Neuroscience 151 (2008) 1173–1183

SEROTONERGIC AND NORADRENERGIC LESIONS SUPPRESS THE ENHANCING EFFECT OF MATERNAL EXERCISE DURING PREGNANCY ON LEARNING AND MEMORY IN RAT PUPS

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Abstract—The beneficial effects of exercise on learning and memory are well documented but the effects of prenatal exposure to maternal exercise on offspring are not clear yet. Using a two-trial-per-day Morris water maze for five consecutive days, succeeded by a probe trial 2 days later we showed that maternal voluntary exercise (wheel running) by pregnant rats increased the acquisition phase of the pups' learning. Maternal forced swimming by pregnant rats increased both acquisition and retention phases of the pups' learning. Also we found that the rat pups whose mother was submitted to forced-swimming during pregnancy had significantly higher brain, liver, heart and kidney weights compared with their sedentary counterparts. On the other hand we estimated the cell number of different regions of the hippocampus in the rat pups. We found that both exercise models during pregnancy increased the cell number in cornus ammonis subregion 1 (CA1) and dentate gyrus of the hippocampus in rat pups. To determine the role that noradrenergic and serotonergic neurotransmission and *N*-methyl-D-aspartate (NMDA) receptors hold in mediation of the maternal exercise in offspring, we used N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4), *p*-chloroamphetamine (PCA) and MK-801 to eliminate or block the above systems, respectively. Blocking the NMDA receptors, significantly abolished learning and memory in rat pups from all three experimental groups. Elimination of noradrenergic or serotonergic input did not significantly attenuate the learning and memory in rat pups whose mothers were sedentary, while it significantly reversed the positive effects of maternal exercise during pregnancy on rat pups' learning and memory. The presented results suggest that noradrenergic and serotonergic systems in offspring brain seem to have a crucial specific role in mediating the effects of maternal physical activity during pregnancy on rat pups' cognitive function in both models of voluntary and forced exercise. **© 2008 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: physical activity, hippocampus, offspring, DSP-4, PCA, MK-801.

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Abbreviations: ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; CA1, cornus ammonis subregion 1; DG, dentate gyrus; DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; F.swimming, forced swimming; HPA, hypothalamic–pituitary–adrenal; LTP, long-term potentiation; MWM, Morris water maze; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; PCA, *p*-chloroamphetamine; PND, postnatal day; S.E.M., standard error of the mean; V.exercise, voluntary exercise.

Several reports have studied the beneficial effects of physical activity and exercise on brain function such as improvement in learning and memory (Fordyce and Wehner, 1993; Kramer et al., 1999), cognitive function (Laurin et al., 2001), neurogenesis (van Praag et al., 1999) and recovery from brain injury (Grealy et al., 1999). It has been observed that exercise can improve the performance of experimental animals in tests of spatial learning (Vaynman et al., 2004; van Praag et al., 1999). On the other hand whether or not prenatal exposure to exercise (during pregnancy) has the same beneficial effects on fetus remained for the most parts unexplored. Recently it has been reported that maternal forced exercise during pregnancy significantly enhances the hippocampal brain-derived neurotrophic factor (BDNF) mRNA expression in neonatal rat pups and the hippocampal neurogenesis and spatial memory later in progeny (Kim et al., 2007; Lee et al., 2006; Parnpiansil et al., 2003). In these reports using multiple T maze and step-down avoidance tasks the positive effect of maternal physical activity during pregnancy on offspring spatial memory has been studied. Another aspect which remains to be explored is the mechanism(s) by which maternal exercise during pregnancy may affect the offspring learning and memory. A number of mechanisms such as noradrenergic and serotonergic neurotransmission (Garcia et al., 2003; Ivy et al., 2003), BDNF receptor activation (Vaynman et al., 2003), *N*-methyl-D-aspartate (NMDA) receptor activation (Vaynman et al., 2003), insulin like growth factor-I (IGF-I) receptor activation (Ding et al., 2006; Carro et al., 2001) and vascular endothelial growth factor (VEGF) receptor activation (Fabel et al., 2003) have been suggested as the mediators of exercise effects on brain. It has been shown that BDNF promotes the phosphorylation of synapsin I by activation of TrkB receptors in the presynaptic terminals, resulting in neurotransmitter release (Parnpiansil et al., 2003). NMDA receptors have a well-established interaction with BDNF (Suen et al., 1997). It has been proposed that BDNF interaction with other molecules such as NMDA receptors may significantly modulate its

