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ORIGINAL PAPER

The interaction between stress and exercise, and its impact on brain function

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Abstract In response to acute adversity, emotional signals shift the body into a state that permits rapid detection, identification, and appropriate response to a potential threat. The stress response involves the release of a variety of substances, including neurotransmitters, neurotrophic factors, hormones, and cytokines, that enable the body to deal with the challenges of daily life. The subsequent activation of various physiological systems can be both protective and damaging to the individual, depending on timing, intensity, and duration of the stressor. Successful recovery from stressful challenges during early life leads to strengthening of synaptic connections in health-promoting neural networks and reduced vulnerability to subsequent stressors that can be protective in later life. In contrast, chronic intense uncontrollable stress can be pathogenic and lead to disorders such as depression, anxiety, hypertension, Alzheimer's disease, Parkinson's disease, and an increased toxic response to additional stressors such as traumatic brain injury and stroke. This review briefly explores the interaction between stress experienced at different stages of development and exercise later in life.

Keywords Voluntary running · Maternal separation · Stress exercise

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Introduction

Exercise is generally considered to be health-promoting, but at high intensity it is can also be a stressor with negative consequences instead of an activity that contributes to human well-being. Regular moderate aerobic exercise promotes antioxidant capacity in the rodent brain (Camiletti-Moirón et al. 2013). In contrast, anaerobic or high-intensity exercise reduced the protective response of the brain to oxidative stress (Camiletti-Moirón et al. 2013). In addition, the beneficial effects of exercise can be modified by prior exposure to stress, raising concerns about its efficacy as a therapeutic modality in adulthood (Mabandla et al. 2009; Mabandla and Russell 2010). A number of studies have recently been published focusing on the interaction between stress, exercise, and brain function.

Exercise challenges homeostasis, it stimulates the sympathetic nervous system to release adrenaline and noradrenaline (Christensen and Galbo. 1983; Droste et al. 2007). Noradrenergic projections arising from the locus coeruleus regulate neuronal function via β-adrenergic receptors in areas of the brain that are critically involved in learning and memory, such as the hippocampus, prefrontal cortex, and amygdala (Timmermans et al. 2013). High-intensity exercise also stimulates the hypothalamic-pituitary-adrenal (HPA) axis to secrete corticotropin releasing factor (CFR), vasopressin, and glucocorticoids (McKeever et al. 1987; Freund et al. 1991; Droste et al. 2003; 2007). These hormones alter a variety of physiological functions to facilitate adaptation to homeostatic challenge (De Kloet et al. 2005).

Excitatory glutamate synapses play a critical role in synaptic transmission, synaptic plasticity and behavioural adaptation (Timmermans et al. 2013). At glutamate synapses, the ionotropic AMPA receptor mediates rapid transmission and changes in its trafficking have been proposed to be a core mechanism for synaptic plasticity (Zhang et al. 2013). This is important in understanding how stress can influence

behaviour since the stress-induced release of glucocorticoids regulates synaptic plasticity by altering glutamate receptor function in limbic brain structures such as the hippocampus, amygdala, and prefrontal cortex (De Kloet et al. 2005; Tse et al. 2011). Glucocorticoids enhance the influx of calcium via glutamate NMDA receptors, facilitating both long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus (Tse et al. 2011). However, high concentrations of corticosterone reduced LTP in hippocampal slices (Zhang et al. 2013). Prenatal stress induced depression-like behaviour and reduced NMDA subunit (NR1 and NR2A) levels in several brain regions (Sun et al. 2013). AMPA receptors cycle in and out of the postsynaptic membrane. Norepinephrine released during exercise stimulates phosphorylation of GluR1 and delivery of GluR1-containing AMPA receptors to the synapse during LTP, thus enhancing learning and memory formation (Hu et al. 2007). Acute stress causes rapid insertion of Ca^{2+}-permeable AMPA receptors into the synapse to facilitate LTP in the hippocampus (Whitehead et al. 2013). Drugs that prevent glucocorticoid-induced surface dispersal of AMPA receptors from the synapse restored LTP in acutely stressed animals (Zhang et al. 2013). These results attest to the complexity of the interaction between stress and glutamate receptor function.

