ARTICLE IN PRESS

European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

The olfactory bulbectomy model in mice and rat: One story or two tails?

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ARTICLE INFO

Article history:
Accepted 9 October 2014

Keywords:
Antidepressant
Cognitive decline
Neurodegeneration
Species-specific
Animal model
Rodent

ABSTRACT

Olfactory bulbectomy (OBX), the surgical removal of the olfactory bulbs, lead, both in mice and rats, to a specific set of behavioral changes in social behavior, cognitive function and activity. The latter is often used as a readout measure to predict antidepressant effects of new compounds. More recently, the model is used to study neurodegeneration and the associated cognitive decline. Although most of the OBX-induced behavioral and neurochemical changes seen in mice and rats are very similar, there are also some remarkable differences. For instance, OBX has different effects on BDNF and the 5-HT$_{2c}$ receptor of these two species. These species differ also in how they respond to certain treatments after OBX. In this review we describe these species-specific differences and discuss what they may mean in terms of translational value.

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1. Introduction

Surgical removal of the olfactory bulbs (OBX) in rats or mice leads to a number of behavioral, cognitive and neurochemical changes. The OBX-paradigm is often used as a pharmacological model for predicting antidepressant efficacy. A wide range of known or presumed antidepressant drugs has been tested for their ability to normalize the typical hyperactivity that results from removal of the olfactory bulbs. Whether the underlying neurobiological mechanisms of this model resemble the neurobiological state of depressed patients is still a matter of debate. But the overwhelming number of antidepressant drugs tested in this model, not only acting on the serotonin transporter (Cryan et al., 1998; Breuer et al., 2007; Roche et al., 2007) or the 5HT$_{1A}$ receptor (Borsini et al., 1997; Mar et al., 2000), but also on very diverse receptors like the dopamine D$_3$ receptor (Breuer et al., 2009a), the noradrenalin transporter (Harkin et al., 1999), the vassopressin V$_{1B}$ receptor (Breuer et al., 2009b; Iijima et al., 2014), the corticotropin-releasing factor receptor 1 (Chaki et al., 2004; Frisch et al., 2010) and the neuropeptide Y receptor 1 (Goyal et al., 2009) makes it a valuable tool for assessing the effects of novel antidepressant drugs.

Moreover, this model is also studied for the robust cognitive impairments it shows. These cognitive impairments are thought to be the result of the neurodegeneration secondary to removal of the olfactory bulbs. Both the abilities to acquire and to retrieve memory are impaired after OBX surgery. Although most OBX studies are done in rats, there are also an extensive number of studies done in mice. Most effects of OBX are comparable in both species. Most importantly, both species become hyperactive and have serious memory deficiencies after removal of the olfactory bulbs.

However, there is a difference between rats and mice in the way they respond to some types of antidepressant treatment but also in the recovery of learning and memory deficiencies.

The differences in the effects of OBX between rats and mouse may have implications for the translation of the results to the human patient.

It might be less valid to extrapolate results from a species that shows a high potential to recover from severe neurodegeneration, because this seems less related to the human condition. On the other hand, studying such species-specific differences in the ability to recover from neurodegenerative processes, might eventually lead to a better understanding of how we may promote regeneration in the human brain.

2. Brief history of the olfactory bulbectomy model

In 1971, Marks et al. investigated rats with bilateral lesions of the olfactory bulbs to evaluate the effect of anosmia on learning performance. A little bit later, a clear impairment in passive avoidance learning after olfactory bulbectomy (OBX) was reported (Thomas, 1973). Further studies showed other OBX induced behavioral changes in sexual behavior (Sato et al., 1974; Larsson, 1975; Pollak and Sachs, 1975), in food intake and the preference for food (Leung et al., 1972; Larue, 1975), in the effects of handling (Loyber et al., 1977), and in maternal care (Schwartz and Rowe, 1976). In 1976, Van Riezen et al.

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http://dx.doi.org/10.1016/j.ejphar.2014.10.033
0014-2999/© 2014 Published by Elsevier B.V.

Please cite this article as: Hendriksen, H., et al., The olfactory bulbectomy model in mice and rat: One story or two tails? Eur J Pharmacol (2014), http://dx.doi.org/10.1016/j.ejphar.2014.10.033

speculated that the behavioral changes of olfactory bulbectomized rats could be used to detect novel anti-depressants (van Riezen et al., 1976) and a year later the olfactory bulbectomized rat was presented as a model for depression and the detection of anti-depressant efficacy (van Riezen et al., 1977; Wren et al., 1977).

After its proposal as a pharmacological predictive model for antidepressants, the research expanded further in this direction. The brain chemistry of the animals (Tonnaer et al., 1980) was further examined and the list of tested antidepressants grew. Currently the OBX-model is used both as a pharmacological predictive test for antidepressant efficacy of drugs as well as a model to study cognitive decline and neurodegeneration.