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doi:10.1016/j.neuroscience.2007.10.051

effects on hippocampal plasticity (Vaynman et al., 2003). Activation of NMDA receptors generates long-term potentiation (LTP), whereas inhibition and deletion of NMDA receptors impair LTP and spatial learning and memory (Sakimura et al., 1995; Tsien et al., 1996). Wheel and treadmill running were found to increase norepinephrine (NE) level in several brain regions such as hippocampus and propranolol (a beta receptor blocker) could suppress the enhancing effect of physical exercise on hippocampal BDNF mRNA (Ivy et al., 2003). The place that serotonergic system takes in mediating the exercise effects on brain is not clearly understood albeit evidence exists that exercise increases 5-HT release and metabolism (Meeusen et al., 1996; Chaouloff, 1994). Furthermore it is reported that $5\text{-HT}_{2A/C}$ blockade by ketanserin, could attenuate the exercise induced increase in BDNF mRNA level in CA4 region of the hippocampus (Ivy et al., 2003). But administration of the 5-HT_{1A} receptor antagonist WAY100635 did not attenuate exercise induced BDNF mRNA levels, and on the contrary enhanced the BDNF mRNA up-regulation in the CA4 region (Ivy et al., 2003). This finding shows the involvement of at least some of the serotonergic receptors (although less evidently) in mediating the effects of exercise on brain function. However the effect of maternal exercise during pregnancy on a developing brain can be mediated differently because in contrary to the mother's brain; the connection between the fetus and the exercising muscles is only through the placental barrier. This can lead to this suggestion that maternal mediators of exercise effects should pass through the placenta and affect the fetus, though such a hypothesis is not documented and the responsible factor(s) is not identified yet.

Forced exercise (as treadmill running or swimming) and voluntary exercise (V.exercise) (as wheel running) are among the animal models which can be used to study the effect of exercise on brain. Forced exercise models are obligatory and consist of stressful experiences that may activate the hypothalamic–pituitary–adrenal (HPA) axis and increase the levels of circulating adrenal steroids while spontaneous running is not an intense stressor (Yanagita et al., 2007). Although several workers have indicated that prenatal stressful events can be associated with an impairment of learning (Fujioka et al., 2006; Coe et al., 2003; Lordi et al., 1997), it has been demonstrated that short lasting or mild prenatal stressors (such as short lasting restraining) could enhance neurogenesis, neuronal differentiation in hippocampus and spatial learning in offspring (Fujioka et al., 2006; Cannizzaro et al., 2006; Fujioka et al., 2001). The neurobiological mechanism underlying the modifying effect of maternal exposure to mild stress, on learning performance in the offspring is proposed to be the rise in maternal corticosterone which may exert a facilitative influence on the development and maturation of HPA axis and hippocampus (Cannizzaro et al., 2006). On the other hand the animals who are submitted to the forced models of exercise usually do the exercise only for short periods of time per day while V.exercise simulates aspects of human behavior in which animals choose how much to run themselves (Vaynman et al., 2004). It has been reported that sub-lactate threshold treadmill running (15 m/min for 30 min) in rats does not increase c-Fos induction (a marker for neuronal activation) in hypothalamus (Soya et al., 2007). Nevertheless significant increase in c-Fos induction in various hypothalamic regions and plasma adrenocorticotropic hormone was observed during supra-lactate threshold intensity (25 m/min for 30 min) treadmill running (Soya et al., 2007). These reports indicate that exercise intensity is another factor that should be considered in activation of HPA axis.

In the present study using a Morris water maze test (MWM), the effects of maternal V.exercise and forced swimming (F.swimming) during pregnancy on the offspring cognitive function were studied. Also the role of NMDA receptors and serotonergic and noradrenergic systems in the effects of prenatal exposure to exercise on offspring spatial learning and memory was evaluated. Additionally, the effect of performing both exercise models in pregnant rats on cell number in cornus ammonis subregion 1 (CA1), dentate gyrus (DG) and subiculum of the newborn rat pup hippocampus and the weight of different organs were calculated.

EXPERIMENTAL PROCEDURES

Animals

All animals were obtained from breeding colony of Semnan University of Medical Sciences, Semnan, Iran. Male Wistar rats (210±10 g) were allowed to mate with female virgin Wistar rats (210±10 g) during a 24 h period. Female rats were checked for the presence of a vaginal plug twice at midnight and at 5 a.m. the next day. Once the vaginal plug was observed the animal was considered as pregnant. The pregnant rats have been randomly assigned to sedentary, F.swimming and V.exercise groups (N=36 in each group) and were housed individually in cages with a 12-h light/dark cycle at 22–24 °C temperature, with food and water *ad libitum*. In each group the animals which have had the vaginal plug but were not pregnant were omitted from the study when their lack of pregnancy was confirmed. All experimental procedures were carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals and all experiments conformed to Semnan University of Medical Sciences Guidelines on the ethical use of laboratory animals. Also in each experiment care was taken to minimize the animals' suffering and to use the minimum number of the animals. From day 21 after mating female rats were checked twice daily for birth, at 9 a.m. and 6 p.m. The day that pups were first observed was taken as postnatal day 0 (PND0) and each mother and its pups were considered as a colony.

Drugs and injections

On PND29, the rat pups were weaned and were randomly assigned to different sub-groups based on the group that their mother had been submitted to, with eight rat pups in each group (four male and four female). The rat pups whose mother was from sedentary, F.swimming and V.exercise groups were assigned to the following sub-groups: control (no treatment), NS (received 200 μl of normal saline i.p. every day during the MWM trials 30 min before the training), MK-801 (received 0.05 mg/kg MK-801 i.p. every day during MWM trial, 30 min before the training), NS-PND33 (received 200 μl of normal saline i.p. on PND33), *p*-chloroamphetamine (PCA) (received a single i.p. injection of PCA 10 mg/kg on PND33), NS-PND29 (received 200 μl of normal saline i.p. on PND29), N-(2-chloroethyl)-N-ethyl-2-bromoben-

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