European Journal of Pharmacology 777 (2016) 147–155

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural pharmacology

Effects of baclofen and raclopride on reinstatement of cocaine self-administration in the rat

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ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form
1 March 2016
Accepted 2 March 2016
Available online 3 March 2016

Keywords:
Abuse
Addiction
Baclofen
Reinstatement
Relapse
Self-administration

ABSTRACT

At present there is no satisfactory treatment against relapse of drug-seeking behavior. Relapse can be modeled in laboratory animals using reinstatement procedures, whereby previously extinguished self-administration for a drug is reinstated by different factors, such as exposure to cues or drug priming. It is thought that activation of gamma-aminobutyric acid (GABA) B receptor complexes could represent a promising approach to pharmacotherapy for diminishing relapse potential with drugs possessing reinforcing properties.

The effects of baclofen (a prototypic $GABA_B$ receptor agonist) on cue-induced cocaine reinstatement were evaluated in the rat with or without a priming injection of cocaine. The effects of raclopride (an antagonist of dopamine D_2 receptors) were also evaluated.

Cue-induced reinstatement under vehicle resulted in a significant increase in the number of presses on the active lever, as compared with extinction lever responding. This effect was accentuated in rats receiving a priming injection of cocaine (cocaine-plus-cue-induced reinstatement). Baclofen, at doses without effects on food-motivated operant behavior (2.5 and 5 mg/kg i.p.), dose-dependently decreased the number of active lever presses during cue-induced reinstatement. Baclofen had slightly weaker effects on cocaine-plus-cue-induced reinstatement. Raclopride (0.08 and 0.15 mg/kg s.c.) had similar effects against cue-induced reinstatement although it failed to inhibit cocaine-plus-cue-induced reinstatement at the lower dose.

Baclofen dose-dependently and selectively decreased reinstatement of cocaine self-administration. The data obtained provide support for the potential anti-craving efficacy of baclofen in the treatment of cocaine drug-seeking.

1. Introduction

Drug abuse represents a massive health burden (Gastfriend 2014). Cocaine addicts suffer from a high rate of relapse aggravated by the weak efficacy of current anti-addiction therapies (Karila et al. 2012; Kim and Lawrence 2014).

Studies of animals exposed to addictive drugs are useful for evaluating substances abuse and dependence liability (Moser et al. 2011; Froger-Colléaux et al. 2011) and efficacy of anti-abuse treatments (Ahmed 2012). Reinstatement procedures, whereby previously extinguished drug self-administration reoccurs on exposure to a variety of factors, are considered as preclinical models of relapse (Bossert et al. 2013). Classically, animals are first trained to self-administer an addictive substance (O'Connor et al., 2011). Once self-administration behavior is acquired, the animals are submitted to extinction sessions during which operant behavior is no longer reinforced. These phases present similarities with the situation where installation of abuse behavior is followed by forced abstinence in cocaine consumers (Crombag et al. 2008). After extinction, animals are then exposed to cues previously associated with drug delivery, such as sounds (Meil and See 1996), priming drug administration (De Wit and Stewart, 1981), drug-associated context (Crombag and Shaham 2002), or exposure to stressful events (Erb et al. 1996). Reinstatement models try to replicate the case of abstinent cocaine users relapsing following exposure to paraphernalia (cues), occasional intake of the drug previously abused (priming) or stressful life events (Shaham et al. 2003; Mantsch et al. 2014).

It has been suggested that cocaine addiction could be modulated by substances increasing GABA transmission (Filip et al., 2015). In rodents the $GABA_B$ receptor agonist baclofen decreased cocaine self-administration using a progressive ratio schedule of reinforcement (Roberts et al. 1996). This observation was extended

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http://dx.doi.org/10.1016/j.ejphar.2016.03.008
0014-2999/

using a discrete trial fixed ratio procedure evaluating the effects of baclofen over extended period of time (Roberts and Andrews 1997). A clinical study showed that baclofen reduced cocaine consumption in humans (Ling et al. 1998). Nevertheless, even if these encouraging data were replicated (for review see Vocci and Elkashef 2005) some divergent results suggest that baclofen does not eliminate all subjective effects of cocaine (Haney et al. 2006; Kahn et al. 2009) or of cocaine-associated cues (Young et al. 2014). Similarly, in animals baclofen did not reduce cocaine self-administration under low-effort demanding schedules (Roberts et al. 1996; Shoaib et al. 1998) whereas it was active according to a second-order schedule of reinforcement (Di Ciano and Everitt 2003). This is coherent with the behavioral economics concept (Bentzley et al. 2013), postulating the existence of a complex relationship between the efforts that a subject is ready to exert to obtain a drug and its reinforcing effects (Brebner et al. 2000; Oleson et al. 2011).

It has also been shown that baclofen administered before a priming administration of cocaine was able to reduce the reinstatement of self-administration in rats (Campbell et al. 1999). These data were confirmed against cocaine-induced reinstatement and cue-induced reinforcement (Filip and Frankowska 2007).

