Behavioural Brain Research 262 (2014) 57–67

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Wheel-running mitigates psychomotor sensitization initiation but not post-sensitization conditioned activity and conditioned place preference induced by cocaine in mice

Annabelle Geuzaine, Ezio Tirelli*

Université de Liège, Belgium

ARTICLE INFO

Article history:
Received 3 April 2013
Received in revised form
31 December 2013
Accepted 5 January 2014
Available online 13 January 2014

Keywords:
Physical exercise
Running wheel
Cocaine
Initiation of sensitization
Conditioned place preference (CPP)
Addiction

ABSTRACT

Previous literature suggests that physical exercise allowed by an unlimited access to a running wheel for several weeks can mitigate chronic neurobehavioral responsiveness to several addictive drugs in rodents. Here, the potential preventive effects of unlimited wheel-running on the initiation of psychomotor sensitization and the acquisition and extinction of conditioned place preference (CPP) induced by 10 mg/kg cocaine in C56BL/6J mice were assessed in two independent experiments. To this end, half of the mice were singly housed with a running wheel at 28 days of age for 10 weeks prior to psychopharmacological tests, during which housing conditions did not change, and the other half of mice were housed without running wheel. In Experiment 1, prior to initiating sensitization, psychomotor activity on the two first drug-free once-daily sessions was not affected by wheel-running. This was also found for the acute psychomotor-activating effect of cocaine on the first sensitization session. Psychomotor sensitization readily developed over the 9 following once-daily sessions in mice housed without wheel, whereas it was inhibited in mice housed with a wheel. However, that difference did not transfer to post-sensitization conditioned activity. In contrast with the sensitization results, mice housed with a wheel still expressed a clear-cut CPP which did not extinguish differently from that of the other group, a result in disaccord with previous studies reporting either an attenuating or an increasing effect of wheel-running on cocaine-induced conditioned reward. The available results together indicate that interactions between wheel-running and cocaine effects are far from being satisfactorily characterized.

1. Introduction

Clinical therapeutic studies suggest that physical exercise could constitute an effective adjuvant treatment for drug craving and relapse, especially in the case of tobacco and cannabis addiction albeit comparable studies on alcoholism and other drug addictions have yielded less convincing results (see [1,2] for references and reviews). Also, an overall inverse relationship between regular physical activity and substance use or abuse seems to emerge from a number of longitudinal and epidemiological studies dealing with the preventive aspects of exercise [3,4].

In spite of a few conflicting results, preclinical animal models provide convincing evidence for a preventive and therapeutic effectiveness of physical activity in decreasing drug responsiveness and addiction. In the related studies, various regimes and methods of physical exercise were administered weeks or months before (prevention) or a short time after (therapy) chronic absorption of representative drugs such as alcohol, cocaine, ecstasy, heroin, morphine, nicotine or methamphetamine (see [2] for references and review). For example, rats having unlimited access to a running wheel in their home-cage over several weeks (one of the most popular methods to provide animals with exercise) can exhibit unambiguously reduced rates of acquisition, maintenance or escalation of intravenously self-administered cocaine, heroin or methamphetamine, as compared to rats that were not provided a wheel, suggesting clear preventive properties of wheel-running [5–10]. Regarding the therapeutic effectiveness of wheel-running, reinstatement of intravenously self-administered cocaine or nicotine following a period of extinction, a procedure modelling relapse,

* Corresponding author at: Université de Liège, Département de Psychologie, Cognition & Comportement, Boulevard du Rectorat N°5/Bâtiment/N°32, 4000 Liège, Belgium. Tel.: +32 4 366 20 16.
E-mail address: ezio.tirelli@ulg.ac.be (E. Tirelli).

0166-4328/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2014.01.002

was mitigated in rats having access to a running wheel only 2 h per day during a 14-day abstinence period [11,12].

Studies examining the effect of wheel-running on drug-induced conditioned place preference (CPP) or conditioned reward, another major animal model of drug addiction, seem more conflicting. Contrarily to what reported in self-administration studies, mice and rats housed with a running wheel for several weeks displayed a facilitated formation of CPP to cocaine [13,14]. We know of no articles reporting an inhibiting effect of wheel-running on cocaine-induced CPP. The outcomes of the available studies examining the effects of wheel-running on CPP to an opioid are clearly heterogeneous, since a facilitating [15,16], an inhibiting [17] or no effect at all [18] on CPP to morphine or a kappa agonist were found in rats housed with a running wheel. Note that in this latter study, unlimited wheel-running did curb stress-potentiated morphine CPP and in Lett and co-workers study (2002) rats had a limited access to a wheel over 8 once-daily 2 h sessions prior to testing. Studies analysing the potential therapeutic effects of wheel-running on CPP to an opioid have yet to be carried out. The fact that the two models do not measure exactly the same phenomenon certainly explains this partially inconsistent pattern of results. Let us remember that CPP differs from the intravenous drug self-administration procedure in that it relies on several contextual and associative learning mechanisms and involves the administration of the drug prior to testing with only a passive experience with its direct reinforcing effects during acquisition [19,20]. Drug self-administration and CPP complement each other.

