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GLUCOCORTICOID RECEPTOR MEDIATED THE PROPOFOL SELF-ADMINISTRATION BY DOPAMINE D1 RECEPTOR IN NUCLEUS ACCUMBENS

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Abstract—Propofol, a widely used anesthetic, can cause addictive behaviors in both human and experimental animals. In the present study, we examined the involvement of glucocorticoid receptor (GR) signaling in the molecular process by which propofol may cause addiction. The propofol self-administration model was established by a fixed ratio 1 (FR1) schedule of reinforced dosing over successive 14 days in rats. On day 15, the rats were treated with dexamethasone, a GR agonist (10–100 μg/kg), or RU486, a GR antagonist (10–100 μg/kg) at 1 h prior to the last training. The animal behaviors were recorded automatically by the computer. The expression of dopamine D1 receptor in the nucleus accumbens (NAc) was examined by Western blot and the concentrations of plasma corticosterone were measured by enzyme-linked immunosorbent assay (ELISA). To further examine the specificity of GR in the process, mineralocorticoid receptor (MR) antagonist, spironolactone, and dexamethasone plus MR agonist, aldosterone, were also tested. Administration of dexamethasone (100 μg/kg) or RU486 (⩾10 mg/kg) significantly attenuated the rate of propofol maintained active nose-poke responses and infusions, which were accompanied by reductions in both plasma corticosterone level and the expression of D1 receptor in the NAc. Neither spironolactone alone nor dexamethasone combined with aldosterone affected the propofol-maintaining self-administrative behavior, indicating GR, but not MR, modulates the propofol reward in rats. In addition, neither the food-maintaining sucrose responses under FR1 schedule nor the locomotor activity was affected by any doses of dexamethasone or RU486 tested. These findings provide evidence that GR signaling may play an important role in propofol reward. © **2016 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: corticosterone, dexamethasone, D1 receptor, propofol, self-administration.

INTRODUCTION

Drug abuses and addictions have been major social and health concerns. In order to effectively prevent and treat drug abuses, it becomes increasingly important for us to know how addictive drugs work. Propofol, an intravenous anesthetic, has been widely used in the clinic due to its characteristics of short action as well as quick and smooth recoveries compared with other anesthetics. However, in recent years, propofol has been considered an addictive drug in anesthesiology, as increasing reports showed that propofol was capable of inducing pleasure, euphoria, and dependence. A clinical survey of 126 academic anesthesiology programs in the United States during 1995–2005 has found that 18% of the departments showed propofol abuse with the incidence of 1‰ (Wischmeyer et al., 2007). Also, other clinical studies have suggested that even second-hand exposure to aerosolized propofol for elongated time in the operation room increased sensitization and created a risk factor for the occupational addiction (McAulliffe et al., 2006). In the animal studies, the reinforcing property of propofol was confirmed by animal experiments, in which repeated doses of propofol led to addictive behavior of rats with conditioned place preference and self-administration tests (Lesage et al., 2000).

While it is generally accepted that propofol is addictive, the mechanism by which it works remains unclear. Recently, it has been proposed that glucocorticoid receptor (GR) signaling may be involved in drug addictions. For example, adrenalectomy, which depleted endogenous glucocorticoid (GC), corticosterone, significantly inhibited the dependence on morphine (Marinelli et al., 1998; Deroche-Gamonet et al., 2003), and treatments of rats or mice with corticosterone promoted the seeking behavior of drugs (Piazza et al., 1991). On the contrary, the cocaine-seeking behavior was inhibited and the concentration of dopamine was decreased significantly by knocking out the gene of GR in mice or by injecting GR antagonist, respectively

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

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(Marinelli et al., 1998; Deroche-Gamonet et al., 2003). Such studies indicated that GR played important roles in regulating the addictive process of abused drugs, such as cocaine and morphine (Wang et al., 2008; Ambroggi et al., 2009).

The mesolimbic dopamine system is the common final pathway of drug reward, which takes place mostly in the nucleus accumbens (NAc), an important region in the brain (Bolaños and Nestler, 2004). Multiple drugs implement the reward effects by increasing the concentration of dopamine in the NAc (Koob, 1999). GC was reported to be involved in regulating dopamine release and dopamine receptor expression in the NAc (Barrot et al., 2000; Stonehouse et al., 2003). Studies from our group and others have indicated that propofol notably increases the dopamine concentration in the NAc (Pain et al., 2002), which may mediate propofol reward by activating dopamine D1 receptors (Lian et al., 2013). Based on these observations, we hypothesized that GC or GR signaling might be involved in the propofol reward by regulating the dopaminergic system.

