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Research article

Glucocorticoid receptor in rat nucleus accumbens: Its roles in propofol addictions

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ABSTRACT

Propofol has been demonstrated as a drug of abuse in humans. Our previous study indicated that dexamethasone, a potent agonist of glucocorticoid receptor (GR), inhibited propofol-maintained rat self-administration behaviors by systematic injection. However, the direct effect of GR in the nucleus accumbens (NAc) on propofol self-administration behavior has not been explored. The propofol-maintained self-administration was established in rats after a successive 3-h daily self-administration of propofol for 14 days. On day 15, 30 min prior to the last training, rats received one of three doses (0.3, 1.0, or 3.0 μg/site) of dexamethasone or vehicle via intra-NAc injection. The number of active nose-poke responses, propofol injections, and inactive nose-poke responses was recorded. Dopamine D1 receptor and c-Fos expressions were detected. Plasma corticosterone level was measured by enzyme-linked immunosorbent assay. Intra-NAc administration of dexamethasone (1.0 and 3.0 μg/site) facilitated the active nose-poke responses, which was accompanied by the upregulation of D1 receptor and c-Fos in the NAc. Plasma corticosterone level was not changed in dexamethasone-treated groups. This study provides crucial evidence that GR in the NAc plays an important role in regulating propofol self-administration behaviors in rats, which may be mediated by changes in D1 receptor and c-Fos expressions, and this also needs further examination with GR antagonist in the future.

1. Introduction

Propofol is a commonly used intravenous anesthetic due to its ability for a rapid onset and a smooth recovery. However, propofol has been reported to induce pleasure, euphoria, and dependence. Propofol abuse has been increased since the first reported addicted case [1]. Several animal studies have examined the reinforcing property of propofol by the conditioned place preference and self-administration experiments, which are widely adopted and highly regarded paradigms used in addictive studies [2], but the underlying mechanism of propofol addiction remains unclear.

The mesolimbic dopamine system, mainly constituted by ventral tegmental area and nucleus accumbens (NAc), is a common pathway in drug reward seeking. Numerous drugs were reported to elicit rewarding effects by mainly increasing dopamine levels in the NAc [3,4], a dopaminergic projecting site mediating the reinforcing effects. Furthermore, glucocorticoids (GCs) are crucial in determining the euphoric responses to drugs of abuse and increasing drug-seeking behaviors [5]. Corticosterone is a main type of GCs in rats, which has been demonstrated to be able to regulate drug reward, and the suppression of its production has been shown to inhibit cocaine sensitization [6]. In contrast, cocaine-seeking behavior was increased by elevating plasma corticosterone concentration in animal models after exposure to the environmental stressors [7]. The increased drug-seeking behavior may also be related to dopamine receptor expression since D1 and D2 receptor expressions are significantly reduced post-adrenalectomy [8]. GCs selectively bind to the glucocorticoid receptor (GR) *in vivo*. GR is abundant in many brain regions, including the NAc [9]. Additionally, GR signaling pathway also regulates drug addictions and promotes dependence [10,11]. Cocaine intravenous self-administrative behavior

Abbreviations: GR, glucocorticoid receptors; GC, glucocorticoids; NAc, the nucleus accumbens; VTA, ventral tegmental area; FR1, the fixed ratio 1; ACTH, adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal axis; D1 receptor, dopamine D1 receptor; D2 receptor, dopamine D2 receptor; ANOVA, analysis of variance; ELISA, enzyme-linked immunosorbent assay

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is suppressed in mice with GR antagonist treatment or after a complete GR loss [12]. In our previous study, we found that the propofol self-administrative behavior in rats was mainly associated with D1 receptor but not D2 receptor in the NAc [13]. Moreover, GR is essential in propofol self-administrative behaviors and its effect may be mediated by D1 receptor in the NAc [14].

However, in our previous study, we demonstrated an indirect effect of dexamethasone on propofol self-administration by inhibiting plasma corticosterone level, which can attenuate D1 receptor expression in the NAc [14]. Yet, we cannot rule out the direct effect of dexamethasone in regulating propofol self-administration. c-Fos, a biomarker for the regional neuronal activation that was associated with the drug-seeking behavior in the NAc, was reported to be modulated by D1 receptor [15]. Thus, in the present study, we examined the effects of intra-NAc injection of dexamethasone on the propofol self-administration behaviors, and explored the relationships among the plasma corticosterone concentration, D1 receptor, and c-Fos expressions in the NAc.

