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Original research article

Locomotor stimulation by acute propofol administration in rats: Role of the nitrergic system

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ABSTRACT

Background: The addictive potential of propofol has been scientifically discussed. Drugs' psychostimulant properties that can be assessed *via* measurements of locomotor activity are linked to their addictive properties. No studies that have investigated the effects of propofol on locomotor activity have been reported to date. The present study sought to investigate the effects and possible mechanisms of action of propofol on locomotor activity in rats.

Methods: Adult male albino Wistar rats (250–330 g) were used as subjects. The locomotor activities of the rats were recorded for 30 min immediately following intraperitoneal administration of propofol (20 and 40 mg/kg), saline or vehicle ($n = 8$ for each group). NG-nitro arginine methyl ester (L-NAME, 15–60 mg/kg), a nitric oxide (NO) synthase inhibitor, and haloperidol (0.125–5 mg/kg), a non-specific dopamine receptor antagonist, were also administered to other groups of rats 30 min prior to the propofol (40 mg/kg) injections, and locomotor activity was recorded for 30 min immediately after propofol administration ($n = 8$ for each group).

Results: Propofol produced significant increases in the locomotor activities of the rats in the first 5 min of the observation period [$F(2,21) = 9.052$; $p < 0.001$]. L-NAME [$F(4,35) = 3.112$; $p = 0.02$] but not haloperidol [$F(4,35) = 2.440$; $p = 0.067$] pretreatment blocked the propofol-induced locomotor hyperactivity. L-NAME did not cause any significant change in locomotor activity in naïve rats [$F(2,21) = 0.569$; $p = 0.57$].

Conclusions: Our results suggest that propofol might cause a short-term induction of locomotor activity in rats and that this effect might be related to nitrergic but not dopaminergic mechanisms.

Introduction

Propofol (2,6-diisopropylphenol) is a short-acting intravenous anaesthetic drug that is widely used for anaesthesia induction and intensive care procedures, such as endoscopy, colonoscopy and short-term invasive surgical attempts, to provide dose-dependent sedation and hypnosis. Propofol also provides control of stress responses and has anticonvulsant and amnesic activities [1,2].

The addictive potential of propofol has been debated in scientific area since the early 90s. In 1992, Follett and Farley from Albany Medical Center in New York published a case-report describing an anaesthesiologist who initially self-administered propofol to relieve stress but later began to crave the drug [3]. Previously some reports have also been published that have indicated some pleasant effects upon wakening from propofol, including euphoria [4,5]. It has also been found that propofol induces pleasant mood changes in humans at subanaesthetic doses [6]. The addictive and abuse potential of propofol received increased attention following the death of Michael Jackson, who was a popular singer [7].

Indeed, several articles and case reports have highlighted the abuse and dependence potential of propofol, particularly among health professionals [8–13]. Some findings that have been obtained from experimental animals have also supported the idea that propofol might have addictive and abuse potential. For example, conditioned-place preference is induced by propofol administration in rats [14,15]. The anxiolytic effects of propofol have been demonstrated in rodents [16,17], and some anxiolytics, such as benzodiazepines and barbiturates, have abuse potential and cause physical dependence in experimental animals and

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humans [18]. The reinforcing effects of propofol have been tested in rats, mice and baboons using drug self-administration procedures. These studies have revealed that propofol has prominent reinforcing effects in baboons [19] and rats [20] but not in mice [21]. Furthermore, in a recent study, Lian et al. [22] suggested that the self-administration of propofol is mediated by dopamine D1 receptors in the nucleus accumbens (NAc) in rats. It has also been proposed that propofol might increase the excitation of the dopaminergic neurons of the ventral tegmental area (VTA), which is an important brain region for reward and addiction, by increasing afferent glutamatergic transmission, which is an important dynamic of physical dependence [22,23].

The psychostimulant properties of a drug can be assessed by measuring locomotor activity, and these psychostimulant effects have been linked to the addictive properties of the drug [24]. The acute administration of psychostimulant agents, such as cocaine [25], amphetamine [26] and caffeine [27,28], induces locomotor stimulation and produces significant increases in open-field locomotor activity in rodents. Low and stimulant doses of ethanol also produce locomotor stimulant effects in rodents [29,30]. All of these agents cause dependence in abusers. Although propofol is an anaesthetic agent that is generally classified as a depressant, examinations of the effects of propofol on locomotor activity might yield interesting results. No studies that have investigated the effects of propofol on locomotor activity have yet been published.

