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Olfactory bulbectomy in mice triggers transient and long-lasting behavioral impairments and biochemical hippocampal disturbances

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ABSTRACT

Major depressive disorder (MDD) is a neuropsychiatric disease that is associated with profound disturbances in affected individuals. Elucidating the pathophysiology of MDD has been frustratingly slow, especially concerning the neurochemical events and brain regions associated with disease progression. Thus, we evaluated the time-course (up to 8 weeks) behavioral and biochemical effects in mice that underwent to a bilateral olfactory bulbectomy (OBX), which is used to modeling depressive-like behavior in rodents. Similar to the symptoms in patients with MDD, OBX induced long-lasting (*e.g.*, impairment of habituation to novelty, hyperactivity and an anxiety-like phenotype) and transient (*e.g.*, loss of self-care and motivational behavior) behavioral effects. Moreover, OBX temporarily impaired hippocampal synaptosomal mitochondria, in a manner that would be associated with hippocampal-related synaptotoxicity. Finally, long-lasting pro-oxidative (*i.e.*, increased levels of reactive oxygen species and nitric oxide and decreased glutathione levels) and pro-inflammatory (*i.e.*, increased levels of pro-inflammatory cytokines IL-1, IL-6, TNF-α and decreased anti-inflammatory cytokine IL-10 levels) effects were induced in the hippocampus by OBX. Additionally, these parameters were transiently affected in the posterior and frontal cortices. This study is the first to suggest that the transient and long-lasting behavioral effects from OBX strongly correlate with mitochondrial, oxidative and inflammatory parameters in the hippocampus; furthermore, these effects show a weak correlation with these parameters in the cortex. Our findings highlight the underlying mechanisms involved in the biochemical time course of events related to depressive behavior.
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1. Introduction

Major depressive disorder (MDD) is a chronic and heterogeneous neuropsychiatric disease with a variable course and extremely high worldwide prevalence and incidence (Belmaker and Agam, 2008; Mann, 2005; Vos et al., 2012). This disorder is characterized by profound disturbances in emotional regulation, motivation, social cognition and other systemic physiological aspects that result in a poor quality of life and disability (Belmaker and Agam, 2008; Black et al., 2016). The treatment for depressive patients commonly includes a combination of psychotherapy and pharmacotherapy (Karyotaki et al., 2016); however, despite the recent advances in antidepressive drug development, more than 30% of patients do not benefit from conventional antidepressant treatments and remain with persistent symptomatology that leads to a chronic disease state (Balestri et al., 2016; Berton and Nestler, 2006). Progress in understanding the pathophysiology of major depression has been frustratingly slow (Berton and Nestler, 2006; Kim et al., 2016). Impairments in cognitive functioning (Black et al., 2016; Bora et al., 2013) and evidence of neurodegenerative symptomatology in patients with MDD (Hurley and Tizabi, 2013; Kim et al., 2016) highlight the importance of identifying the molecular pathways that contribute to the progressive nature of this disorder. The pathogenesis and temporal course of the disorder is complex and variable; thus, modeling human depressive abnormalities in animals is extremely challenging but could significantly contribute to a better understanding of the mechanisms associated with the disease (Nestler and Hyman, 2010).

Abbreviations: MDD, major depressive disorder; OBX, olfactory bulbectomy; CNS, central nervous system; OFT, open field test; i.p., intraperitoneal; ΔΨ, mitochondrial membrane potential; FL1-H, mitochondrial mass fluorescence intensity; FL3-H, mitochondrial membrane potential fluorescence intensity; ROS, reactive oxygen species; GSH, glutathione.

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In this context, the bilateral olfactory bulbectomy (OBX) has garnered attention as an animal model of depression (Hendriksen et al., 2015; Kelly et al., 1997; Song and Leonard, 2005). This model is based on the hypothesis that removal of the olfactory bulbs, which are part of the limbic system, affects their extensive efferent neuronal networks and disturbs the connection and function of the whole limbic system (Song and Leonard, 2005). The limbic circuit is essential for the maintenance of mood, emotional and memory components of behavior; thus, OBX induces depressive-like behaviors (Czeh et al., 2015; Hendriksen et al., 2015). Prominent behavioral changes that resemble the symptomatology observed in MDD patients (Hendriksen et al., 2015; Kelly et al., 1997; Song and Leonard, 2005) are apparent in the OBX animal model of depression, including anhedonia (Freitas et al., 2012) (*e.g.*, an impairment in self-care and motivational behavior), increased sensitivity to stressful environments (Hendriksen et al., 2015; Song and Leonard, 2005; Zueger et al., 2005) (*e.g.*, hyperactivity in the open field test), enhanced irritability (Song and Leonard, 2005) (*e.g.*, increased murecidal behavior and territorial aggression), and memory and cognition impairments (Holubova et al., 2016) (*e.g.*, deficits in the passive avoidance test and Morris water maze). Moreover, anatomical, cellular and biochemical changes similar to those observed in MDD patients were found in the central nervous system (CNS) of rodents that underwent an OBX, including a reduction in hippocampal volume (Wrynn et al., 2000), changes in synaptic strength (Czeh et al., 2015), impairments in mitochondrial metabolism (Rinwa et al., 2013), increased oxidative/nitrosative stress and inflammatory markers (Holzmann et al., 2015; Yang et al., 2014), and enhanced cell death (Gomez-Climent et al., 2011; Jarosik et al., 2007). Importantly, the chronic treatment of animals with antidepressants reverses the behavioral phenotypes and anatomical, cellular and biochemical changes induced by OBX (Freitas et al., 2012; Hendriksen et al., 2015; Song and Leonard, 2005). These data support the use of OBX as an important animal model to investigate the pathophysiology of MDD.