In the present study, we examined the effects of either activated (dexamethasone a potent GR agonist), or inhibited (RU486, a specific GR antagonist) on the propofol self-administration, and these pre-treatments on either serum corticosterone concentration and/or the expression of D1 receptor in the NAc.

EXPERIMENTAL PROCEDURES

Animals

Adult male Sprague–Dawley rats, weighing 250–300 g, were purchased from the Experimental Animal Center of Wenzhou Medical University. All experiments and procedures were approved by the Animal Care and Use Committee of Wenzhou Medical University, and all operations were performed under anesthesia with sodium pentobarbital, and efforts were made to minimize the number of animals used and their suffering. Animals were housed in individual cage under a 12-h/12-h light–dark cycle at 22–24 °C, receiving free access to food and water. After the chronically indwelling intravenous catheters were successfully implanted, the rats were randomly assigned into the control and treated groups, and at the end of the experiments, the rats were killed under deep anesthesia with sodium pentobarbital for further analysis.

Drugs

Propofol, obtained from Astrazeneca (10 mg/ml, Diprivan, Italy), was prepared fresh daily during the training period. Based on a previous study, a single dosage of propofol (1.7 mg/kg/injection) was used daily for rat self-administration behavior training (McAulliffe et al., 2006). Other agents, including dexamethasone, RU486, spironolactone, and aldosterone were purchased from Sigma Chemical Co. (Sigma, USA), and these agents were dissolved in 50% ethanol.

Apparatus

The experiments were done with custom-made operant boxes, sized 30 cm × 30 cm × 30 cm, with the hemline 5 cm from floor, as being described in our previous studies (Yang et al., 2011; Lian et al., 2013). The reward (self-administration) behavior training was done by a single dosage of propofol daily through jugular injection with a 5-ml syringe attached to a syringe pump at the speed of 1.2 ml/min. In the food-maintained training, sucrose particles were used. The fixed ratio 1 (FR1) training schedule was selected for both trainings. The locomotor activity was tested in a specific motor monitoring device (Panlab, Barcelone Spain) to evaluate the general locomotor activity versus specific addictive property. The experiment procedures were recorded automatically by an IBM–compatible personal computer with a MED Associates interface, which runs self-programed software written in Borland Delpi 6.0.

Surgery

Surgical implantation of intravenous catheters was performed using a previously described method (Zhou et al., 2007). Briefly, under sodium pentobarbital anesthesia, the rats were implanted with chronically indwelling intravenous catheters, which were flushed daily with 0.2 ml saline–heparin solution to maintain the patency of the catheters. After surgical procedure, the rats were treated with penicillin B once every day through the implanted catheter during the recovery period for at least 7 days to prevent infection.

Propofol self-administration training

Rats were trained for self-administering drugs as previously described (Zhou et al., 2007). During a continuous 14-day period, a 3-h training session was done daily. Rats were moved from their home cages to the operant chambers and then attached the catheter connectors to the infusion line. Each session started with the illumination of the green light inside the active nose-poke hole. The rats received a single propofol infusion of 1.7 mg/kg following poking the active nose-poke under the schedule of FR1. Each infusion was paired with a 5-s illumination of the house light and the noise from the infusion pump. In the meantime, a time-out period was imposed for 30 s, during which further poking produced no programed consequences but was recorded by the computer automatically. Illumination of the green light in the active nose-poke signaled the end of the time-out period, which responds in the inactive nose-poke produced no programed consequence. All active nose-poke, inactive nose-poke and the number of propofol injections were recorded by the computer, and the sessions ended after 3 h or reaching 100 propofol injections. One hour prior to the session on day 15, the trained rats were intraperitoneally injected with vehicle, dexamethasone (10, 30, or 100 μg/kg), RU486 (10, 20, or 40 mg/kg), spironolactone (10, 20, or 40 mg/kg), or dexamethasone (100 μg/kg) combined with aldosterone (10, 30, or 100 μg/kg).