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ORIGINAL PAPER

Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats

Lelanie Marais · Dan J. Stein · Willie M. U. Daniels

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Abstract Early life stress in humans can affect the development of neurons and neurotransmitter systems and predispose an individual to the subsequent development of depression. Similarly, in rats, maternal separation causes anxiety and depressive-like behavior and decreased corticosterone levels. Patients receiving pharmacological treatment for depression often experience negative side-effects or do not respond optimally and therefore the use of exercise as alternative antidepressant treatment is investigated. The aim of the study was to see whether rats subjected to both early life stress and chronic stress later in life show differences in depressive-like behavior, neurotrophin levels, stress hormone levels and antioxidant capacity of serum after chronic voluntary exercise as treatment. Rat pups were maternally separated and one group were allowed access to running wheels for 6 weeks while control rats were also handled and put in cages without running wheels. All rats were subjected to chronic restraint stress during adulthood. A forced swim test was done to test for depressive-like behavior. Neurotrophins were measured in the ventral hippocampus and striatum; baseline stress hormones were measured in blood plasma as well as the anti-oxidative potential of serum. Compared to controls, rats that exercised had no difference in baseline stress hormones, but had decreased immobility times in the forced swim test, increased brain derived neurotrophic factor (BDNF) levels in the striatum and decreased anti-oxidative potential of their serum. The mechanism by which depressive-like behavior was improved may have been mediated through increased striatal BDNF levels, resulting in increased neuroplasticity and the prevention of neuronal death.

L. Marais (✉)
Division of Medical Physiology, Stellenbosch University, Tygerberg PO Box 19063, 7505, South Africa
e-mail: lrichter@sun.ac.za

D. J. Stein
Department of Psychiatry, University of Cape Town, Cape Town, South Africa

W. M. U. Daniels
Discipline of Human Physiology, University of Kwazulu-Natal, Durban, South Africa

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Introduction

Patients on antidepressant treatment often experience one or more adverse side-effects that decrease their quality of life and prevent remission and because of this, treatment is sometimes discontinued (Kelly et al. 2008; Hu et al. 2004). Apart from side-effects, it has also been reported that a high rate of patients do not respond to (19–34%) or only partially respond (29–46%) to antidepressant treatment (Fava and Davison 1996). Evidently, there is a need for alternative treatment options in addition to current pharmacotherapy. A recent review on clinical studies have shown that exercise is effective as antidepressant treatment; it can be also be used in combination with other treatment and that the side-effects are minimal (Daley 2008).

In humans, early life stress (Gilmer and McKinney 2003) and other stressful life events (Paykel 2001; Kendler et al. 1999) have been associated with the development of depression. Increased depressive-like behavior was also observed in rats subjected to both early life stress and subsequent chronic stress during adulthood, but not in rats subjected to only one of these stressors (Marais et al. 2008). These results suggest that early life stress can predispose an individual to the development of depression, which is then precipitated by a subsequent stressor. Imaging studies have shown that the volume of the hippocampus, striatum and frontal cortex is decreased in patients with depression (Bremner et. al. 2000; Sheline et. al. 1999; Drevets et al. 1997; Krishnan et al. 1992; Husain et al. 1991). In the hippocampus, such a decrease in volume was attributed to a marked reduction in neurogenesis or increased neuronal atrophy resulting from high circulating glucocorticoid levels after stressful events (Gould et al. 2000; McEwen 2000).

Maternal separation in rodents may be a particularly useful model of early adversity and depression and the mechanism may involve alterations in neurotrophins (Marais et al. 2008; Kuma et al. 2004; Manni et al. 1998). A decreased number of neurons, decreased proliferation and increased apoptosis of hippocampal neurons have also been observed in maternally separated rodents (Fabricius et al 2008; Mirescu et al 2004; Lee et al. 2001). Thus, animal studies indicate that maternal separation stress leads to alterations in neurotrophins, with decreased growth and survival of neurons.

