Behavioural Brain Research 311 (2016) 228–238

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Corticosterone and dopamine D2/D3 receptors mediate the motivation for voluntary wheel running in C57BL/6J mice

Mohamed Elsaed Ebada [1], David A Kendall, Marie-Christine Pardon *

University of Nottingham Medical School, School of Life Sciences, Neuroscience Group, Queen's Medical Centre, Nottingham, NG7 2UH, United Kingdom

HIGHLIGHTS

- Corticosterone synthesis contributes to voluntary wheel running performance.
- Effects of corticosterone on motivation to exercise are not mediated by GRs.
- Blockade of dopamine D2/D3 receptors dose-dependently reduces running activity.
- Reducing motivation to exercise is not sufficient to alter behaviour in C57BL6 mice.

ARTICLE INFO

Article history:
Received 7 February 2016
Received in revised form 7 April 2016
Accepted 23 May 2016
Available online 24 May 2016

Keywords:
Corticosterone
Voluntary wheel running
Dopamine D2/D3 receptors
Glucocorticoid receptors
Memory
C57BL/6J mice

ABSTRACT

Physical exercise can improve cognition but whether this is related to motivation levels is unknown. Voluntary wheel running is a rewarding activity proposed as a model of motivation to exercise. To question the potential effects of exercise motivation on subsequent behaviour, we used a pharmacological approach targeting some reward mechanisms. The stress hormone corticosterone has rewarding effects mediated by activation of low affinity glucocorticoid receptors (GR). To investigate whether corticosterone synthesis motivates exercise *via* activation of GRs and subsequently, impacts on behaviour, we treated C57BL/6J mice acutely with the inhibitor of corticosterone synthesis metyrapone (35 mg/kg) or repeatedly with the GR antagonist mifepristone (30 mg/kg) prior to 1-h running wheel sessions. To investigate whether reducing motivation to exercise impacts on behaviour, we antagonised running-induced dopamine D2/D3 receptors activation with sulpiride (25 or 50 mg/kg) and assessed locomotor, anxiety-related and memory performance after 20 running sessions over 4 weeks. We found that corticosterone synthesis contributes to running levels, but the maintenance of running behaviour was not mediated by activation of GRs. Intermittent exercise was not associated with changes in behavioural or cognitive performance. The persistent reduction in exercise levels triggered by sulpiride also had limited impact on behavioural performance, although the level of performance for some behaviours was related to the level of exercise. Altogether, these findings indicate that corticosterone and dopamine D2/D3 receptor activation contribute to the motivation for wheel running, but suggest that motivation for exercise is not a sufficient factor to alter behaviour in healthy mice.

1. Introduction

The benefits of an active lifestyle for physical and mental health are widely accepted. In both animals and humans, physical exercise improves cognitive function across the lifespan and slows down the progression of cognitive disorders such as Alzheimer's disease [1], but the underlying mechanisms are not fully understood. Encouraging people to exercise is, therefore, a promising strategy to promote health but the level of participation is related to motivation factors such as interest/enjoyment and competence which were also found to be related to positive mental health outcomes [2]. It is however unknown whether motivational aspects of exercise, rather than the exercise level *per se,* contribute to the cognitive and behavioural effects.

Voluntary wheel running has been proposed as a preclinical model of exercise motivation rather than of general locomotor activity based on a large body of evidence supporting the hypothesis that rodents engage in wheel running because it has positive

* Corresponding author.
E-mail address: marie.pardon@nottingham.ac.uk (M.-C. Pardon).
[1] Present address: Pharmacology Department, National Organization for Drug Control and Research (NODCAR), Dokki, Cairo, Egypt.

http://dx.doi.org/10.1016/j.bbr.2016.05.051
0166-4328/

salience for them (for review see [3,4]). Wheel running was indeed found to be reinforcing and rewarding and to activate brain rewards pathways. For instance, rats lever-press for an opportunity to run [5], develop conditioned place preference to the context associated with running [3,5] and show a rebound response to forced abstinence [3]. Furthermore, the effects of voluntary wheel running on the brain mimic those of other natural rewards and drugs of abuse [6,7]. Thus, the level of exercise during voluntary wheel running is an indicator of motivation to exercise. The effects of voluntary exercise on the brain and behaviour also differ from those of forced exercise even when the form and level of exercise are controlled. Forced exercise is routinely induced using a treadmill. The direct comparisons of treadmill and voluntary wheel running showed that both procedures improved spatial memory, but forced exercise also recruited fear-related neural pathways and increased aversive memory [8]. The fact that treadmill running may be seen as a different form of exercise than wheel running could contribute to the differential effects. However, by comparing forced and voluntary wheel running, it was shown that both procedures increased behavioural and neurochemical indices of reward, which appeared elicited by distinct mechanisms possibly differentiating the motivation to exercise from its rewarding effects [9]. Furthermore, similar levels of forced and voluntary wheel running were found associated with an increase in hippocampal neurogenesis that was greater in the forced exercise group who also showed increased anxiogenic-like behaviour [10]. Thus, altogether these data suggest that the motivation to exercise can exert effects on brain and behaviour that are independent of exercise levels.

