Neuropharmacology 62 (2012) 2010–2017

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

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

Memantine partly rescues behavioral and cognitive deficits in an animal model of neurodegeneration

Yuliya Borre*, Esmeralda Bosman, Susan Lemstra, Koen G. Westphal, Berend Olivier, Ronald S. Oosting

Department of Pharmacology, Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute of Neuroscience, Utrecht University, Universiteitsweg 99, 3584 CG, Utrecht, Netherlands

ARTICLE INFO

Article history:
Received 29 July 2011
Received in revised form
5 December 2011
Accepted 26 December 2011

Keywords:
Memantine
Neurodegeneration
Olfactory bulbectomy
Memory
Learning
Glutamate
Neuroprotection

ABSTRACT

Memantine, a non-competitive NMDA receptor antagonist, is used for the treatment of Alzheimer's disease (AD) and off-label as an anti-depressant. Here we investigated possible anti-depressant, cognitive enhancing and neuroprotective effects of memantine in the olfactory bulbectomized (OBX) rat. OBX is used as a screening model for antidepressants and shows cognitive disturbances. In Experiment I, memantine treatment started 14 days after OBX surgery (this setup is similar to what we use for screening of potential antidepressants) and 2 days before surgery in experiment II. In both experiments, memantine (20 mg/kg, p.o) was administered once daily for 28 days. Animals were tested in the open field (locomotor activity), passive avoidance (fear learning and memory), and holeboard (spatial acquisition and memory) before and after the bulbectomy. Memantine, when administered before surgery, prevented OBX-induced hyperactivity and partly fear memory loss. These behavioral effects were present for at least 3 weeks after cessation of treatment. Memantine, however did not improve spatial memory. When administered 2 weeks after OBX surgery, memantine was ineffective in normalizing open field hyperactivity and improving cognitive deficits. Interestingly, after the animals were retrained in passive avoidance, memantine- treated OBX rats (both in experiment I and II) showed improved fear learning and memory. Our findings suggest that memantine has both neuroprotective and cognitive enhancing effects without antidepressant-like properties in the OBX rat. Based on our results, we propose that memantine may be more beneficial to AD patients when administered early in the disease process.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia (Hampel et al., 2010), is often accompanied by depressive symptoms (Lee and Lyketsos, 2003). In fact, a history of depression has been associated with an increased risk of developing AD (Green et al., 2003) and several antidepressants have been shown to improve some of the cognitive deficits in AD patients (Mossello et al., 2008; Keowkase et al., 2010).

Both in AD and depression, glutamatergic N-methyl-D-aspartate (NMDA) receptors are thought to play important roles in the pathologies of both AD and depression, where NMDA-receptor mediated excitotoxicity appears to be a critical step (Dong et al., 2009; Lipton, 2007). In addition, it has been suggested that NMDA-receptors are constantly active in AD, resulting in impaired neurotransmission (signal-to-noise ratio hypothesis) (Wenk, 2006; Parsons et al., 2007). Evidence for a potential role of NMDA receptors in major depression comes, among others, from post-mortem studies in which changes in NMDA receptor levels in patients were detected and from studies in which the NMDA receptor antagonist ketamine has fast-acting anti-depressant effects (Hashimoto, 2009).

Memantine is a voltage-dependent NMDA receptor antagonist and is used for the treatment of moderate-to-severe AD. Clinical trials have demonstrated cognitive and behavioral improvements already after a few weeks of treatment (Gauthier et al., 2005; Schulz et al., 2011 and Peskind et al., 2006). Memantine is also used off-label anti-depressant, but its efficacy remains a matter of debate (Zdanys and Tampi, 2008). Animal studies clearly demonstrate that memantine has a broad range of effects. For example, it reverses the recognition memory deficits in aged rats (Pieta Dias et al., 2007) and enhances spatial memory in healthy animals (Minkeviciene et al., 2008). While some studies report improved spatial cognition by memantine, others report memantine-induced cognitive deficits or no effect on spatial memory (Creeley et al., 2006; Quan et al., 2011). Furthermore, memantine has been shown to reduce

* Corresponding author. Tel.: +31617432753.
E-mail addresses: yborre@gmail.com, y.e.borre@uu.nl (Y. Borre).