Exercise, like antidepressant administration, increased neurotransmitter availability as well as neurotrophin expression in clinical and rodent studies (Blier et al. 1987; Duman 2002; Engesser-Cesar et al. 2007; Min et al. 2003; Russo-Neustadt et al 2000). Both brain-derived neurotrophic factor (BDNF) and serotonin (5-HT) activate signaling pathways and activate transcription factors that influence the expression of proteins to regulate neural plasticity, stress resistance and cell survival. An increase in 5-HT can therefore indirectly increase neurotrophin expression through activation of transcription factors (Mattson et al. 2004). Other studies that pointed towards an interaction between antidepressants, exercise and neurotrophin expression included the upregulation of BDNF mRNA after both antidepressant treatment and voluntary exercise (Russo-Neustadt et al. 2001), the increase in BDNF

levels in the hippocampus after acute treadmill running (Soya et al. 2007) and increased BDNF in the hippocampus following chronic voluntary exercise after traumatic brain injury (Griesbach et al. 2008). Vaynman et al. (2003) also found that voluntary exercise not only increased mRNA levels of BDNF, but also that of its primary receptor tropomyosin related kinase receptor B (TrkB) and the transcription factor c-AMP response element binding (CREB) in the hippocampus. Similarly, in humans, serum BDNF levels were increased together with the improvement in cognitive function after acute cycling exercise (Ferris et al. 2007).

Various forms of exercise have been used in animal studies, such as treadmill running, swimming and wheel running. Forced exercise coupled with stressors, for example electric shocks during treadmill exercise or putting the rats in water, may increase corticosterone levels and subsequently minimize the beneficial effect of the exercise on neuron structure and function . For instance, significantly higher plasma corticosterone levels were seen in rats after a single forced swim test (Hall et al 2001) while moderate intensity but not low intensity treadmill running also increased plasma corticosterone for up to 60 min after running (Soya et al. 2007). In our experiments, we used voluntary wheel running with rats having free access to running wheels only during their active phase in order to minimize the induction of stress while exercising. Apart from the effects of increased corticosterone, oxidative stress may also be induced by exercise as an effect of aerobic metabolism (Davies et al. 1982). The increase in free radical formation after exercise can induce damage to proteins and therefore it is important to measure oxidative status after exercise.

The aim of the present study was to further elucidate the current understanding of the mechanism by which exercise exerts its beneficial effects, using a rat model for depression. Our model of early adversity to induce depression was maternal separation, with a subsequent chronic stressor during adulthood. We wanted to establish what the effect of chronic exercise is on behavior, hypothalamic pituitary adrenal-axis activity, neurotrophin levels and the antioxidant potential of the serum of stressed rats.

Materials and methods

This project was approved by the Committee for Experimental Animal Research of the University of Stellenbosch (project number: P04/10/020). The experiments were performed in the Central Research Facility of the University of Stellenbosch. Male Sprague-Dawley rats were used for experiments. Rats were housed under standard laboratory conditions (12 h/12 h light/dark cycle; lights on at 6:00 am; food and water supplied *ad libitum*).

Experimental design

Maternal separation as an early life stressor

All rat pups were separated from their mothers on day 2–14 for 3 h per day in the morning (Marais et al. 2008). For this procedure, the pups were removed from their mother and placed under infrared lights keeping the ambient temperature at 30–33 °C

in an isolated room. Pups were weaned on day 21 and male rats were kept together in standard cages: 2 or 3 sedentary controls or 2 exercised rats.

Exercise

A randomly selected group of maternally separated rats were subjected to chronic voluntary exercise as a treatment. These rats were placed in cages equipped with running wheels during their active phase (corresponding to the dark cycle from 6:00 am to 6:00 pm) for a period of 6 weeks, on day 40–82 for 5 days of the week. Experimental rats were kept in pairs in the exercise cages, each having access to their own running wheel so that we could monitor whether they ran or not. The two animals in a cage were kept apart with a perforated Perspex separator between them that facilitated visual and oral communication between the rats. The control group of maternally separated rats were similarly handled but had no access to exercise wheels.

Chronic stress during adulthood

All rats were chronically restrained for five consecutive days during adulthood, from day 76 to 80. Rats were placed in Perspex restrainers for 3 h each day during the morning and then put back in their home cages. The rats were allowed to continue exercising during their active phase.

Blood and tissue collections

Rats were decapitated for blood and tissue collection on day 83 at 9:00 in the morning. Trunk blood was collected immediately after decapitation for stress hormone level determinations (in EDTA tubes to collect plasma) as well as for the antioxidant assay (in polypropylene tubes to collect serum). The brain was dissected on a cooled Perspex sheet to collect the ventral hippocampus and striatum for neurotrophin level determinations.

