin, 2007). Also, phosphorylation of Tyr1472 on the NA2B subunit by Fyn is involved in NMDA receptor trafficking and synaptic plasticity (Lau and Zukin, 2007). More specifically, the dephosphorylation of Tyr1472 on the NA2B subunit promotes clathrin-coated endocytosis of NMDA receptors (Lau and Zukin, 2007). Furthermore, phosphorylation of the NA2B subunit at the Ser1303 site by PKC or CaMKII seems to regulate the maximum conductance of NMDA receptor (G.Y. Liao et al., 2001). Although previous studies have shown that LiCl affects some of the aforementioned phosphorylations of the AMPA/NMDA receptors, the corresponding effects of aripiprazole are largely unknown. Considering the multiple side effects, including toxicity, of LiCl and the limited efficacy of aripiprazole, there is a dire need for novel therapies with fewer side effects and better efficacy. In this regard, comparison of the already existing pharmacotherapies could indicate some key common elements and distinguishing features that could be utilized in the discovery and development of new and improved drugs for the treatment of BD.

This study was designed to assess the effects of acute and chronic administration of LiCl and aripiprazole on brain stimulation reward (BSR) and molecular markers of neuroplasticity in distinct regions of the limbic forebrain. For the behavioral studies we utilized the ICSS paradigm in rats. In separate experiments in rats, immunoblotting was performed to study phosphorylation levels of CREB at the Ser133 site, GluA1 subunit at the Ser831 and Ser845 sites, as well as NA1 subunit at the Ser896 and Ser897 sites and NA2B subunit at the Ser1303 and Tyr1472 sites in the prefrontal cortex (PFC) and ventral (vSTR).

2. Experimental procedures

2.1. Animals and treatments

Male Sprague-Dawley rats (5–8 per group) weighing 280–320 g were used. LiCl (Sigma-Aldrich, St. Louis, MO, U.S.A.) was dissolved in 0.9% NaCl and aripiprazole (Abilify®, Otsuka Pharmaceutical Europe, Ltd.) was diluted in sterile water. All drugs were injected intraperitoneally (i.p.) at a volume of 1 mg/kg of body weight. Experiments were conducted in accordance with the European