Curiously, the study of the potential influence of wheel-running on drug-induced psychomotor sensitization has so far been somewhat neglected, albeit this behavioral procedure is one of the simplest to implement. Psychomotor sensitization involved two main phases that are subserved by partially different neuroadaptative processes: its initiation and its expression [21]. Initiation refers to the intermittent administration of the drug that induces a session-by-session augmentation of the psychomotor-activating effect. Subsequently, this effect can be elicited upon acute drug challenge, reflecting the expression of sensitization. Since it is a long-lasting phenomenon, it is thought to underlie drug craving and relapse to drug use [21,22]. In a paper published after the completion of the results reported here, Diaz et al. [23] found an inhibited long-term expression of cocaine-sensitized psychomotor activity in rats using intensively a running wheel with which they were housed for 5 or 10 weeks before and throughout experimentation, as compared with rats neglecting the wheel or living without wheel. The initiation of sensitization was not measured during the 5 once-daily cocaine injections given 15 days prior to testing and the baseline levels were neither measured nor incorporated into the data analyses. Note that decreased levels of both the initiation and the expression of sensitization induced by cocaine, ethanol, or morphine were also reported in rodents housed in a composite environment that included a wheel set up among many other items such as plastic toys, pipes, nesting material and congeners [24–26].

The present study aimed at determining to which extent the unlimited access to a running wheel influence the initiation of psychomotor sensitization and the formation of conditioned reward induced by a representative dose of cocaine in C57BL/6J mice. Experiment 1 dealt with the possible effects of a 10-week period of housing with a running wheel prior to and during testing on novelty-induced psychomotor activity, the psychomotor activation induced by a single injection of cocaine, the ulterior development of psychomotor sensitization and the manifestation of post-sensitization conditioned activity successively in the same animals. Experiment 2 addressed separately the potential effect of the same running wheel history on the formation of CPP to cocaine and its extinction.

2. Materials and methods

2.1. Animals

A total of 80 male C57BL/6J mice obtained from JANVIER, Le-Genest-Saint-Isle, France, at 28 days of age were used in the present study (2 cohorts of 40 mice, one per experiment, being purchased successively). All mice were housed in individual standard polycarbonate cages (15.5 × 31.5 cm surface × 13 cm height) with pine sawdust bedding and unlimited access to tap water and food (standard pellets, CARFIL QUALITY, Oud-Turnhout, Belgium). The colony room was maintained on a 12:12 h dark-light cycle (lights on at 07:30 h) and at an ambient temperature of 19–23 °C. All experimental treatments and animal maintenance were reviewed by the University of Liege Animal Care and Experimentation Committee, which gave its approval according to the Belgian implementation of the animal welfare guidelines laid down by the European Community (EEC Council Directive N°86/609 of the 24 November 1986; Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes).

2.2. Running wheels and housing

In both experiments, mice were randomly assigned upon arrival in the colony room to one of the two housing conditions, where they remained throughout the period of experimentation. Half of the cages contained one polycarbonate low-profile running wheel with an open running surface (ENV-044, Med Associates; St Albans, VT, USA), and the other half contained no wheel. A wheel was constituted of a saucer-shaped disk (diameter 15 cm) mounted on a cup-shaped base (height 4.5 cm) via a bearing pin so as to being inclined from the vertical plane at an angle of 35°. The base was fixed on a stable acryl-glass plate. To ascertain that all mice performed daily running, wheel revolutions were continuously recorded via a wireless system at least throughout the period of experimentation. Each wheel was connected to a USB interface hub (Med Associates, DIG-804) which relayed data to a Wheel Manager Software (SOF-860, Med Associates). Since we intended to keep physical activity to a minimum in the mice housed without a wheel, we deliberately omitted to use home-cages with a locked wheel because it is known that mice usually display much climbing activity in such cages, a behavior barely exhibited in presence of an unlocked wheel [14,27,28]. Note also that locked and unlocked wheels do not necessarily exert an effect on the same behavioural and neural targets, suggesting that the former, which act as an inanimate physical-spatial enrichment, may not provide an appropriate control for the latter [29–31].

2.3. Drug treatments

(−)-Cocaine hydrochloride (BELGOPIA, Louvain-La-Neuve, Belgium) was dissolved in an isotonic saline solution (0.9% NaCl) and injected always at 10 mg/kg via either the subcutaneous (Experiment 1) or the peritoneal (Experiment 2) route in a volume of 0.01 ml/g of body weight, the control treatments consisting of an equal volume of isotonic saline solution. The dose and the route of administration were chosen on the basis of previous studies from this laboratory [32,33].

2.4. Behavioral apparatuses

Used in Experiment 1, a battery of 8 home-made activity chambers connected to a computer running a custom-written software for data collection was used to quantify cocaine-free and cocaine-induced psychomotor activity. Each chamber was constituted of a removable transparent polycarbonate tub (22 × 12 cm