Parameters measured

Behavior

On day 81 the rats were habituated for 15 min to a forced swim test in a cylinder with a height of 32 cm, diameter of 32 cm, water depth of 28 cm (to ensure that the adult rats could not reach the bottom with their tails to keep their noses above the water) and temperature of 25°C. 24 h later, rats were placed in the cylinders again and their behavior recorded for 5 min. Immobility time was considered as rats floating passively, making small movements to keep their heads above the water level (El Khoury et al. 2006; Marais et al. 2008). Total immobility time (seconds) was measured during the 5 min trial on day 82 as a measure of depressive-like behavior. The forced swim test was done in the morning to allow the rats to keep exercising during their active phase.

HPA-axis

Trunk blood was collected after decapitation in EDTA tubes, centrifuged for 10 min. at 4°C and plasma stored in liquid nitrogen until analysis. Adrenocorticotrophic hormone (ACTH) was measured using a ^{125}I immunoradiometric assay from Euro-Diagnostica. Plasma was thawed and a volume of 200 μl was assayed in duplicate, with overnight incubation. Corticosterone was measured using the ImmuChem ^{125}I corticosterone radioimmunoassay (MP Biochemicals). 10 μl of plasma were diluted in 2 ml of the steroid diluent and 100 μl of the dilution assayed in duplicate. Radioactivity was measured with a Packard gamma counter.

Neurotrophins

Following decapitation, the ventral hippocampus and striatum were dissected from the brain and stored in liquid nitrogen for the determination of BDNF, nerve growth factor (NGF) and neurotrophin-3 (NT-3) levels. These were measured with Promega ELISA kits. Samples were weighed and 300 μl lysis buffer added to each sample. Samples were sonicated for 30 seconds and centrifuged at 4 °C for 20 min. The supernatant was stored at −20 °C until analysis. All samples were assayed in duplicate and a 1:2 dilution was used for NT-3 and a 1:4 dilution for BDNF and NGF. Absorbance was read on an ELISA plate reader (Bio-Tek Synergy HT) and the concentration of each sample was calculated by the computer by plotting the absorbance values on standard curve with known concentrations generated by the assay.

Anti-oxidative potential of serum

Trunk blood was collected after decapitation in clean tubes, centrifuged for 10 min. at 4°C and serum stored in liquid nitrogen until analysis. The anti-oxidative potential of serum was measured in vitro by adding it to a system that produces hydroxyl radicals. The latter causes the formation of highly fluorescent mono-hydroxylated benzoic acid products. Anti-oxidants present in serum inhibit the hydroxylation of benzoic acid. The mixture consisted of 10 mM benzoic acid, 10% ascorbic acid, phosphate buffered saline, serum and hydrogen peroxide, and was adapted to a micro-method of Van Rensburg et al. (2006). The assay was done in a black 96-well plate and each sample was assayed in triplicate. Four assay controls were included, namely (i) PBS and benzoic acid; (ii) PBS, benzoic acid and control serum; (iii) PBS, benzoic acid, control serum and ascorbic acid; and (iv) PBS, benzoic acid and ascorbic acid. Fluorescence was measured with a Perkin-Elmer LS50B luminescence spectrophotometer (excitation 305 nm; emission 440 nm). Readings were taken at baseline, 3 h, and again at 20 h after all the reagents were added. This was done to ensure that the reaction took place before the first reading and then allowed to run overnight with the second reading at 20 h.

Statistical analysis

Statistical analysis was done using GraphPad Prism 4 software. Sedentary rats were compared with exercised rats using Mann-Whitney tests. A non-parametric test was

used because of relatively small group numbers. The significance level was considered as $p<0.05$.

Results

Immobility time of exercised rats was significantly less than that of sedentary rats in the forced swim test (Fig. 1.) There was no significant difference in the baseline plasma ACTH and corticosterone levels between exercised and sedentary rats (data not shown). There was also no significant difference in the neurotrophin levels of the ventral hippocampus between the 2 groups (data not shown). Rats that exercised had increased BDNF levels in the striatum compared to sedentary rats (Fig. 2.), but no difference was found in NGF or NT-3 levels (data not shown). Exercised rats had significantly lower serum anti-oxidative potential measured at both 3 h (data not shown) and 20 h (Fig. 3.), with the baseline value subtracted, after the start of the assay. The increase in relative fluorescence is an indication that there are less anti-oxidants in the serum.