Similar to many other psychiatric disorders, the neurochemical mechanisms involved in the progression of MDD remain elusive. The time course of changes in the brain that accompany long-lasting depressive behaviors in patients is unclear. However, parallel to the progress made in the depression field, substantial data presented in the literature show that neuroinflammation plays an important role in MDD (Barnes et al., 2016; Maes et al., 2011a). Patients with major depression exhibit all of the cardinal features of inflammatory response in peripheral blood and in cerebrospinal fluid (CSF), including increased expression of pro-inflammatory cytokines, as well as their receptors in brain tissue (post mortem). It is, accompanied by a significant imbalance in the redox homeostasis, leading to a high functional damage in intracellular signaling molecules, and could influence the neuronal, astrocytic and microglial homeostasis, contributing to the neurodegenerative processes presented in the MDD (Barnes et al., 2016; Haroon and Miller, 2017; Maes et al., 2011a,b; Miller and Raison, 2016). Interestingly, OBX appears to be suitable animal model to explore the brain mechanisms associated with chronic depressive behaviors. Indeed, the OBX-induced disruption of neuronal connections between the olfactory bulbs and other brain regions resembles the neurodegenerative events in patients with MDD (Hendriksen et al., 2015). The majority of OBX studies focused mainly in two different time points (2 and/or 4 weeks after OBX surgery). Thus, there is lack of information on longer time course of the behavioral and neurochemical changes induced by OBX. To identify the putative pathways that contribute to the progression of MDD, we evaluated for 8 weeks the effects of OBX in mice by assessing behavioral patterns (*i.e.*, hyperactivity, habituation to novelty and anhedonia) and neurochemical parameters (*i.e.*, brain mitochondrial, oxidative, nitrosative and inflammatory markers) in MDD-related brain areas (*i.e.*, hippocampus, posterior cortex and frontal cortex).

2. Material and methods

2.1. Animals

Male C57BL/6 mice (45–50 days old, 20–25 g) were obtained from Fundação Estadual de Produção e Pesquisa do Rio Grande do Sul, Porto Alegre, Brazil. Animals were housed 5 per cage and housed in a room under a 12-h/12-h light/dark cycle with a controlled temperature (22 ± 1 °C) and *ad libitum* access to food and water. The cages were placed in the experimental room 24 h prior to behavioral tests, for acclimatization. All experiments were completed between 2:00 and 6:00 pm. All procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the local Ethics Committee (project number 24577). All efforts were made to minimize animal suffering and the number of animals used in the experiments.

2.2. Experimental schedule

To evaluate the long-term behavioral and neurochemical changes in an OBX model of depression, we designed 3 experimental schedules according to the time after surgery: 2 weeks (2W), 4 weeks (4W) and 8 weeks (8W). Naïve animals underwent an open field test (OFT) 1 day before the OBX (OFT1) to verify their baseline exploratory activity and discard any animals with behavioral abnormalities. Next, the animals were assigned to the Sham (mice that underwent the surgical procedure, but bulbs were left intact) or OBX (mice that underwent OBX) group.

The experimental scheme for the animals evaluated for 2 weeks after surgery (2W) is depicted in Fig. 1A. Accordingly, 2 weeks after surgery, the mice underwent a second OFT (OFT2). Two hours later, the mice underwent the splash test. The mice were anesthetized and euthanized the following day, and brain samples were collected. Fig. 1B shows the experimental schedule for animals evaluated for 4 weeks after surgery (4W). Two weeks after surgery, the mice underwent OFT2. A third OFT was completed 4 weeks after surgery (OFT3). The mice were submitted to the splash test 2 h after OFT3. On the following day, the mice were anesthetized and euthanized for sample collection. Fig. 1C shows the experimental schedule for animals evaluated for 8 weeks after surgery (8W). The schedule was similar to the 4W group, except OFT3 was performed 8 weeks (instead of 4 weeks) after surgery.

2.3. Bilateral olfactory bulbectomy (OBX)

2.3.1. Surgical procedure

The bilateral OBX was performed as previously described (Freitas et al., 2012) with minor modifications. Briefly, mice were anaesthetized via an intraperitoneal (i.p.) injection of xylazine (6 mg/kg) and ketamine (100 mg/kg) diluted in saline. The head was shaved and a burr hole (approximately 2 mm in diameter) was made in the skull above the olfactory bulbs 4 mm rostral to bregma. Both olfactory bulbs were then dissected with surgical micro scissors and removed by suction with a glass Pasteur pipette. Animals were excluded from the study if the bulbs were not completely removed or the frontal cortex was injured (Freitas et al., 2012).

2.4. Behavioral tests

2.4.1. Open field test (OFT)

The OFT was used as previously described (Zueger et al., 2005) to investigate locomotor/exploratory activity, habituation and anxiety. Mice were placed near the sidewall in a gray wooden box (50 × 50 × 50 cm, length × width × height) with a 200 lx white light intensity and then recorded individually for 10 min with a video-camera (positioned above and at *ca.* 90° to the square arena) that was connected to a monitor. The behavioral performance of mice was analyzed using the AnyMaze®

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