Behavioural Brain Research 297 (2016) 20–27

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Olfactory bulbectomy increases reinstatement of methamphetamine seeking after a forced abstinence in rats

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HIGHLIGHTS

- Further validation of an animal model of depression-addiction dual disorder.
- Olfactory bulbectomy increases reinstatement of METH seeking behavior.
- Forced abstinence is a valid translational approach to model drug relapse.

ARTICLE INFO

Article history:
Received 6 August 2015
Received in revised form
21 September 2015
Accepted 25 September 2015
Available online 22 October 2015

Keywords:
methamphetamine
self-administration
reinstatement
olfactory bulbectomy
depression
Sprague-Dawley rats

ABSTRACT

Drug addiction is commonly associated with depression and comorbid patients also suffer from higher cravings and increased relapse rate. To address this issue preclinically we combined the olfactory bulbectomy (OBX) model of depression and intravenous methamphetamine self-administration procedure in rats to assess differences in relapse-like behavior.

Male Sprague-Dawley rats were divided randomly into two groups; in one group the bilateral olfactory bulbectomy (OBX) was performed while the other group was sham operated. After recovery, intracardiac catheter was implanted. Intravenous self-administration procedure was conducted in operant boxes using nose-poke operandi (Coulbourn Instruments, Inc., USA) under fixed ratio 1 schedule of reinforcement. Methamphetamine was available at dose 0.08 mg/kg/infusion. After stable methamphetamine intake was maintained, a period of forced abstinence was initiated and rats were kept in their home-cages for 14 days. Finally, one reinstatement session was conducted in operant boxes with no drug delivery.

In the reinstatement session the mean of 138.4 active nose-pokes was performed by the OBX group, while the sham group displayed 41 responses, i.e. 140 % and 48 % of basal nose-poking during maintenance phase in OBX and sham operated group respectively. OBX group also showed significantly more passive nose-pokes indicating hyperactive behavioral traits in bulbectomized rats. However, the % of active operandum preference was equal in both groups.

Olfactory bulbectomy model significantly increased reinstatement of methamphetamine seeking behavior. This paradigm can be used to evaluate potential drugs that are able to suppress the drug-seeking behavior.

1. Introduction

The likelihood of drug addiction and depression to occur together in the same individual is approximately 5 times greater than what would be expected by the prevalence of each disorder alone [1,2] and leads to increased suicide rates among depressive individuals [3]. A widely accepted theory to explain depression and drug addiction comorbidity is the "self-medication hypothesis", arising from common risk factors and similarities in the underlying neurobiology of depression and drug addiction [4,5]. This theory indicates that individuals with depression have deficits in brain reward systems and may turn to drugs that create euphoric feelings to compensate for their anhedonia and motivational inadequacy [6–8] and there is supporting clinical evidence for methamphetamine [9] and other drugs [10]. Consequently,

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http://dx.doi.org/10.1016/j.bbr.2015.09.035
0166-4328/

individuals with affective disorders suffer from higher cravings and increased relapse rate [11] which is the most demanding problem faced by clinicians [12]. Despite the high prevalence of drug addiction and depression comorbidity, there are only few animal models examining drug abuse behaviors in depression and relapse of drug addiction [13]. Thus, the composite animal model used here should provide a basis for investigation of the mechanisms underlying the interaction between depression and addiction [14].

Bilateral olfactory bulbectomy is a well-established model of depression with high face, construct, and predictive validity which closely mimics neurochemical, neuroanatomical, behavioral and endocrine changes seen in patients with major depression [15]. Our team has developed a rat model of depression and addiction dual disorder where olfactory bulbectomized animals showed a significantly higher vulnerability in methamphetamine intravenous self-administration (IVSA) paradigm [14] and differential dopamine and serotonin release in nucleus accumbens shell after methamphetamine challenge [16]. Similar findings were reported earlier also for self-administration of amphetamine [17] and for self-administration and dopamine release induced by CB1 receptor agonist WIN55,212-2 [18]. Interestingly, this behavioral effect was not replicated in a similar study with cocaine [19].

To mimic relapse in the IVSA paradigm, extinction training is usually employed when the animal still has a regular access to the operant box but the drug delivered by infusion pump is replaced by vehicle. After reaching a specific extinction criteria, one last session is conducted and the reinstatement of the drug seeking behavior is primed by an environmental factor (stress, cue) or a drug dose [20]. In the OBX model of depression combined with drug IVSA Frankowska et al. (2014) and Amchova et al. (2014) proved significantly later extinction of cocaine- and CB1 agonist-seeking behavior in the OBX rats. However, this approach does not mimic the human situation as the patient usually discontinues the drug taking in a different, not drug-related environment. Therefore, a forced abstinence paradigm was suggested as more translational. In this model the animal does not have access to the operant self-administration and is kept in the home cage for certain time period [21,22].