Discussion

Rats receiving exercise treatment after being maternally separated as pups and again chronically stressed as adults, showed less immobility in a forced swim test than rats that did not exercise. Therefore, chronic voluntary exercise was effective in reducing depressive-like behavior in stressed rats. Our results were in accordance with the findings of previous studies showing that chronic wheel running in mice produces antidepressant-like effects in various tests including the forced swim test, tail suspension test and learned helplessness test (Duman et al. 2008; Duman et al. 2009). Although the decreased immobility scores in the forced swim test cannot be directly extrapolated to depressive behaviour in humans, it is noteworthy that clinical studies also reported reduced symptoms of depression in patients receiving augmentation with chronic exercise treatment compared to patients that did not exercise (Dimeo et al. 2001; Craft 2005; Trivedi et al. 2006).

The 6 weeks of exercise resulted in a significant increase in striatal BDNF. Binding of neurotrophins to Trk receptors stimulates the growth, plasticity and survival of neurons (Huang and Reichardt 2003), and therefore the observed raised

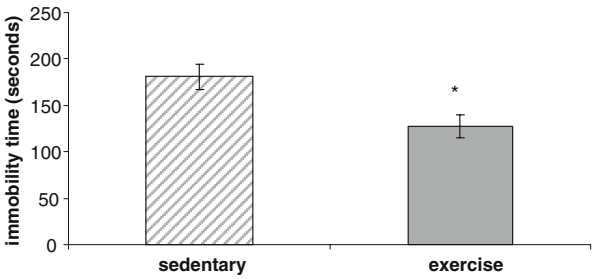

Fig. 1 Immobility time in the forced swim test was lower in rats that exercised ($n=12$) compared to sedentary rats ($n=11$). *$p<0.05$. Values expressed as means±standard error of the mean

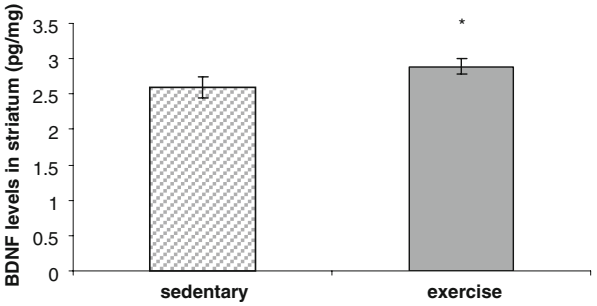

Fig. 2 BDNF levels in the striatum were increased in rats that exercised (n=10) compared to sedentary rats (n=11). *p<0.05. Values expressed as means±standard error of the mean

levels in BDNF should have a positive effect on the functioning of striatal neurons in exercised rats. BDNF has been shown to be neuroprotective and can prevent decline in brain function associated with neurodegeneration (Henningan et al. 2007). Min et al. (2003) found that exercise increases 5-HT synthesis in the dorsal raphe nucleus. Increased BDNF in the striatum could therefore be a result of increased release of 5-HT from neurons originating in the raphe nucleus. This is plausible since the expression of BDNF may be mediated through increased signaling of 5-HT that activates transcription factors such as CREB (Mattson et al. 2004). In support of this suggestion is data showing that wheel running in rats increased mRNA of CREB and synapsin I, a synaptic protein involved in neurotransmitter release (Vaynman et al. 2003), activated the phosphatidylinositol 3-kinase pathway via Trk receptors and increased p-CREB in the hippocampus (Chen and Russo-Neustadt 2005).

