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Research report

Dexmedetomidine induces conditioned place preference in rats: Involvement of opioid receptors

Tuğçe Uskur[a], M. Aydın Barlas[a], A. Gökhan Akkan[a], Andleeb Shahzadi[a], Tayfun Uzbay[b,*]

[a] Istanbul University, Institute of Health Science,Cerrahpasa Medical Faculty, Department of Medical Pharmacology, Istanbul, Turkey
[b] Uskudar University, Neuropsychopharmacology Application and Research Center (NPARC), Altunizade Mah, Haluk Turksoy Sok, No: 14 34662 Üsküdar, Istanbul, Turkey

HIGHLIGHTS

- Dexmedetomidine (DEX) is an alpha-2 adrenergic agonist anesthetic agent.
- DEX produces conditioned place preferences (CPP) in rats.
- DEX-induced CPP was reversed by non-specific opioid antagonist naloxone treatment.
- DEX-induced CPP seems to be related to opioidergic mechanisms.
- Thus, DEX might have the potential to be addictive.

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ABSTRACT

Dexmedetomidine (DEX) is an alpha-2 adrenergic agonist drug recently introduced to anesthesia practice. Certain agents used in anesthesia practice have been associated with abuse and addiction problems; however, few studies have investigated the role of DEX on addictive processes. Here, the effects and possible mechanisms of action of DEX on conditioned place preference (CPP), a model used for measuring the rewarding effects of drug abuse in rats, was investigated. The CPP apparatus was considered "biased" as the animals preferred the grid side to the mesh side. Male Wistar albino rats weighing 250–300 g were divided into several groups, including control (saline), morphine (10 mg/kg), DEX (2.5–20 μg/kg), naloxone alone (0.5 mg/kg) and a combination (0.5 mg/kg naloxone plus 20 μg/kg DEX) (n = 7–8 for each group). The CPP effects of morphine, DEX, saline and the combination were evaluated. All the drug and saline administrations except naloxone were performed by intraperitoneal (ip) injections. Naloxone was injected subcutaneously (sc) when given alone or in combination with DEX. Morphine (10 mg/kg) and DEX (5–20 μg/kg) produced CPP that were statistically significant relative to saline-injected rats. DEX-induced CPP was significantly reversed by pretreatment with naloxone, an opioid antagonist. Naloxone alone treatment did not cause any significant effect on CPP. Our results suggest that DEX produces CPP effects similar to morphine in rats and that opioidergic mechanism may be responsible for DEX-induced CPP. Thus, DEX might have the potential to be addictive, and this possibility should be considered during clinical application of this drug.

1. Introduction

Some anesthetic agents, such as certain inhalants, ketamine, cocaine and short-acting barbiturates and benzodiazepines, have the potential to be abused, and they can cause a pathological dependence in animals and humans over time [1]. The addictive potential of anesthetic agents, especially those used for premedication, has been the subject of much debate in the scientific arena. Recently, several reports have highlighted the abuse and dependence potential of propofol, a short-acting intravenous anesthetic drug that is widely used for anesthesia induction and intensive care procedures without any limitations [2–4]. Thus, detecting potential abuse of anesthetic agents is of primary importance in clinical practice and for public health.

Dexmedetomidine (DEX) is a highly selective alpha-2 adrenergic receptor agonist drug that has recently been introduced to intensive

* Corresponding author. Fax: +90 216 474 12 56.
E-mail addresses: uzbayt@yahoo.com, tuzbay@uskudar.edu.tr (T. Uzbay).

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care units and used as an adjuvant to local anesthetics for its sedative and analgesic effects. It produces dose-dependent sedative, anxiolytic and analgesic (spinal and supraspinal level) effects without respiratory depression [5–7]. Studies investigating the abuse or addictive potential of DEX in the literature are very limited. A few studies have indicated that DEX may be helpful for the detoxification process and for controlling some symptoms of the withdrawal syndrome involved in with some addictive products. For example, it has been suggested that DEX can successfully be used as a sedative-analgesic to control withdrawal-related psychomimetic symptoms and to facilitate smooth detoxification and weaning from opioids, ethanol and nicotine [8–11]. In addition, it has been demonstrated that DEX can attenuate the expression of tolerance to the analgesic effect of morphine and enhanced morphine-induced analgesia in rats [12]. The dependence potential of DEX itself has not been subjected in detailed studies yet. Consequently, the safety and efficacy of the use of DEX in the treatment of withdrawal symptoms or addiction potential for itself are still uncertain.

