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Antimanic-like activity of candesartan in mice: Possible involvement of antioxidant, anti-inflammatory and neurotrophic mechanisms

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Abstract
Activation of the brain angiotensin II type 1 receptor (AT1R) triggers pro-oxidant and pro-inflammatory mechanisms which are involved in the neurobiology of bipolar disorder (BD). Candesartan (CDS) is an AT1 receptor antagonist with potential neuroprotective properties. Herein we investigated CDS effects against oxidative, neurotrophic inflammatory and cognitive effects of amphetamine (AMPH)-induced mania. In the reversal protocol adult mice were given AMPH 2 mg/kg i.p. or saline and between days 8 and 14 received CDS 0.1, 0.3 or 1 mg/kg orally, lithium (Li) 47.5 mg/kg i.p., or saline. In the prevention treatment, mice were pretreated with

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CDS, Li or saline prior to AMPH. Locomotor activity and working memory performance were assessed. Glutathione (GSH), thiobarbituric acid-reactive substance (TBARS) and TNF-α levels were evaluated in the hippocampus (HC) and cerebellar vermis (CV). Brain-derived neurotrophic factor (BDNF) and glycogen synthase kinase 3-beta (GSK-3beta) levels were measured in the HC. CDS and Li prevented and reversed the AMPH-induced increases in locomotor activity. Only CDS prevented and reversed AMPH-induced working memory deficits. CDS prevented AMPH-induced alterations in GSH (HC and CV), TBARS (HC and CV), TNF-α (HC and CV) and BDNF (HC) levels. Li prevented alterations in BDNF and phospho-Ser9-GSK3beta. CDS reversed AMPH-induced alterations in GSH (HC and CV), TBARS (HC), TNF-α (CV) and BDNF levels. Li reversed AMPH-induced alterations in TNF-α (HC and CV) and BDNF (HC) levels. CDS is effective in reversing and preventing AMPH-induced behavioral and biochemical alterations, providing a rationale for the design of clinical trials investigating CDS's possible therapeutic effects.

1. Introduction

Although advances have been made, understanding of the pathophysiology of BD remains elusive. Animal models have been important tools for investigating BD neurobiology and novel treatment approaches (Young et al., 2011). The pharmacological animal model of mania induced by D-amphetamine (AMPH) is associated with behavioral and biochemical manifestations including oxidative imbalance, mitochondrial damage and alterations in neuroplasticity (Frey et al., 2006b) which resemble BD pathophysiology (Berk et al., 2011).

Postmortem brain and clinical studies have demonstrated peripheral as well as central nervous system alterations in diverse parameters of oxidative stress and antioxidant enzymes (Andreazza et al., 2008), including decreased levels of glutathione (GSH) and increased thiobarbituric acid reactive substance (TBARS), a marker of lipid peroxidation. Deficits in GSH result in oxidative imbalance and subsequent oxidation of phospholipids, proteins, and DNA (Kulak et al., 2013).

Involvement of inflammatory mechanisms and neuroimmune alterations is seen in the pathophysiology of BD (Berk et al., 2011). Immune disturbances have been related to the severity and recurrence of mood episodes, illness progression, cognitive dysfunction and higher rates of comorbidities (Berk et al., 2011). Accordingly, increased peripheral levels of pro-inflammatory cytokines have been reported at differing stages of the illness, such as IL-6 and TNF-α, during depressive episodes as well as IL-2, IL-4, IL-6 and TNF-α in mania when compared with euthymic patients and healthy subjects (Kim et al., 2007). To date, as far as we know no studies have evaluated alterations in TNF-α levels in animals submitted to the AMPH-induced model of mania.

Neurotrophic signaling pathways are also compromised in BD and, in this regard, brain-derived neurotrophic factor (BDNF) and glycogen synthase kinase 3-beta (GSK-3beta) are two important targets related to this pathway (Picchini et al., 2004). Serum BDNF is reduced in BD during manic and depressive episodes when compared and euthymic patients and healthy controls, even in drug-naive patients (de Oliveira et al., 2009). This neurotrophin is also decreased in discrete brain areas of AMPH induced animal models of mania (Frey et al., 2006a; Macêdo et al., 2012). Regarding GSK-3beta, a growing body of evidence indicates a link between this kinase and the therapeutic effects of mood stabilizers (Gould and Manji, 2005). Lithium inhibits GSK-3beta both directly and indirectly, and these mechanisms may be related to the neuroprotective effects of this mood stabilizer (Picchini et al., 2004).

There are substantial unmet needs in the pharmacotherapy of BD. For example, the chronic use of the classical mood stabilizer lithium is related to insufficient response, unwanted side effects, i.e. renal and thyroid dysfunction, subtle emotional and cognitive impairment and weight gain (Licht, 2012). There are few available treatments for the management of cognitive dysfunction in BD (Dean et al., 2012). This reinforces the need for genuinely novel pharmacotherapies for BD.

The last decade had witnessed an increased interest in the study of the brain renin–angiotensin system (RAS) (McKinley et al., 2003). This system is related to pro-inflammatory and pro-oxidant effects in brain areas related to mood regulation, such as the hippocampus (Bild et al., 2013). Angiotensin II (AngII) receptor blockers (ARBs) are pleiotropic agents with anxiolytic (Saavedra et al., 2006) and neuroprotective activities (Yagi et al., 2013). Additionally these substances present antioxidant action (Bild et al., 2013) as well as up-regulate BDNF levels (Kishi et al., 2012).

Based on the reported psychopharmacological effects of ARBs, we recently hypothesized that these agents may provide a novel treatment opportunity for the prevention and/or treatment of BD (de Gois Queiroz et al., 2013). Noteworthy, there is an excess burden of cardiovascular risk factors in BD patients compared to the general population (Kilbourne et al., 2004). Furthermore, in many forms of experimental hypertension, the neuropeptide AngII as well as components of the intrinsic brain RAS presents with an increased expression and activity (Veerasingham and Raizada, 2003). There is limited data to suggest a higher rate of hypertension in BD than the general population (Kilbourne et al., 2004). In keeping with this view the RAS system may play a role in the shared biology linking BD to cardiovascular morbidity.

Thus, based on the preclinical and neuroprotective effects of ARBs (Lu et al., 2005), in the present study we aimed to investigate the effects of the AngII type 1 receptor antagonist candesartan (CDS) against behavioral (hyperlocomotion and cognitive deficits) and neurochemical (oxidative imbalance, increase in TNF-α levels and decrement in

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