In spite of existing data strongly supporting our proposal that the increase in BDNF in the striatum may be related to increased 5-HT levels, it is unknown whether it was the case in our rats, because neurotransmitter levels were not measured in the present study. Exercise has also been shown to increase 5-HT in the frontal cortex and ventral hippocampus of rats (Béquet et al. 2001; Gomez-Merino et al. 2001) and therefore should upregulate BDNF expression in these brain areas. Our study, however, showed no differences in BDNF levels in the ventral hippocampus of rats that exercised compared to sedentary rats. Our findings further suggest that

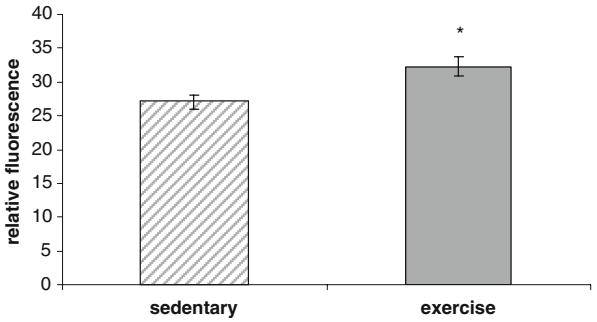

Fig. 3 The anti-oxidative potential of the serum of exercised rats (n=11) was lower than that of sedentary rats (n=11), at the 20 h time interval. *p<0.05. Values expressed as means±standard error of the mean

the effect of exercise may be BDNF specific, since exercise did not upregulate NGF or NT-3 levels in the ventral hippocampus or striatum. However, these results are compatible with earlier findings indicating that mainly BDNF is involved in antidepressant effects (Duman et al. 2008; Shirayama et al. 2000; Siucak et al. 1996). This view is also supported by a report of Johnson et al. (2003) who found BDNF, but not NT-3, to be increased in the hippocampus of mice that ran in wheels while a positive correlation was made between BDNF levels and running distance. Our results and previous studies therefore agree that mainly BDNF and not any other neurotrophins are likely to be involved in the beneficial effect of exercise.

We chose to use voluntary exercise with free access to running wheels so that the rats would experience minimal stress when exercising, because high levels of corticosterone can have a toxic effect on the brain and increase cell death (Sapolsky 1985a; Sapolsky 1985b; Sapolsky et al. 1985). The average baseline corticosterone or ACTH levels did not differ between the two groups, so although maternal separation may lead to increased plasma corticosterone levels as previously seen (Marais et al. 2008), exercise did not alter the basal secretion of corticosterone in our maternally separated rats. We did not measure corticosterone levels during or directly after the end of an exercise session, so we cannot say whether exercise itself induced a stress response or not. Blood was only collected about 3 h after the last active cycle in which the rats were allowed to exercise. Previous studies found increases in corticosterone levels after acute forced exercise but not after low intensity running (Hall et al 2001; Soya et al. 2007) and even chronic voluntary running in hamsters induced corticosterone release (Borer et al. 1992). Low intensity running increased BDNF mRNA and neurogenesis in the rat hippocampus, while high intensity running did not have the same beneficial effects (Lou et al. 2008). These observations are important as they suggest that differences in the duration and intensity of exercise can determine its beneficial effects.

An acute effect of exercise seen in this study is that it decreased the anti-oxidant potential of rat serum. This is consistent with previous studies showing that both acute swimming and restraint stress in rats similarly reduced the anti-oxidant potential of serum and that depletion of anti-oxidants occurs when free radical concentration increases (Van Rensburg et al. 2006). Aerobic exercise increases the production of free radicals and this leads to oxidative stress (Davies et al. 1982). Nevertheless, chronic exercise did not increase free radical accumulation or oxidative protein damage in rat brain tissue (Toldy et al. 2005; Ogonovsky et al. 2005; Radak et al. 2006). It is thought that adaptation occurs during chronic exercise after initial increases in reactive oxygen species. This apparently occurs by altering signaling pathways that lead to the upregulation of anti-oxidants and other pro-survival genes (Radak et al. 2005). Neurotrophins also protect against oxidative stress by upregulating anti-oxidants (Mattson et al. 1995) and in our study, increased levels of BDNF could therefore be beneficial in this process.

Conclusions

Chronic voluntary exercise was beneficial to rats that were subjected to early life stress and a subsequent stressor during adulthood. It reduced depressive-like behavior measured

during a forced swim test and increased levels of BDNF in the striatum. Our results are consistent with a range of data suggesting that exercise has neuroplastic effects, and that this may be mediated by BDNF. Further work on this rat model is needed to establish the effect of exercise on neurotransmitter synthesis and release and the expression of neuroplasticity related proteins.

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