Conditioned place preference (CPP) is a learned behavior revealed in numerous vertebrates, including humans. CPP is an ordinary preclinical animal model for evaluating the rewarding and aversive effects of drugs or other chemical substances. It is a type of Pavlovian conditioning. This paradigm has been widely used in psychopharmacology and behavioral neuroscience studies for measuring the motivational effects and reinforcing properties of addictive drugs [13–16]. There is a general assumption that an acquired place preference is based on classical conditioning derived 'incentive motivation'. However, this may be an oversimplification of the multiple learning processes involved [16]. The drugs studied using CPP are the subject of numerous reports in the literature. Systemic administration of psychostimulants [17,18], nicotine [19], opiates [17], ethanol [20], some benzodiazepines, such as alprazolam [21], and cannabinoids [22] reliably produce dose-dependent CPP in animals. All of these agents are also addictive.

The involvement of alpha-2 adrenergic receptors in the mechanism of CPP has been the subject of several experimental studies. Some studies demonstrated that clonidine, an alpha-2 adrenergic agonist, produced CPP in rodents [23,24]. Tahsili-Fahadan et al. [25] also suggested that agmatine, an endogenous polyamine metabolite formed by decarboxylation of L-arginine, potentiates morphine-induced CPP modulation by alpha-2 adrenoceptors. Interestingly, other studies have produced controversial results suggesting that the drugs affect alpha receptors. For example, clonidine, tizanidine and xylazine, alpha-2 adrenergic agonists, have been proposed to decrease morphine-induced CPP in mice [26]. In another study, it was shown that phenylephrine, a selective alpha-1 antagonist, and clonidine decreased morphine-induced CPP and that prazosin and yohimbine, selective alpha-1 and alpha-2 antagonists respectively, increased morphine-induced CPP in mice [27]. Thus, the contribution of alpha-2 receptors to CPP is still being debated. Furthermore, the effect of DEX on CPP has not yet been evaluated.

The primary objective of this study was to investigate the effects of DEX on CPP in rats along with determining a potential mechanism of action for these effects. To this end, we recorded the CPP of rats after the administration of DEX plus naloxone, a non-specific opioid receptor antagonist.

2. Material and methods

2.1. Animals and laboratory

Adult male (250–300 g) Wistar albino rats were used as the test subjects. The animals were obtained from the Research Institute of Experimental Medicine, Istanbul University (DETAE) and Üsküdar University Experimental Research Unit (USKUDAB). Four rats were housed per Plexiglass cage. The rats were placed in a quiet temperature- and humidity-controlled room ($22 \pm 2\,^{\circ}C$ and $60 \pm 5\%$, respectively) in which a 12/12 h 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 (10.00 a.m.–02.00 p.m.).

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) (Publication No. 85-23, revised 1985). Local ethical committee approval was also obtained (Istanbul University, Institute of Experimental Medicine Experimental Animal Ethics Committee, Approval No. 2012/74 02/01/2013).

2.2. Drugs

DEX and naloxone HCl were purchased from MEDITARA LTD. (İzmir, Turkey) and Sigma Chemical Co. (USA), respectively. Morphine HCl was purchased from (Macfarlan Smith LTD., Edinburgh, UK).

Morphine HCl and naloxone HCl were dissolved in 0.9% saline. The DEX doses were administered by intraperitoneal (ip) injection to the animals from direct pharmaceutical preparations in the same volume of 0.5 ml/250 g by further dilution with saline. The doses of morphine and naloxone were administered to the animals by ip and subcutaneously (sc), respectively, in volumes of 1 ml/kg. The control animals received saline.

Drug stocks were prepared fresh each morning.

2.3. Apparatus

A CPP apparatus was used in this study, and it consisted of a Plexiglas box ($60 \times 30 \times 30$ cm) with opaque black (grid)/white (mesh) walls and a droppings tray 2.5 cm under the floor. The chamber was divided into two compartments. The floor of compartment "A" was given a different texture by placing a stainless steel mesh (4×4 mm) sheet on the grid floor during the experiment, whereas the floor of compartment "B" consisted of stainless steel grid rods (3 mm diameter) mounted 7 mm apart.

2.4. Procedure

Wet and dry cloths were used to clean the apparatus thoroughly between subjects. Preliminary experiments were performed to assess the stimulus inconsistency of the floor of the apparatus, demonstrating the average time spent by untrained animals on the grid and mesh floors and how that deviated from expectations based on chance. The apparatus was considered "biased" as the animals preferred the grid side to the mesh side. Usually, place conditioning is observed in a biased apparatus only when a drug has been paired with the non-preferred compartment [28]. A biased experimental design was used by pairing drugs with the mesh floor. The CPP protocol used here are in accordance with previous studies [29,30] followed by minor modifications.

A one compartment training protocol was used, followed by habituation, pretesting, conditioning and preference test trials. During each conditioning trial, the rat had free access to the entire box with the same tactile cues and grid or mesh on both sides of the box. An animal was operationally defined as "in mesh or grid side of the box" once both forepaws were in contact with the same side. All procedures were conducted between 10:00 a.m. and 02:00 p.m.

The study included 8 groups ($n = 7$ or 8 for each group). After the pretesting session, the animals were randomly assigned to the control, morphine (10 mg/kg), DEX (2.5, 5.0, 10 and 20 μg/kg),