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Research report

Alterations of reward mechanisms in bulbectomised rats

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HIGHLIGHTS

- First characterisation of ethanol reward mechanisms in bulbectomised rats.
- Voluntary ethanol intake was increased in bulbectomised rats.
- Bulbectomised animals needed a higher dose of ethanol to produce place preference.
- Bulbectomy led to changes in animals' reward threshold.

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ABSTRACT

The positive association between alcoholism and depression is a common clinical observation. We investigated the relationship between depression and reward mechanisms using a validated animal model for depressive-like behaviour, the olfactory bulbectomy in rats.

The effects of bilateral olfactory bulbectomy on reward mechanisms were studied in two different experimental paradigms – the voluntary self-administration of ethanol and the conditioned place preference to alcohol injection and compared to the effects of ethanol on locomotor activity and body core temperature. The voluntary ethanol intake was increased significantly in bulbectomised rats in a drinking experiment and also after a period of abstinence. Conditioned place preference (CPP) was induced in all animals. However, bulbectomised rats needed a higher dose of alcohol to produce CPP. The sedative effect of ethanol on locomotor activity was reduced in bulbectomised animals. Measurement of body temperature revealed a dose-dependent hypothermic effect of ethanol in both groups.

These results suggest that the reward mechanisms may be altered in this animal model as a common phenomenon associated with depression. Furthermore, they support the hypothesis that the addictive and/or rewarding properties of some drugs of abuse may be modified in depression.

1. Introduction

A strong positive association between alcoholism and depression is a common clinical and epidemiological observation [1–4]. It was reported that the time to relapse is shorter, the drop-out rate is increased, and long-term alcohol consumption is greater for patients with comorbid major depression or anxiety disorder than for those with an alcohol use disorder with no comorbid mental disorder [5,6]. Although an overall gender difference in prevalence of depression has been well established, data from different continents and countries revealed lower alcohol use comorbidity in women [4,7–15]. However, the nature of the relationship is little understood. Thus, comorbidity of substance abuse and mental illness is an important problem for modern psychiatry [16–19]. To shed more light on this relationship intensive clinical and preclinical research is needed.

Animal experiments have demonstrated an inductive role of the depressive state on subsequent vulnerability to alcohol [20]. Moreover, for the establishment and maintenance of alcoholism a dysfunction of the brain's reward system is considered an important factor [21–25]. Recently, it was demonstrated that a substrain of fawn-hooded rats (FH/Wjd) showed co-occurring depressive-like behaviour and high voluntary intake of ethanol [26]. Our intention was to investigate the relationship between depression and reward mechanisms using a validated animal model for depressive-like behaviour, i.e. olfactory bulbectomy in rats [27–29]. It is characterised by a high predictive validity to investigate the possible biochemical or neurobiological mechanism(s) of depression, as well as the antidepressantlike property of test molecules [30]. The olfactory system in rats represents an important part of

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the limbic system in which the hippocampus and the amygdala contribute to emotional and memory components of behaviour. Disrupted connections between the bulbs and other brain regions were discussed as the basis for developing specific disturbances after the removal of the olfactory bulbs. The bulbectomy results in behavioural (e.g. learning impairments, increased sensitivity to stressful environment, reduced grooming, anhedonia, impaired food-motivated behaviour etc.), neuromorphological (e.g. reduced number of synapses and dentritic spines, reduction in cell proliferation), neurochemical (e.g. reduction in the concentration of brain noradrenaline and serotonine, hypoactivity of the glutamatergic system, increased GABA turnover), neuroendocrine (e.g. increased activity of the hypothalamic–pituitary–adrenal axis, changes in leucocyte and lymphocyte subpopulation, increased synthesis of proinflammatory cytokines and prostaglandin) and immune (e.g. reduction in the weights of the thymus gland and the spleen, decrase in mitogen-stimulated lymphocyte proliferation) alterations which model several domains of symptomatology seen in human affective disorders (for reviews, cf. [31,32]). More specifically, the bulbectomised rat has been considered as a model of agitated depression [30]. Importantly, the irritability of the animals initiated by the lesion was attenuated by the chronic, but not acute, administration of clinically used antidepressant drugs [33,34].

Previously, we reported that olfactory bulbectomy in rats causes a syndrome of slowly developing, long-lasting behavioural, endocrine, and neurochemical abnormalities, which can be normalised by using the tricyclic antidepressant imipramine [35], thus proving the validity of this model. In the present study, we investigated the effects of olfactory bulbectomy on reward mechanisms in two different experimental paradigms – the voluntary self-administration of ethanol and the conditioned place preference to alcohol injection – and made a comparison with the effects of ethanol on locomotor activity and body core temperature.

