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Research report

Exercise-induced improvement in cognitive performance after fimbria-fornix transection depends on the timing of exercise administration

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ABSTRACT

Background: Exercise after brain injury holds major therapeutic potentials, but it is still uncertain whether such an intervention should take place during the critical time window of intrinsic repair mechanisms.
Objective: To assess the effects of acute or delayed voluntary exercise in running wheels on post-injury allocentric place learning in an 8-arm radial maze.
Methods: Forty-eight pre-shaped male rats underwent fimbria-fornix transection (FF) or control surgery (Sham). The animals were divided into six groups: FF group with no access to exercise (FF/NE); FF group starting exercise 1 day post-surgery (FF/E + 1); FF group starting exercise 8 days post-surgery (FF/E + 8); FF group starting exercise 21 days post-surgery (FF/E + 21); Sham group with no access to exercise (Sham/NE), and Sham group starting exercise 1 day post-surgery (Sham/E + 1). After 7 days of exercise 6 h/day, all animals underwent 28 place learning acquisition sessions.
Results: The FF/E + 21 group showed an enhanced acquisition of the task compared to FF/NE. The FF/E + 1 and FF/E + 8 groups also showed an enhanced task acquisition relative to FF/NE, however with a slower acquisition than the FF/E + 21 group.
Conclusion: The data underscores the link between exercise and functional recovery after brain injury and emphasizes the importance of optimal timing of this intervention.

1. Introduction

The advantageous effects of exercise on recovery after brain injury are supported by a large number of studies. Voluntary exercise, both acute and chronic, increases levels of hippocampal activity (Holschneider et al., 2003, 2007) and induces hippocampal neurogenesis, cell proliferation and survival in the injured and aging brain (Ehninger and Kempermann, 2003; Speisman et al., 2013; van Praag et al., 1999). Data from both human and animal studies suggest a beneficial link between exercise and cognitive functioning (Hillman et al., 2008; Wogensen et al., 2015), which is (at least partly) mediated by upregulation of neurotrophic and growth factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and fibroblast growth factor (FGF) (Berchtold et al., 2010; Butler et al., 1987; Farmer et al., 2004; Gomez-Pinilla et al., 1997; Griesbach et al., 2004a,b, 2009; Kleim et al., 2003; Neeper et al., 1996; Vaynman et al., 2003, 2004).

The effects of voluntary exercise in running wheels have been investigated in a variety of models of CNS injury and their positive effects have been demonstrated both when administered pre- and post-injury (Berchtold et al., 2010; Kleim et al., 2003). However, it is still a matter of debate whether post-injury exercise should be administered early or in a delayed manner in order to achieve the best clinical cognitive outcome (for review, see Wogensen et al., 2015). For instance, while Griesbach et al. (2004a,b) reported negative effects of early voluntary exercise, Shen et al. (2013) published positive consequences of an early posttraumatic exercise. It can be argued that an early intervention regimen holds potential for boosting the intrinsic repair mechanisms, while a delayed intervention

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enables longer spontaneous recovery and may thus be more efficient. The timing of a behavioural treatment is of crucial importance for successful outcome, but the number of preclinical studies investigating the topic is so far sparse. Whether to start early or later after injury appears to depend on severity of lesion, the nature of behavioural rehabilitative intervention, and the function to be recovered (Barbay et al., 2006; Biernaskie et al., 2004; Butler et al., 1987; Griesbach et al., 2004a,b, 2007; Malá et al., 2012; Shen et al., 2013).

In the present study we manipulated the length of the post-traumatic pause and investigated whether posttraumatic voluntary exercise administered at different time points (1, 8, and 21 days post-injury) enhances cognitive recovery to different degrees. In neurally intact (control) animals, we only evaluated the effect of acute voluntary exercise. This was based on the presumption that the level of spontaneous recovery is stable after a sham control surgery, and hence the timing of exercise is expected to have a similar effect on cognitive performance regardless of whether exercise is administered early or late.

