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Transcranial direct current stimulation improves short-term memory in an animal model of attention-deficit/ hyperactivity disorder

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Abstract
Attention deficit hyperactivity disorder (ADHD) is characterized by impairing levels of hyperactivity, impulsivity and inattention. However, different meta-analyses have reported disruptions in short and long-term memory in ADHD patients. Previous studies indicate that mnemonic dysfunctions might be the result of deficits in attentional circuits, probably due to ineffective dopaminergic modulation of hippocampal synaptic plasticity. In this study we aimed to evaluate the potential therapeutic effects of a neuromodulatory technique, transcranial direct current stimulation (tDCS), in short-term memory (STM) deficits presented by the

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spontaneous hypertensive rats (SHR), the most widely used animal model of ADHD. Adult male SHR and Wistar Kyoto rats (WKY) were subjected to a constant electrical current of 0.5 mA intensity applied on the frontal cortex for 20 min/day during 8 days. STM was evaluated with an object recognition test conducted in an open field. Exploration time and locomotion were recorded, and brain regions were dissected to determine dopamine and BDNF levels. SHR spent less time exploring the new object when compared to WKY, and tDCS improved object recognition deficits in SHR without affecting WKY performance. Locomotor activity was higher in SHR and it was not affected by tDCS. After stimulation, dopamine levels were increased in the hippocampus and striatum of both strains, while BDNF levels were increased only in the striatum of WKY. These findings suggest that tDCS on the frontal cortex might be able to improve STM deficits present in SHR, which is potentially related to dopaminergic neurotransmission in the hippocampus and striatum of those animals.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a disorder characterized by hyperactivity, impulsivity and inattention (Biederman and Faraone, 2002). Its pathophysiology, although not fully understood, involves alterations in the dopaminergic transmission, mainly in the mesocorticolimbic system (Biederman and Faraone, 2002), together with reduced activation in fronto-basal ganglia networks (Hart et al., 2013).

Different meta-analyses have reported that ADHD patients have disruptions in short and long-term memory (Hervey et al., 2004; Skodzik et al., 2013). Studies have not identified hippocampal structural or functional changes in those patients (Ellison-Wright et al., 2008; Valera et al., 2007), even though this region is one of the most important for declarative memory consolidation (Kandel et al., 2014). Since the encoding of information is dependent on the activity of attentional circuits (Kentros et al., 2004; Muzzio et al., 2009), long-term deficits in ADHD might be related to attentional deficits (Skodzik et al., 2013). The influence of attention on the encoding of information is probably due to dopaminergic modulation of hippocampal synaptic plasticity (Kentros et al., 2004; Li et al., 2003; O'Carroll et al., 2006; Rossato et al., 2009), suggesting an involvement of the dopaminergic system in ADHD mnemonic problems.

The spontaneous hypertensive rats (SHR) are the most widely accepted animal model of ADHD (Sagvolden et al., 2005). They present dysregulations in fronto-basal ganglia connectivity that seems to be related to abnormal dopaminergic signaling (Sagvolden et al., 2005). These animals also present deficits in short and long-term memory (Meneses et al., 2011; Pandolfo et al., 2013; Pires et al., 2009; Prediger et al., 2005a, 2005b), both improved with modulation of dopaminergic systems. Mnemonic deficits in SHR support this lineage as a suitable model in the study of memory disruptions found in ADHD patients.

Transcranial direct current stimulation (tDCS) is a technique that consists of applying a weak, constant, low intensity electric current between two electrodes over the scalp in order to modulate cortical excitability (Nitsche and Paulus, 2000). Anodal stimulation increases neuronal activity while cathodal stimulation inhibits it (Nitsche and Paulus, 2000). Many researchers have applied tDCS on the prefrontal cortex (PFC) in humans, and this approach seems to influence a wide array of brain functions, like working (Fregni et al., 2005) and declarative memory (Manenti et al., 2013). Concerning ADHD, however, we are not aware of previous studies examining the effects of tDCS on cognitive functions.

Bearing in mind that ADHD pathophysiology may involve inadequate modulation of frontal circuits, and that tDCS is able to modulate cortical excitability, we investigated the effects of tDCS in an animal model of ADHD, the SHR rats. The aim of the present study was to evaluate whether repeated tDCS applications over the frontal cortex might modify aberrant short-term memory (STM) (Pires et al., 2009) and hyperlocomotion (Sagvolden et al., 2005) seem in SHR. Brain-derived neurotrophic factor (BDNF) and dopamine (DA) levels were quantified due to its importance for the encoding of information (Leal et al., 2014; Rossato et al., 2009). We expected an improvement in STM and a reduction in the locomotion, together with an increase in BDNF and DA mainly in the hippocampus.

2. Experimental procedures

2.1. Animals

Adults (60 days old) male WKY (n=20) and SHR (n=28) rats, weighing 220–350 g, from our own colony were used. They were kept in groups of five animals per cage, maintained in a room under controlled temperature (22±2), on a standard 12 h light/dark cycle. Animals had access to water and chow ad libitum. All experiments and procedures were approved by the Institutional Committee for Animal Care and Use (GPPG-HCPA protocol no. 14-0103) and performed in accordance with the Guide for the Care and Use of Laboratory Animals 8th edition (2011). The maintenance of the animals followed the law 11.794 (Brazil), which establishes procedures for the scientific use of animals. The experiment used the number of animals necessary to produce reliable scientific data.

2.2. Experimental design

Rats were habituated to the maintenance room for 1 week before the experiment started. After this period, animals from