2. Material and methods

2.1. Animals

Adult male Sprague-Dawley rats, weighing 250–300 g, were purchased from the Experimental Animal Center of Wenzhou Medical University. All of the experimental procedures were approved by the Animal Care and Use Committee of Wenzhou Medical University. The animals were caged individually in a temperature-controlled (22–24 °C) room under a 12-h light/dark cycle, with free access to water and food. After propofol self-administration training, rats were randomly assigned into either the control or one of the three dexamethasone treatment groups (0.3, 1.0 or 3.0 μg/site in the bilateral NAc).

2.2. Drugs

Propofol (10 mg/ml, Diprivan, Astrazeneca, Italy) was prepared fresh for daily injection of 1.7 mg/kg/once based on a previous study [16]. Dexamethasone (Sigma, USA) was dissolved in artificial cerebrospinal fluid (ACSF).

2.3. Self-administration apparatus

The apparatus specifications are described in our previous study [14]. A fixed ratio 1 (FR1) training schedule was chosen. The locomotor activity was tested with a specific motor monitoring device (Panlab, Barcelone, Spain). All experimental procedures were automatically recorded.

2.4. Surgery

The implantation of jugular vein intravenous catheters and how to keep the catheters patency and prevent infection was as described in previous study [14]. The guide cannulae (20-gauge, Small Parts Inc., USA) was implanted in the NAc bilaterally for intra-NAc injections (A/P +1.5 mm, M/L ± 2.0 mm, D/V −6.7 mm) [13].

2.5. Propofol self-administration training

The process of how to establish the propofol self-administration training model in rats was the same as described in the previously published studies [13,14]. The number of active nose-pokes and injections would be increasing gradually as the training proceeded in most trained propofol self-administration rats and reached a stable state after successive 14-day training, the variability should be less than 10% at the last 3 sessions. Rats that did not reach the criteria would be excluded from further test.

2.6. Sucrose self-administration training

Rats were trained for food rewarding with sucrose pellets (Dustless precision pellets, Bio-Serv, USA) under a FR1 schedule of a 0.5-h session consecutively for 7 days. The paradigm for sucrose self-administration training was similar to that of propofol, and a 45-mg sucrose pellet was delivered as the reward by a conditioned cue after each active nose-poke. The sessions ended after 0.5 h or 100 sugar pellets whichever occurred first.

2.7. Locomotor activity test

A total of 4 h, a rat with 1-h acclimation followed by a 3-h test period to monitor the effects of dexamethasone injection on general activities. Multiple metrics were used to quantify locomotion, such as path length, activity time, times of activity and speed were recorded.

2.8. Microinjection procedure

After successful propofol self-administration training, rats were treated with intra-NAc dexamethasone injection suspended in ACSF, at dosage of 0.3, 1.0 or 3.0 μg/site, 30 min prior to the testing session on

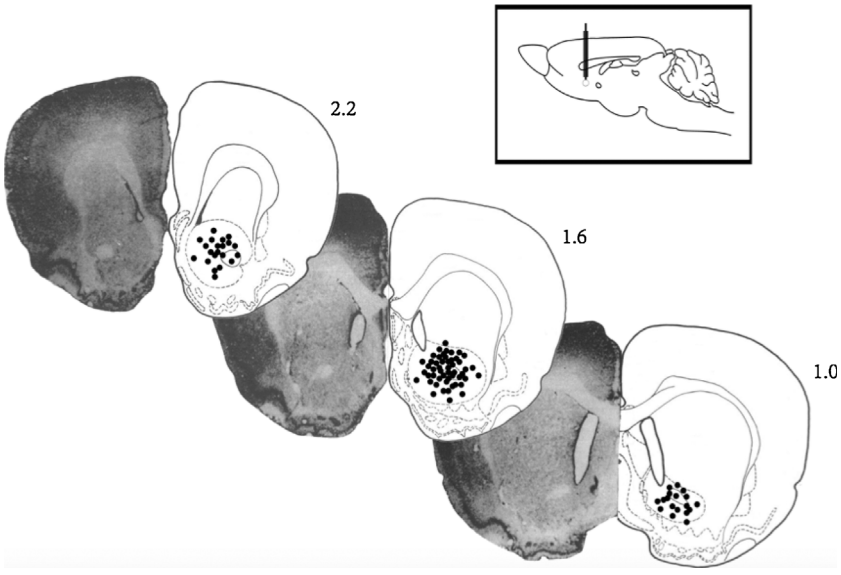

Fig. 1. Histological reconstructions of the brain to illustrate the dexamethasone and vehicle injecting sites in the NAc.