The long-term effects of a stressor on an individual are largely determined by its intensity, duration and the success or failure of the individual to cope with the stressor. Successful recovery from life events leads to strengthening of synaptic connections in health-promoting neural networks that protect the individual from similar challenges in later life. It is well known that neural networks are altered by experience, the outcome of which leads to the encoding of new information that the body can use to survive similar recently experienced conditions and enhance future performance as a result of exceeding previously perceived limitations.

In response to acute environmental adversity, emotional signals exert a powerful influence on behaviour and shift the body into a state that is optimal for detection, identification, and generation of an appropriate response to a possible threat. The stress response involves the release of a variety of substances that enable an individual to deal with the challenge. These include neurotransmitters, hormones, neurotrophic factors, and cytokines. The physiological systems that are activated by these messengers can either protect or damage the body depending on the timing, intensity, and duration of the stressor. In this brief review we explore the interaction between stress experienced at specific stages of development and the benefit of subsequent exercise in later life.

Early developmental stress

Stressors in daily life are necessary for development of the brain. The body learns to adapt to daily challenges to avoid injury and to ensure a successful outcome. However, circumstances in which an individual is unable to achieve success and avoid injury can be damaging and impair cognitive function in later life. Chronic uncontrollable stress can promote disease.

Monti et al. (2013) showed that mild head trauma during the early stages of development caused impairment of memory performance in adulthood. He also showed that individuals who had suffered mild head trauma in early life had reduced hippocampal volumes in adulthood. Many studies have found reduced volume of limbic brain areas (hippocampus, nucleus accumbens, basolateral amygdala and prefrontal cortex) in middle-aged and elderly humans with stress-related disorders such as depression (Lai et al. 2000; Steffens et al. 2003; Campbell et al. 2004; Russo and Nestler 2013). Histological analysis of post-mortem brains of depressed subjects suggested that the reduced brain volume may be due to loss of glia and a decrease in the number of synaptic connections between neurons (Russo and Nestler 2013). There is considerable evidence to suggest that axonal outgrowth is inhibited in the prefrontal cortex and that structure-related proteins are decreased in limbic brain areas of animal models of depression (Daniels et al. 2012; Dimatelis et al. 2013)

We have shown that mild pre-or postnatal stress can increase the vulnerability of dopamine neurons to a toxic insult, the infusion of 6-hydroxydopamine (6-OHDA) into the brains of Sprague–Dawley rats. For example, prenatal stress decreased the number of tyrosine hydroxylase-positive cell bodies in the substantia nigra in adult rats, following 6-OHDA infusion into the medial forebrain bundle, and maternal separation caused a greater loss of tyrosine hydroxylase staining in the ipsilateral striatum in response to 6-OHDA infused into the striatum of 35-day-old rats (Pienaar et al. 2008; Mabandla et al. 2009). In all studies, dopamine neuron degeneration was accompanied by greater impairment of contralateral forelimb motor function in the stressed rats.

Exercise

It is generally accepted that exercise is beneficial for aging humans as well as patients with Parkinson's disease or Alzheimer's disease (Chapman et al. 2013). Supervised aerobic exercise (3 × 1-hour sessions/week for 12 weeks) improved immediate and delayed memory performance which was associated with increases in both left and right hippocampal cerebral blood flow (Chapman et al. 2013). In addition, the two cardiovascular parameters, VO_2 max and rating of perceived exertion, showed gains, compared to the control group. Nevertheless exercise is a stressor and the timing, intensity, duration, and confounding effects of

exercise are unknown. Stress can be beneficial. A mild stressor, immersion of a hand in ice-cold water for 3 min after a training session, significantly improved memory recall in a predictive learning task (Hamacher-Dang et al. 2013). Physical exercise reduced many of the motor symptoms of Parkinson's disease (Aýan et al. 2013; Nadeau et al. 2013) and the cognitive decline that occurs in Alzheimer's disease (Farina et al. 2013).