The present study was performed to compare the effects of systemic baclofen against cue-induced and cocaine-plus-cue-induced reinstatement procedures which differ by the intensity of reinstatement of self-administration behavior. We also studied the effects of raclopride using the same procedures since dopamine D_2 antagonists are widely studied for their anti-relapse effects (Cervo et al. 2003).

2. Materials and methods

2.1. Animals

Male Sprague Dawley rats (250–285 g) were purchased from Janvier-Labs (Le Genest Saint Isle, France). Upon arrival, rats were housed in individual cages and were acclimated to the housing environment for 5–7 days. Rats had restricted access to food throughout the experiments (15 g/rat/day before the surgery and then 18 g/rat/day). The rats were housed under a 12/12 h light/dark cycle (light cycle: 7:00 a.m.–7:00 p.m.). All experimental procedures were approved by Porsolt's internal ethical review committee and are in accordance with French Government and NIH guidelines.

2.2. Equipment

Experiments were conducted in operant chambers (MED Associates, Inc., St. Albans, Vermont, U.S.A.) measuring $25.5 \times 29.5 \times 19$ cm high and located within sound-attenuating, ventilated cubicles. Each chamber was equipped with two levers located either side of a 5×5 cm, a cue light and a tone generator (2900 Hz sonalert, approx 79 DB). A 2.5 cm translucent stimulus light was located above the food hopper. Experimental events were controlled and monitored, and data were collected and stored, by a computerized system (MED-PCIV, MED Associates, Inc.) and associated interface (SG-502, MED Associates, Inc.).

2.3. Surgical procedure/catheter implantation

Rats were implanted with a chronic indwelling intravenous (i.v.) jugular catheter. For catheter implantation, rats were anesthetized (isoflurane 5% delivered in 2000 ml oxygen for induction, then isoflurane 2–3% in 500–1000 ml oxygen) and given 100 mg/kg s.c. amoxicillin (Clamoxyl®) and 7.5 mg/kg s.c. carprofen (Rimadyl®). Surgery was conducted under aseptic conditions. The fur was shaved around the neck and an incision was made at the front of the neck above the jugular vein (visibly pulsing), and the vein was cleared of connective tissue and supported on a plastic strip. The catheter (IVSA28, provided by Camcaths, United Kingdom) was sterilized by autoclaving (121 °C for 30 min), filled with heparinized physiological saline (30 UI/ml) and then inserted into the vein towards the heart for 2.25 cm. The presence of blood in the catheter was verified by aspiration, and a suture was made at the heart end. The catheter was then externalized at the back of the neck. Withdrawal of blood from the catheter was again checked before the incisions were closed with a discontinuous suture. The catheter was filled with approximately 0.05 ml of heparinized glycerol (50 UI/ml). Rats were fitted with a mesh jacket (RJ02, Lomir Biomedical, Inc., Malone, New York, U.S.A.) to which the exteriorized catheter body was attached.

2.4. Cocaine self-administration acquisition

Beginning at least 3 days after surgery, daily sessions (Monday to Friday, maximum duration of 120 min) were conducted during which rats could receive a maximum of 200 i.v. infusions of the baseline drug (cocaine 0.35 mg/kg/infusion) under an FR1 schedule of lever pressing. For each rat only one lever was active. Responding on the inactive lever was recorded but had no programmed consequences. Immediately prior to the beginning of daily sessions, rats received a non-contingent (i.e., “priming”) infusion of cocaine (0.35 mg/kg/infusion). The house light was on during periods when i.v. infusions were available. During these sessions when rats pressed the active lever, the cue light turned on for 3 s. After 2 s of cue light on, a tone signal (2900 Hz sonalert, approx 79 dB) turned on for 1 s together with activation of the infusion pump. Each infusion was followed by a 30-s timeout, during which the chamber was dark and lever presses had no programmed consequence. The infusion duration was 4–6 s and the infusion volume was approximately 138–210 μl (0.519 ml/kg; infusion rate 2.075 ml/min), depending on the weight of the subject.

During the time out period, responses on the active lever were recorded but no pump activation/cocaine infusion occurred. Rats were required to maintain at least 16 infusions per day for at least 10 consecutive testing days with a mean number of active lever presses of 40 during the last 2 sessions before being moved to the extinction phase. Animals that did not reach this criterion were not included in the study. This selection allowed evaluating in further steps only rats showing clear motivation to self-administer cocaine.

2.5. Extinction

Animals that had reached criterion as described above were then moved to the extinction phase. Rats were connected to the infusion pump during these sessions but the extinction sessions differed from the self-administration sessions in that active lever presses no longer produced drug infusions, cue light/tone presentations, or noise from the infusion pump. These sessions lasted 2 h and were given daily (Monday to Friday). During one of these extinction sessions, rats were pretreated with physiological saline intraperitoneally or subcutaneously (i.p. or s.c., respectively) 30 min before the start of the testing session to habituate them to the administration procedure. Rats were considered to have extinguished when during 2 consecutive sessions they exhibited an average of less than 12 presses on the active lever or a maximum of 25% of the number of presses on the active lever that occurred during the last 2 sessions of cocaine self-administration, whichever came first.