The aim of this study was to assess relapse-like behavior in the OBX model of depression after short maintenance phase of methamphetamine self-administration. We have chosen the highly translational forced abstinence paradigm and we expected higher methamphetamine seeking behavior of the OBX rats in the reinstatement session.

2. Methods

2.1. Animals

Twenty male albino Sprague-Dawley rats (8 weeks old, with weight range of 200-225 g at the beginning of the experiment) were purchased from Charles River (Germany). The rats were housed individually in standard rodent plastic cages. Environmental conditions during the whole study were constant: relative humidity 50-60 %, room temperature 23 °C ± 1 °C, inverted 12-hour light-dark cycle (6 a.m. to 6 p.m. darkness). Food and water were available *ad libitum*. There were two experimental groups: SHAM = sham operated rats (n=8 at the beginning of the study) and OBX = olfactory bulbectomized rats (n=12 at the beginning of the study). All experiments were conducted in accordance with all relevant laws and regulations of animal care and welfare. The experimental protocol was approved by the Animal Care Committee of the Masaryk University, Faculty of Medicine, Czech Republic, and carried out under the European Community guidelines for the use of experimental animals.

2.2. Drugs and treatments

Methamphetamine (METH) from Sigma Chemical, Co., St Louis, MO, USA available in the operant cage for IV self-administration was 0.08 mg/kg per infusion with the maximum number of infusions obtainable in one session set to 50 as was routinely used in our laboratory [14,23].

2.3. Olfactory bulbectomy surgery

At the beginning of the study the rats were randomly divided into two groups and the bilateral ablation of the olfactory bulbs was performed in accordance with the standard method [24] as described earlier [14,18]. In brief, animals were anaesthetized with ketamine 50 mg/kg and xylazine 8 mg/kg given intraperitoneally. The top of the skull was shaved, swabbed with an antiseptic solution, after which a midline frontal incision was made in the skin on the skull. After exposure of the skull, 2 burr holes were drilled at the points 7 mm anterior to the bregma and 2 mm lateral to bregma suture. Both olfactory bulbs were aspirated while paying particular attention not to damage the frontal cortex. Prevention of blood loss was achieved by filling the dead space with a haemostatic sponge. The skin above the lesion was closed with suture and the antibacterial neomycin and bacitracin powder was applied. Sham operated rats underwent the identical anaesthetic and drilling procedures as OBX animals, but their bulbs were left intact. Afterwards animals were treated with non-steroidal anti-inflammatory meloxicam (0.2 ml/kg SC). A period of 14 days was allowed for the recovery from the surgical procedure. During this period, animals were handled daily for few minutes to eliminate aggression, which could otherwise arise [15,25]. At the end of the experiment, rats were euthanized by an anaesthetic overdose and the brains were dissected for confirmation of the successful removal of the olfactory bulbs. Animals with incomplete removal of the olfactory bulbs were eliminated from the analysis.

2.4. Intravenous drug self-administration surgery

The IV self-administration catheter was implanted after recovery from the OBX surgery following standard procedure described earlier [14,18,23]. In brief, animals were deeply anesthetized with IP injections of 50 mg/kg ketamine plus 8 mg/kg xylazine. Catheter was inserted 3.7 cm [26] into the right external jugular vein to the right atrium and securely sutured. A subcutaneous tunnel was made and the catheter exited the skin in the midscapular area. Since the implantation, the catheters were flushed daily by heparinized 0.05 g/kg cefazolin dissolved in saline with 2.5 IU/kg heparin and finally 0.05 ml heparin solution (5 IU/kg) to prevent infection and occlusion of the catheter. When a catheter was found to be blocked or damaged, the animal was excluded from the analysis.

2.4.1. Intravenous self-administration protocol

Methamphetamine self-administration was conducted as previously described [14,23] in 10 standard experimental boxes (30 × 25 × 30 cm, Coulbourn Instruments, USA) using nose-poking as operandum. Each cage was provided with two nose-poke holes allocated on one side and programmed by software Graphic State Notation 3.03 (Coulbourn Instruments, USA). Nose-pokes in the active hole led to the activation of the infusion pump and administration of a single infusion followed by a 10 sec timeout, while nose-poke stimulation was recorded but not rewarded, i.e. fixed ratio (FR) schedule of reinforcement. Specifically, training sessions were initially conducted under a FR-1 schedule of reinforcement. When the animal fulfilled the following acquisition criteria for three consecutive sessions: a) at least 70 % preference of the drug-paired active nose-poke, b) minimum intake of 10 infusions per session, or