0028-3908/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2011.12.034

anxiety and display antidepressant-like effects in animals (Minkeviciene et al., 2008; Rogóz et al., 2002; Réus et al., 2010).

In addition to directly blocking NMDA receptors (Lipton, 2006; Xia et al., 2010 and Parsons et al., 2007), memantine may elicit its (neuroprotective) effects by attenuating neuroinflammation (Rosi et al., 2006 and Wu et al., 2009) and by stimulating the release of neurotrophic factors (Wu et al., 2009; Meisner et al., 2008 and Marvanová et al., 2001).

In the present study, we used the olfactory bulbectomized (OBX) rat as an animal model for neurodegeneration, cognitive decline and depression-related symptoms. In literature, the OBX rat is primarily known as a model for predicting anti-depressant activity, because its hyperactivity is normalized following chronic and not acute administration of an anti-depressant (Breuer et al., 2007 and Song and Leonard, 2005). Furthermore, OBX has been reported to decrease hippocampal neurogenesis, a putative pathogenic mechanism in depression (Koo et al., 2010) and AD (Thompson et al., 2008). In addition, OBX animals model important aspects of Alzheimer's disease, such as hippocampus-dependent learning and memory deficits, impaired hippocampal long-term potentiation, disrupted synaptic density (Hozumi et al., 2003; Jarosik et al., 2007; Moriguchi et al., 2006; Norrholm and Ouimet, 2001; Ostrovskaya et al., 2007; Song and Leonard, 2005) and increased levels of beta-amyloid protein in neocortex and hippocampus (Aleksandrova et al., 2004). Importantly, these OBX-induced cognitive and behavioral impairments are independent of anosmia (Van Riezen et al., 1977; Klein and Brown, 1969). The olfactory bulb projects to different brain areas, including various cortical regions, the amygdala and the hippocampus (Song and Leonard, 2005). Ablation of the olfactory bulbs results in neurodegeneration in these projection areas (Song and Leonard, 2005), possibly explaining the OBX-induced behavioral changes. Moreover, drugs approved for the treatment of AD, such as cholinesterase inhibitor were reported to alleviate cognitive impairments induced by OBX (Hozumi et al. 2003; Yamamoto et al. 2010), providing the model pharmacological validation with respect to AD. Thus, the OBX model may also be useful for modeling (early) Alzheimer's disease with depressive symptoms.

In this study, we used OBX rats to investigate whether memantine has antidepressive-like, cognition-enhancing and/or neuroprotective properties. We performed two different experiments: In experiment I, we started with the chronic drug treatment 14 days post OBX surgery (this setup is similar to what we use for screening potential antidepressants (Breuer et al., 2007)). In Experiment II, aimed to investigate possible neuroprotective effects, memantine treatment started 2 days before OBX surgery. Rats were tested at several time points during and after drug administration in the open field (assessing locomotor activity of the animals), passive avoidance (a task assessing fear memory) and holeboard (a task assessing spatial and reference memory) paradigms.

2. Methods and materials

All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to in vivo techniques, if available.

2.1. Animals and surgery

Male Sprague-Dawley rats (Harlan, Zeist, The Netherlands) weighing between 180 and 220 g upon arrival were used for this experiment. Animals were on a 12-h light/dark cycle, with lights coming on at 7.00 am. Food and water were available *ad libitum* unless specified otherwise.

Olfactory bulbectomy surgery was performed as previously described (Breuer et al., 2007). At the end of the experiment, the animals were sacrificed; their brains were removed and bilateral olfactory bulb ablation verified. All OBX surgeries were performed correctly that there were no animals with partial bulbectomies or damaged prefrontal cortices. Control animals received sham surgery. All experiments were performed in accordance with the Dutch guidelines for care and use of laboratory animals and were approved by the Ethical Committee for Animal Research of Utrecht University, Utrecht, The Netherlands.

2.2. Drug administration

Memantine at 20 mg/kg or water was orally administered (2 ml/kg) in both experiments. The drug was manufactured by Lundbeck (Denmark) and obtained in solution from a local pharmacy. In Experiment I, memantine administration started 14 days post-surgery for 28 days. In Experiment II, memantine administration started 2 days prior to the OBX surgery and continued for 28 days.