The major objective of the present study was to investigate the effects of propofol on locomotor activity in rats. We also aimed to explain possible mechanisms of action of the effects of propofol on locomotor activity. To these ends, we recorded the locomotor activities of rats after the administration of propofol, propofol plus NG-nitro arginine methyl ester (L-NAME, nitric oxide (NO) synthase inhibitor), and haloperidol (a non-specific dopamine receptor antagonist).

Materials and methods

Animals and the laboratory

All procedures in the present study were performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (USA) and the Declaration of Helsinki. Local ethical committee approval was also obtained. Adult male (250–330 g) albino Wistar rats were used as subjects. The animals were obtained from Üsküdar University Experimental Research Unit (USKUDAB) and housed eight per cage in Plexiglas cages. The rats were placed in a quiet and temperature- and humidity-controlled room (22 ± 2 °C and $60 \pm 5\%$, respectively) in which a 12/12-hour light-dark cycle was maintained (light from 7.00 a.m. to 7.00 p.m.). Food and water were available *ad libitum*. All experiments were performed at the same time of day during the light period (9.00 a.m.–11.00 a.m.).

Drugs

Propofol was purchased from Fresenius Kabi Austria GmbH (Graz, Austria). The doses of propofol were administered intraperitoneally (*ip*) to the animals from direct pharmaceutical preparations in the same volume of 0.5 ml/250 g. L-NAME was purchased from Sigma Chemical (St. Louis, MO, USA) and dissolved in 0.9% saline. Haloperidol was also purchased from Sigma Chemical (St. Louis, MO, USA) and dissolved in 0.1% dimethyl sulfoxide (DMSO). DMSO was purchased from the Biomatic Corporation (Wilmington, DE, USA). L-NAME, haloperidol, saline and vehicle were injected *ip* in volumes of 1 ml/kg. Drug stocks were prepared fresh every morning.

Apparatus

Locomotor activity was measured with an open-field activity monitoring system (MAY 9908 model-Activity Monitoring System-Commat Ltd., Ankara, Turkey). This system had eight Plexiglas cages (42 cm × 42 cm × 30 cm) equipped with infrared photocells. Fifteen photocell emitter and detector pairs were located 2 cm above the floor at intervals of 2.5 cm on opposite sides of each activity cage, and another 15 photocell pairs were located 8 cm above the floor. Interruptions of the photocell beams were detected by a computer system, and the location of the animal was calculated by the software at a temporal resolution of 0.1 s. If the calculated locations completely changed, these changes were interpreted as ambulatory activity. Other behavioural responses that caused interruptions of beams but not changes in location were recorded as horizontal activity. Vertical activity, such as rearing, was detected by the photocells located 8 cm above the cage floor.

Procedure

Animals were randomly assigned to the drug regimens ($n = 8$ for each group) and tested in a random order. Propofol (20 and 40 mg/kg) and saline were injected *ip* to the first three groups of the rats. Because our preliminary experiments revealed that doses of propofol greater than 40 mg/kg did not produce any locomotor stimulation and elicited hypnotic activity immediately after the injections, the propofol dose of 40 mg/kg was selected for further experiments.

For the combination treatments, L-NAME (15, 30 and 60 mg/kg) and haloperidol (0.125, 0.25 and 0.5 mg/kg) were injected into rats 30 min before propofol (40 mg/kg) administration. Immediately following the propofol injections and the final saline or vehicle injections (for the control groups), the rats were placed into the activity cages, and locomotor activity was measured for 30 min. Locomotor activity was recorded as the total of the horizontal, vertical and ambulatory activities of the rats. In a preliminary work, we observed that increases in the locomotor activities of the rats peaked within 5 min of the propofol injections. Therefore, we used a 5-min observation period to evaluate the effects of the drugs.

To evaluate the effects of L-NAME (15–60 mg/kg) and haloperidol (0.125–0.5 mg/kg) in naive rats, the drugs and saline or vehicle were also administered to eight independent groups of subjects ($n = 8$ for each group), and the locomotor activities were recorded according to the same protocol.

Statistics

The data are expressed as the means ± SEMs. The data, including the effects of the propofol and combinations doses on the total locomotor activity over 5 min, were evaluated with one-way ANOVA tests. The effects of L-NAME and haloperidol on locomotor activity in the naïve rats were also analysed with one-way ANOVAs. Tukey's tests were used for all *post hoc* analyses. The level of statistical significance was set at $p < 0.05$.

Results

Effects of propofol on the locomotor activities of the rats

The 30 min effects of propofol as divided in every 5 min on locomotor activity are shown in Fig. 1.

The changes in the locomotor activities of the rats over the 5 min following propofol treatment are shown in Fig. 2. A one-way ANOVA test indicated a significant effect [$F(2,21) = 9.052$;