3. Technical procedure

The procedure for surgical removal of the olfactory bulbs of rodents has been described by different groups. The methods used show little variation. Animals are anesthetized with either isoflurane gas (Breuer et al., 2007) or injection anesthetic (Cairncross et al., 1977; van der Stelt et al., 2005) and subsequently placed in a stereotaxic instrument. An incision is made in the scalp above the olfactory bulbs, lidocaine (5%) is administered as local anesthetic to the periosteum (van der Stelt et al., 2005; Breuer et al., 2007). Two holes (2 mm in diameter) are drilled in the skull, 8 mm anterior to bregma and 2 mm from the midline of the frontal bone overlying the olfactory bulbs. Next, the olfactory bulbs are removed using a blunt hypodermic needle attached to a vacuum pump (van der Stelt et al., 2005; Breuer et al., 2007) or are excised using a sharp needle (Wang and Hull, 1980). Blood loss is prevented as much as possible by hemostatic sponges. Next the incision is sutured using resorbable material. Sham operated rats undergo the same procedure without removing the olfactory bulbs. Subcutaneous carprofen (5 mg/kg) is administered post operatively for relief of pain. Animals are allowed to recover for two weeks before further testing (Wang and Hull, 1980; Breuer et al., 2007). This two-week recovery period also allows for the completion of the OBX induced alterations in the rest of the brain. The procedure in mice is very similar (Nesterova et al., 1997; Hozumi et al., 2003).

4. Key features of the OBX model

4.1. Physiology

Some physiological parameters change after olfactory bulbectomy: circadian rhythmicity alters, nocturnal body temperature increases and heart rate decreases. These changes appear within days of the surgery (van Riezen and Leonard, 1990; Vinkers et al., 2009). OBX also induces a decrease in REM sleep (Sakurada et al., 1976). Interestingly, this effect could be normalized with acute administration of fluoxetine (Wang et al., 2012). In mice a shift in circadian rhythm was measured after OBX that could partly be normalized with chronic fluoxetine treatment. (Possidente et al., 1996). A study of (Wollnik, 1992) showed that fluoxetine had no effect on the circadian wheel-running rhythms of rats. This latter study, however, was performed with rats that had intact olfactory bulbs and it might well be that the effects of fluoxetine are more pronounced in animals that underwent OBX surgery than in intact animals.

4.2. Immunology

A number of changes in the immune system are observed after OBX-surgery. In rats, lower numbers of lymphocytes and reduced neutrophil phagocytosis (Cai and Leonard, 1994; Song et al., 1994) and increased macrophage and monocyte activity were found (Song et al., 1994; Song et al., 1996). Another remarkable change seen in the immune response of OBX rats is the attenuated production of interleukin (IL)-1beta and tumor necrosis factor (TNF) when challenged with lipopolysaccharide (LPS) (Connor et al., 2000). Whether similar changes happen in OBX mice is unknown. For a review on the changes in the immune system after OBX see (Leonard and Song, 2002). In mice, an OBX-induced reduction in Lyt2-positive suppressor T cells and an increase in L3T4-positive T helper cells ratio was seen, indicating a persistent activation of the immune system (Komori et al., 2002).

Whether a similar shift in T-lymphocytes occurs in rats following OBX is unknown.

4.3. Endocrinology

Changed activity of the hypothalamus after OBX surgery leads to increases in circular ACTH and corticosterone levels (Marcilhac et al., 1997; Marcilhac et al., 1999a; Breivik et al., 2006), suggested to underlie the enhanced sensitivity for mild stressors of OBX animals. Handling, for example, has a different effect on corticosterone levels in OBX animals compared to controls (Loyber et al., 1977). The higher hypothalamic activity is probably not the result of enhanced levels of hypothalamic CRF, but is more likely caused by higher levels of vasopressin secreted from the increased number of vasopressin positive cells in the external layer of the median eminence (Marcilhac et al., 1999b). In contrast a study with mice did not show increased serum corticosterone levels after bulbectomy (Machado et al., 2012). To complicate matters, also in OBX rats, increased corticosterone levels are not always found (Broekkamp et al., 1986).

4.4. Neurochemistry

The serotonin (5-HT) system seems to play a crucial role in the behavioral changes induced by OBX. 5-HT as well as its metabolite 5-hydroxyindole acetic acid (5-HIAA) are consistently decreased post-operatively. Changes in the serotonergic system are most prominent in the frontal cortex, nucleus accumbens, amygdala and dorsal hippocampus (Jancsar and Leonard, 1984; Redmond et al., 1997; Connor et al., 1999; van der Stelt et al., 2005). Not just the decreased levels, but in particular the imbalance in 5-HT synthesis between different brain areas is thought to be responsible for the typical behavioral features of the OBX model (Watanabe et al., 2003). Also in mice the serotonin system is affected. Less tryptophan hydroxylase and a decreased rate of 5-HT synthesis was found in bulbectomized mice (Neckers et al., 1975; Hellweg et al., 2007), while higher levels of 5-HT_2 receptors are reported (Gurevich et al., 1993).

The concentration of noradrenaline in the telencephalon also decreases after bulbectomy and at the same time the density of beta-adrenoceptors increases in the cortical areas (Jancsar and Leonard, 1984; van Riezen and Leonard, 1990).

The relation between the amount of damage to the olfactory bulb and the changes in noradrenalin (and dopamine) levels in the brain are well studied in rats by (Edwards et al., 1977). Only total bulbectomy with damage to the olfactory penduncle leads to a substantial decrease of noradrenalin in the telencephalon, whereas, partial bulbectomy (only two third of the olfactory bulbs damaged) leads to an increase of noradrenalin in the telencephalon. No significant effects on dopamine content were seen in this study. Unfortunately these authors did not investigate the effects of the partial bulbectomy on behavior.

In OBX mice higher noradrenaline levels in the hypothalamus (Yoshimura and Ueki, 1981) and reduced noradrenalin turnover in the prefrontal cortex (Kamei et al., 2007) have been measured. In rats post OBX levels of glutamate were reported to be lower only

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