These observations are supported and extended by animal studies. Animal studies have shown similar improvements in cognitive function following exercise (Aguiar et al. 2011; Goes et al. 2013; Kim et al. 2013; Wang et al. 2013). Short bouts of mild-intensity exercise improved spatial learning and memory in aging rats (Aguiar et al. 2011). In rat pups subjected to hypoxic ischemia, treadmill exercise (30 min/day) preserved spatial learning and sensory-motor function (Choi et al. 2013; Park et al. 2013). In addition, we found that exercise can be neuroprotective, reducing the loss of dopamine neurons in the 6-OHDA-lesioned rat model of Parkinson's disease (Tillerson et al. 2001; Mabandla et al. 2004; Howells et al. 2005; Mabandla et al. 2009; Zigmond et al. 2009). Similarly, Park et al. (2013) showed that treadmill exercise (30 min/day) in the early adolescent period (4–16 weeks of age) reversed dopamine neuron loss in rats subjected to neonatal ischaemic brain injury.

Interaction between stress and exercise

Exercise during pregnancy has been shown to increase hippocampal plasticity in the offspring postnatally (Bick-Sander et al. 2006). We observed that mild *prenatal* stress (7-hour shift in the light/dark cycle, food deprivation for 24 h, and handling involving moving to new cage and back) reduced resilience. Rats that had been subjected to mild prenatal stress during the third week of gestation suffered an increased loss of tyrosine hydroxylase-positive cells (dopamine neurons) in the substantia nigra of the midbrain in response to unilateral infusion of 6-OHDA (5 μg) into the medial forebrain bundle (Mabandla et al. 2009). In addition, rats that had been subjected to mild prenatal stress did not produce the adaptive decrease in the number of tyrosine hydroxylase-positive neurons in the contralateral substantia nigra seen in non-stressed rats (Mabandla et al. 2009). The increased loss of dopamine neurons in the lesioned hemisphere was accompanied by greater impairment of forelimb function controlled by the lesioned hemisphere. Prenatal stress also reduced the beneficial effect of exercise on forelimb sensory-motor function (Mabandla et al. 2009). A similar interaction between stress and exercise was observed in the initiation of movement of the affected forelimb of rats that had been subjected to the early postnatal stress of maternal separation (dam removed from the litter for 3 h/day from postnatal day 2 to 14) (Mabandla and Russell 2010). Similar to prenatal stress, maternal separation reduced the use of the affected forelimb in the limb use asymmetry test. In contrast, maternal separation did not reduce the beneficial effects of exercise in this test, nor did it exaggerate the loss of dopamine neurons in the substantia nigra ipsilateral to the 6-OHDA-lesioned medial forebrain bundle, as was found after prenatal stress. These findings provided evidence that the timing and the nature of the stressors are critical in determining the beneficial and/or adverse effects of stress on the individual.

The purpose of subsequent studies was to address the critical question of *how* stress experienced during the early stages of development could alter brain function in ways that reduce the beneficial effects of exercise in later years. We had shown that stress experienced early in life reduced not only the exercise-induced changes in neuron survival and behaviour, but also caused changes in brain neuroplasticity. We found that voluntary exercise stimulated the mitogen-activated protein kinase/extracellular signal-regulated protein kinase 1/2 (MAPK/ERK1/2) signalling pathway in the rodent hippocampus and that this stimulation was blocked in rats that had been subjected to the early life stress of maternal separation (Makena et al. 2012). We also showed that maternal separation altered protein levels in the ventral hippocampus and decreased proteins involved in structure, energy metabolism and signalling in the prefrontal cortex of adult rats, and that these changes were mostly reversed by exercise or the stress of constant light exposure for 3 weeks during adolescence (Daniels et al. 2012; Dimatelis et al. 2013). Adolescence has been identified as a critical period during which stress can regulate hippocampal plasticity. Maternal separation followed by forced swim stress during adolescence has been shown to increase hippocampal neurotrophin levels (Faure et al. 2006; 2007). Restraint stress in adulthood potentiated the effects of maternal separation by increasing depression-like behaviour, evidenced as increased time spent immobile in the forced swim test (Marais et al. 2008). We hypothesized that identification of the critical period, intensity, and duration of stressors, as well as the brain areas and the molecular mechanisms affected by early life stress, would lead to a better understanding of the effect of stress on the risk of developing neuropsychiatric and neurodegenerative disorders later in life. We therefore explored this further.