The work reported here examined some mechanisms underlying the motivation for exercise using voluntary wheel running as a model and questioned the relationship between motivational aspects of exercise and its behavioural effects. Forced exercise has a stressful component that may contribute to its effects on the brain [11]. Although less stressful than forced exercise [11], voluntary wheel running also activates the hypothalamic pituitary adrenocortical (HPA) axis and elevates plasma levels of the stress hormone corticosterone [12,13]. Interestingly, corticosterone, when induced or administered at sufficient levels, has direct reinforcing and rewarding properties and enhances reinforcing and rewarding effects of abused drugs *via* activation of the low affinity glucocorticoid receptor (GR) [14–18]. This raises the question of whether corticosterone levels induced by voluntary exercise contribute to the motivation for exercise or are induced as a consequence of exercise. The first goal of this study was therefore to test the hypothesis that corticosterone mediates the motivation to exercise. This was addressed by treating C57BL/6J mice acutely with metyrapone, an inhibitor of corticosterone synthesis, prior to being allowed access to a 1-h running wheel sessions. Additionally, corticosterone release was found to contribute to the improvement in memory induced by voluntary exercise [19]. The second goal of this study was therefore to test the hypothesis that corticosterone provokes the motivation to exercise *via* activation of GR receptors and, as such, impacts on behaviour. This was addressed by treating C57BL/6J mice repeatedly with the GR antagonist mifepristone prior to being allowed access to 1-h running wheel sessions. An intermittent exercise regimen was chosen as the findings can be more translated to human who exercise intermittently than unlimited access to running wheel. Behavioural performance was assessed in locomotor, anxiety-related and memory tests.

The final goal of this study was to investigate whether reducing the motivation for wheel running, impacts on behaviour. Motivation for exercise has been linked to dopaminergic reward pathways. The rewarding effects of voluntary wheel running have been found to be associated with neuroplastic changes in the mesolimbic pathway, that include downregulation of dopaminergic D2 receptor mRNA expression in the nucleus accumbens core of rats [20]. Preference for voluntary exercise over sucrose was also found reduced after treatment with the D2 antagonist haloperidol [21]. Furthermore, the D2 antagonist raclopride reduced voluntary wheel running in mice [22] suggesting that sustained stimulation of D2 receptors contributes to the motivation for exercise. In addition, the motivation for wheel running was found reduced by inactivation of the nucleus accumbens [3], a brain region where D3 receptors, which are less abundant than D2 receptors, are preferentially expressed [23]. Thus, to reduce motivation for wheel running, we used a pharmacological approach targeting exercise-induced activation of dopamine D2/D3 receptors with the antagonist sulpiride [24]. Although dopamine receptors are involved both in locomotor and motivated behaviours, sulpiride was found to be more effective on dopamine receptors located in the mesolimbic reward pathway than in the nigrostriatal dopamine pathways [25] and devoid of effects on spontaneous motor activity [26]. It is, therefore, a suitable drug to block motivation for exercise.

To investigate whether motivation levels are related to the behavioural effects of exercise, we tested the association between exercise levels and Our main findings were that corticosterone synthesis and activation of D2/D3 receptors during voluntary wheel running contribute to exercise levels but had a limited impact on subsequent behavioural performance, suggesting that motivation for exercise is not a sufficient factor to alter behaviour in healthy mice.

2. Materials and methods

2.1. Animals

6-8-week-old male C57BL/6J mice were obtained from Charles River UK, individually caged and left to acclimatize for 1 week. Standard environmental conditions and 12:12 light/dark cycle (lights on at 7:00 a.m.) were applied in the animal holding room throughout all experiments. Mice had *ad libitum* access to food and water and their body weight was recorded weekly. All procedures undertaken in these studies were in accordance with the UK Animal Scientific Procedures Act 1986 under project licence 40/3283. Data are reported according to the ARRIVE guidelines for *in vivo* experiments [27]

2.2. Drug treatment

Metyrapone (corticosterone synthesis inhibitor), mifepristone (RU38486, GR antagonist) and (±)-sulpiride (D2/D3 receptor antagonist) were purchased from Sigma-Aldrich UK. Metyrapone (35 mg/kg, *i.p.*) was dissolved in saline. Mifepristone (30 mg/kg, *i.p.*) was suspended in vehicle A, 1% Tween 80 in saline, and sonicated for 30 s on ice. (±)-sulpiride (25 or 50 mg/kg, *i.p.*) was freshly dissolved in vehicle B (1% acetic acid/saline) and the solution was adjusted to pH 7 with 1 M NaOH.

2.3. Running wheels

Each wheel (11.5 cm in diameter) was tightly fixed to the internal side of the cage lid. A cycle computer was attached to the side of the cage lid and its sensor directed at a distance of <1 cm towards a magnet piece mounted on the wheel to count the number of the revolutions. Cycle computers were calibrated to automatically calculate the running distances over exercise sessions.

2.4. Spontaneous alternation in a T-maze

The apparatus consisted of three arms of equal dimensions (41.5 cm long, 6 cm wide in grey Plexiglas surrounded by 15 cm high walls in transparent Plexiglas) as described previously [28]. After