2. Materials and methods

The experiments reported here were conducted in accordance with the regulations of the National Act on the Use of Experimental Animals (Germany) and EC guidelines.

2.1. Animals

For all experiments, male Wistar rats were used [Shoe:Wist(Shoe), DIMED Schönwalde, Germany]. The animals were housed in groups of five rats in Macrolon IV cages under controlled laboratory conditions with a light-dark cycle of 12:12 (lights on at 6:00 a.m.), temperature 20 ± 2 °C and air humidity 55–60%. The animals had free access to commercial pellets (ssniff R/M-H, ssniff Spezialdiäten GmbH, Soest, Germany) and tap water. Studies on voluntary ethanol intake in adult Wistar rats report varying intake of around 1–4 g/kg/day using continuous access models [36,37].

2.2. Bulbectomy

Bilateral olfactory bulbectomy was performed as described by O'Connor and Leonard [38]. Briefly, rats were deeply anaesthetised with pentobarbital (40 mg/kg, i.p.). The animals were fixed in a stereotactic instrument and a skin incision was made to expose the skull overlying the bulbs. Two 2 mm diameter holes were drilled above the bulbs (6.5 mm anterior to bregma and 2 mm on both sides) and both holes were joined to a slotted hole. The olfactory bulbs were cut and removed by aspiration by use of a deflected pipette. The resulting spaces were filled with haemostatic sponges and the skin was closed by tissue adhesive (Histoacryl ®, Aesculap AG, Tuttlingen, Germany). Sham-operated rats were treated in the same way, including piercing of the dura mater, but their bulbs were left intact.

The rats were bulbectomised at the age of 7 weeks (body weight 220–280 g). After seven weeks, when the behavioural experiments commenced, the body weight was 350–400 g. There were no differences in body weight between bulbectomised and control rats. For tests as described in Sections 2.3–2.6 three separate groups of animals were used.

After the completion of the experiments, each animal was checked to ensure that the olfactory bulbs had been completely removed and there was no damage to the frontal cortex. Only these animals were included in the results and for statistical evaluation.

2.3. Voluntary ethanol intake

Studies on voluntary ethanol intake in adult Wistar rats reported varying ethanol intake and preference [39–41]. To investigate voluntary ethanol intake, animals were housed singly in Macrolon III cages equipped with 3 bottles containing water, 5% or 10% (v/v) ethanol solution. The position of the bottles was changed at weighing. The supply of ethanol was disrupted after 5 weeks (=period 1) of choice for one week. It was shown that ethanol-dependent animals exhibited significant neural hyperexcitability for at least 72 h, but not 1 week, post withdrawal [41]. Thereafter a choice of ethanol or water was offered for a further 1.5 weeks (=period 2). Fluid intake was calculated based on bottle weight measured twice a week. Total fluid intake was defined as water intake + ethanol solution intake and it was expressed as g/kg body weight (bw).

If bulbectomy positively affects alcohol intake, a higher percentage of animals would prefer higher ethanol concentrations. To test this, the number of animals preferring or non-preferring the different solutions was compared. Preference was calculated on the basis of the mean ethanol intake of all animals on the last day in period 1 (non-preferring = individual ethanol intake < mean, preferring = individual ethanol solution intake > mean).

2.4. Conditioned place preference

The apparatus (TSE, Bad Homburg, Germany) consisted of three alleys. The neutral central alley (40 cm × 11 cm) was made of grey polyvinyl chloride (PVC), with a smooth PVC floor. The two end compartments (50 cm × 11 cm) were also made of PVC. One end compartment had white walls and a floor covered with a wire mesh (distance between intersections: 3 cm × 3 mm), whereas the other end compartment had black walls and the floor was covered with a different wire mesh (distance between intersections: 10 cm × 10 mm). The compartments were equipped with guillotine doors. The number of compartment crossings and the time spent in each compartment was measured via infrared photocells mounted next to the entry. A personal computer controlled the experimental sessions and collected data. Pilot studies have shown a strong preference for the black compartment of the apparatus in about 80% of the animals. Therefore, we decided to use the biased protocol. Data obtained using biased compartments can be a valid reflection of drug reward [42,43].

On day 1, the animals were habituated to the apparatus for 15 min. The day after habituation (day 2), a preconditioning session with access to all compartments was performed to determine the animals' compartment preference. The rat was placed in the apparatus for 15 min for this purpose. The compartment where the animal spent less than 50% of the test time was considered to be the non-preferred compartment. On the following four days (days 3–6) the animals were i.p. injected alternately with a dose of either ethanol (0.25; 0.5; 1.0 and 2.0 g/kg body weight (injection volume 10 ml/kg body weight) or saline once per day so that all animals tested received two test drug injections and two saline