Voluntary exercise increased phospho-ERK1/2 (p-ERK1/2) levels in both dorsal and ventral hippocampus in non-separated rats. This effect of exercise was not observed in rats that had been subjected to maternal separation in early life (Makena et al. 2012), possibly due to upregulation of the MAPK phosphatase, MKP-1 (also known as dual specificity protein phosphatase 1), which removes the phosphate from p-

ERK1/2 to inactivate it in stressed rats (Akbarian and Davis 2010). It is well established that exercise increases brain derived neurotrophic factor (BDNF) in the brain, including striatum and hippocampus (Cotman and Berchtold 2002; Marais et al. 2009; Bechara et al. 2013; Fang et al. 2013). Similar to our findings, Fang et al. (2013) showed that stress (2 h/day immobilization for 7 days) in young adult rats, reduced the increase in BDNF expression normally elicited by 3×10-min bouts of 15 m/min treadmill exercise per day for 5 days and also decreased phosphorylation of the BDNF receptor, Trk, and its target proteins in the PI3K/Akt pathway (Akt, glycogen synthetase kinase-3 (GSK-3), mammalian target of rapamycin (mTOR)) leading to translation initiation and protein synthesis. Immobilization stress also caused a reduction in the synaptic markers, synaptophysin, PSD-95, neuroligin 1, and β-neurexin, which was reversed by treadmill exercise (Fang et al. 2013). Insulin-like growth factor-1 and VEGF have also been associated with exercise ameliorating the damaging effects of stress evidenced by improved cognition and increased hippocampal cell proliferation (Ding et al. 2006; Yau et al. 2012).

Exercise has been shown to increase hippocampal dendritic spine density in adulthood possibly as a result of increased negative feedback regulation of the HPA axis, decreasing circulating corticosterone levels (Stranahan et al. 2007; Wosiski-Kuhn and Stranahan 2012). Voluntary exercise (4 weeks of wheel running) has been shown to protect the hippocampus from the damaging effects of elevated corticosterone by increasing hippocampal glucocorticoid receptor levels and decreasing the sensitivity of mineralocorticoid receptors (Droste et al. 2003; 2007). Stress had the opposite effect of reducing glucocorticoid receptor levels. The stress of forced swimming increased corticosterone levels in the exercising rats (Droste et al. 2007). In contrast, if exercised rats were exposed to a novel environment, they showed a much lower corticosterone response to acute stress than control animals (Droste et al. 2007). It appeared that in exercising rats physically demanding stressors enhanced the glucocorticoid response to stressors while mild stressors, such as a novel environment, gave rise to a blunted glucocorticoid response (Droste et al. 2007). The blunted corticosterone response corresponded with the exercising rats showing less anxious behaviour in a novel situation (Droste et al. 2007). It is evident that the health-promoting effects of exercise are mediated by neural networks that are shaped by prior experience and which lead to altered regulation of corticosterone release in response to future stress. In support of mild stress being beneficial and high-intensity exercise being stressful, mild-intensity (5–10 m/min) treadmill exercise (30 min/day for 7 days) was more effective than heavy-intensity (10–16 m/min) exercise in reducing prenatal stress-induced impairment of spatial learning in the Morris Water Maze test (Kim et al. 2013). Similarly, mild-intensity (8 m/min) exercise (30 min/day for 14 days) improved spatial memory performance and hippocampal synaptic plasticity in transient brain ischemic rats whereas high-intensity (20 m/min) treadmill exercise had no effect on spatial memory, hippocampal BDNF, synapsin-1, PSD-95, or dendritic arborization in rats subjected to transient middle cerebral artery occlusion (Shih et al. 2013). Importantly, plasma corticosterone levels were elevated in the high-intensity exercise group, suggesting that excessive exercise overstimulates the HPA axis giving rise to the deleterious effects of glucocorticoids, while mild exercise, being a lesser stressor, is beneficial to brain function (Shih et al. 2013).