2.3. Behavioral testing

Animals were tested repeatedly over time in several behavioral tests. The order of the behavioral tests is shown in Fig. 1.

2.3.1. Total activity and time spent in the center in the open field

Total activity and time spent in the center in the open field (92 × 92 × 40 cm) was automatically tracked (TSE system, Germany) for 5 min. The light intensity was 20 lux at floor level. Previous experiments in our lab (Breuer et al., 2007, 2009) demonstrated that the OBX-induced hyperactivity is a long-term stable phenomenon and does not result in adaptation to the open field arena.

2.3.2. Step-through passive avoidance (PA)

Step-through Passive avoidance (PA) task was performed as previously described (Douma et al., 2011) with minor modifications. During the acquisition trials, animals were placed in the light compartment and the latency time to enter the dark compartment with all four feet was determined in seconds. Once the animal entered the dark compartment, the door was closed and an electric shock (0.6 mA) was delivered for 3 s. Immediately after the shock, the animals were removed and placed back into their home cage. During the retention trials, the animals were placed in a light compartment and the latency time to enter the dark compartment was measured. To ensure that all animals learned the task (OBX animals may have reduced pain sensitivity (Wang et al., 2010), a retention trial was given 5 min after the first acquisition trial during which the animals had to remain in the light compartment for 60 s. If an animal entered the dark compartment within this period, it received another 3 s shock of 0.6 mA and immediately placed back in his home cage. Five minutes later another acquisition trial was performed. This procedure was repeated until the acquisition criteria were reached. All animals learned the task within 3 trials.

In both experiments, the animals were retrained in the PA task several weeks after surgery (Fig. 1). Five minutes after retraining an acquisition trial (with a cut-off time of 60 s) was performed to ensure that the animal had learned the task. If necessary, an animal was shocked until it reached the acquisition criteria.

2.3.3. Holeboard (HLB)

The holeboard apparatus (TSE systems, Germany) consisted of a 44 × 44 × 40 cm box with 16 equally spaced holes on the bottom in a 4 × 4 array. The holeboard paradigm was adapted from (Oades, 1981). Each rat was allowed to find a fixed set of 4 baited holes within 3 min. Once the rat had eaten the 4 pellets, it was removed from the apparatus. A week prior to the holeboard acquisition, animals were food restricted until they reached 85% of their body weight. Then 2 habituation trials were performed, during which the rats were habituated to the apparatus for 2 days with all 16 holes baited with one sucrose pellet. All animals ate the 16 food pellets during the second habituation day. Habituation was followed by 7 days of food search training with 4 holes baited in a fixed pattern. Number and frequency of hole visits were recorded and reference memory was calculated from the total number of visits to

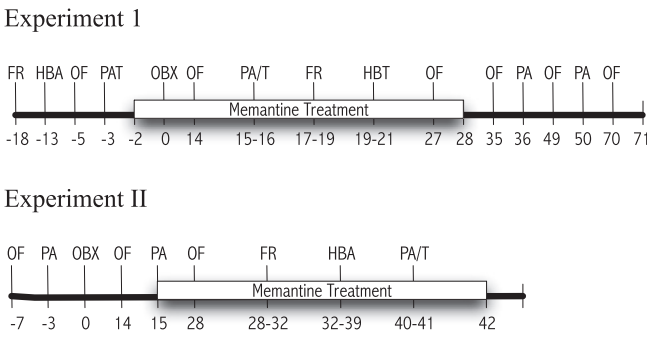

Fig. 1. Experimental layout. The day of OBX surgery is day 0. Each animal was tested in all paradigms. Abbreviations: FR: Food restriction; HBA: Holeboard acquisition; OF: open field; PAT: Passive avoidance training; PA/T: Passive avoidance test/retraining; PA: Passive avoidance test; HBT: Holeboard test.

Download English Version:

https://daneshyari.com/en/article/2493587

Download Persian Version:

https://daneshyari.com/article/2493587

Daneshyari.com