As a brain injury model, we chose an axotomy of the fimbria-fornix (FF) fibre bundle, which causes anterograde and retrograde atrophy and neurodegeneration of the connected structures (hippocampus and septum) and leads to dysfunction of the hippocampus (Cain et al., 2006; Gaskin and White, 2007; Ginsberg and Martin, 1998, 2002; Ginsberg et al., 1999; Mogensen et al., 2004, 2005, 2007; Oddie et al., 2002). The transection of FF represents a partial model (Mogensen, 2011) and relative to more ecological models (such as controlled cortical impact or lateral fluid-percussion injury) it allows an investigation of only a specific set of mechanisms relative to natural as well as intervention-induced recovery. On the other hand, partial models are characterized by well-known consequences at both the neural and functional level. The presently utilized task was an allocentric place learning task administered in an 8-arm radial maze. The task has been shown to be impaired after lesions to FF (Malá et al., 2005, 2007, 2008). At the same time, the effects of exercise were not previously evaluated using this task and this type of lesion. The current setup was therefore used as a test bed regarding the recovery-promoting effects of exercise even in a partial model. Thus, our study aimed at expanding the pool of knowledge regarding exercise as an intervention tool for cognitive dysfunction after brain injury. Finally, given that previous studies have reported elevation in plasticity-related proteins after the first week of voluntary running (Griesbach et al., 2004a,b, 2008, 2009), we hypothesized that 7 days of running will be sufficient to significantly affect the process of posttraumatic recovery.

2. Materials and methods

2.1. Subjects and experimental groups

In total, 48 experimentally naïve adult male Wistar rats (Taconic), with initial body weights of approx. 300 g served as experimental subjects. The animal quarters maintained a stable temperature (22 ± 2 °C) with a 12 h light/dark cycle (lights off at 7.00 am). The humidity was constant throughout the experiment (50 ± 5%). The rats were housed in groups of two in macrolon cages with elevated lid, allowing rearing in the cage. Standard enrichment in the cage comprised a plastic shelter, nesting material and a wooden gnawing stick. The cage was changed twice a week and the rats were given water ad libitum during the entire experiment. The animals were fed commercial rat chow once daily after training and were maintained at approximately 85% of their ad libitum body weights.

All experiments were performed in accordance with the guidelines of the Danish Animal Experimentation Act ("Dyreforsøgstilsynet") and the European Council Directive 2010/63/EU of 22nd of September 2010. All experimental procedures were performed during the dark phase.

Forty-eight rats were subjected to behavioural training and testing and were randomly divided into the following groups:

1. Sham operated group with no access to exercise in running wheels (Sham/NE) (n = 9).
2. Sham operated group with access to exercise in running wheels starting one day post-surgery (Sham/E + 1) (n = 9).
3. FF-transected group with no access to exercise in running wheels (FF/NE) (n = 8).
4. FF-transected group with access to exercise in running wheels starting one day post-surgery (FF/E + 1) (n = 7).
5. FF-transected group with access to exercise in running wheels starting eight days post-surgery (FF/E + 8) (n = 7).
6. FF-transected group with access to exercise in running wheels starting twenty-one days post-surgery (FF/E + 21) (n = 8).

2.2. Apparatus

2.2.1. Running wheels

The running wheel exercise took place in ENV-042 Activity wheels with Modular Holding Cage for rat (MED Associates Inc., USA). The holding cage – from which the animals could freely access the running wheel – was 17.8 cm high, 16 cm wide and 20.3 cm deep and equipped with bedding. The wheel was 35.6 cm in diameter and 11 cm in width with a free wheeling drag of approximately 12 g. The number of wheel revolutions per hour was recorded by a computer using software developed by Ellegaard Systems, A/S, Denmark. The mean number of revolutions was calculated for each period of 6 h/day.

2.2.2. Eight-arm radial maze

All behavioural training and testing was performed in an open, grey, one-unit 8-arm radial maze with 3 cm high walls and 11.7 cm wide corridors. The eight arms radiated equidistantly from a circular central area with a diameter of 50.0 cm. Each arm was 60.0 cm long, and at the end of the arm a circular food well (diameter, 4.8 cm; depth, 2.3 cm) contained reinforcements in form of 45 mg food pellets (Precision Food Pellets, Campden Instruments, Campden, U.K.). The maze was placed in the centre of a well-lit room, approximately 100 cm above the floor. The room was equipped with a multitude of two- and three-dimensional distal cues, and no other animals were present during training and testing.

2.3. Behavioural procedures

2.3.1. Running wheel exercise

Rats in the exercise groups were placed in the running wheel apparatus at the beginning of their dark period. While in the apparatus, they had ad libitum access to water. Preoperatively, the animals were habituated to the running wheels for 2 h/day for 3 days. Postoperatively, experimental groups with access to the running wheels were exercising 6 h/day for 7 consecutive days at different time points according to which experimental group the animal belonged to (see Table 1).

2.3.2. Allocentric place learning task

Preoperatively, all animals were habituated to the maze and shaped (See Table 1 for an overview of behavioural procedures). The habituation lasted for two sessions. Each session allowed the rats 25 min of undisturbed exploration of the maze. During the first habituation session, 45 mg reinforcement pellets were scattered all