Exercise also increased neurogenesis in adult rodent hippocampus (Bechara et al. 2013; Gebara et al. 2013; Kim et al. 2013). Aging is associated with reduced neurogenesis, chronic inflammation and increased microglial proliferation that can be attenuated by exercise, thus suggesting that exercise can be beneficial in old age (Kohman et al. 2012; Gebara et al. 2013). Glucocorticoids have been shown to directly affect hippocampal neuroplasticity, since corticosterone, administration to older rats (at levels found in younger rats) that had undergone adrenalectomy, reinstated hippocampal neurogenesis (Cameron and McKay 1999).

Not only the intensity but also the duration of exercise needs to be defined in order to realize the full structural and functional benefit of exercise for brain function. Patten et al. (2013) evaluated the effects of different periods of voluntary running (3, 7, 14, 28, and 56 days) on both structural (cell proliferation and maturation) and functional (in vivo LTP) changes in the dentate gyrus of adult male Sprague–Dawley hippocampus. They found that both short and long-term periods increased cell proliferation in the dentate gyrus of the hippocampus. However, increases in neurogenesis required longer-term exercise protocols. Increases in immature neurons were not observed until animals had been running for a minimum of 14 days. Similarly, short-term periods of wheel running did not facilitate LTP in the dentate gyrus of adult animals, and reliable increases in LTP were only observed after 56 days of exercise. These results provided a greater understanding of the duration of exercise needed to enhance hippocampal dentate gyrus function. Furthermore, the results indicated that the new neurons produced in response to exercise do not contribute significantly to synaptic plasticity until they mature (Patten et al. 2013).

Mild stressors are health-promoters

Mild repeated stressors have been suggested to be health-promoting (Rothman and Mattson 2013) and there is some evidence that the repeated mild stress of maternal separation can have beneficial effects on cognitive function in rats (Makena et al. 2012). A mild stressor that is frequently overlooked in animal studies is the stress of handling.

Silveira et al. (2011) showed that early handling increases the ability to cope with chronic variable stress in adulthood. Neonatally-handled rats were less susceptible to developing depression-like behaviour. Intermittent energy restriction has been suggested to be central to the beneficial effects of exercise on the brain.

Rothman and Mattson (2013) proposed that intermittent dietary energy restriction, exercise, and cognitive challenges would increase BDNF production with subsequent activation of the PI3K/Akt signalling pathway, leading to DNA translation and increased synthesis of neuroprotective trophic factors, protein chaperones, anti-apoptotic proteins, anti-oxidant enzymes, and DNA repair enzymes on the one hand, and neuroplasticity resulting from increased synthesis of trophic factors, glutamate receptors, and calcium-binding proteins on the other. All of these effects resulting from increased BDNF levels were suggested to protect the brain from developing a range of neurological disorders including depression, anxiety, stroke, Parkinson's and Alzheimer's disease (Rothman and Mattson 2013).

Conclusion

In this brief summary of recent literature on the impact of stress and exercise on the normal and abnormal brain we have focused in large part on work performed in South Africa. We showed that mild pre- or postnatal stress can increase the vulnerability of dopamine neurons to toxic insult. We also showed that stress experienced in the early stages of development reduced not only the exercise-induced changes in neuron survival and behaviour, but also the exercise-induced changes in brain neuroplasticity. We found that voluntary exercise stimulated the MAPK/ERK1/2 signalling pathway in the rodent hippocampus and that this stimulation was blocked in rats that had been subjected to the early life stress of maternal separation. We have argued that a full appreciation of the effects of stress and exercise – as well as their interactions – requires a consideration of the characteristics of both conditions, including their nature, duration, intensity, and the age at which exposure takes place. We have also pointed out that exercise and particularly stress can either promote or impair health. Further research, including the translation of studies in laboratory animals to humans, will be required to fully understand these critical variables.

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