Original Article

Preventive Effect of Maternal Forced Exercise on Offspring Pain Perception and Intensity: The Role of 5-HT_2 and D_2 Receptors

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Abstract

Background: Many previous studies showed that maternal forced exercise can reduce some central disorders in offsprings, but its clear mechanism remains unclear. In this study, the role of 5-HT_2 and D_2 receptors in neuroprotective effects of maternal forced exercise in offspring neurodevelopment and effect on some behaviors were evaluated. **Materials and Methods:** Forty-eight pregnant rats were trained by forced exercise, and some behavioral assays in their offspring were performed in the presence and absence of 5-HT_2 and D_2 receptor antagonists in various experimental groups. **Results:** Our data showed that maternal forced exercise caused increase in latency of pain perception in offsprings in hot plate test, writhing test (WT), and tail flick test. Furthermore, a decrease in intensity was shown by WT. On the other hand, treatment of mothers by forced exercise in combination with 5-HT_2 and D_2 receptor antagonists could inhibit these effects of forced exercise and cause disturbances in pain perception and intensity. **Conclusion:** Our data suggested that maternal forced exercise causes protective effects on offspring pain perception and intensity, and in this effect, 5-HT_2 and D_2 receptors are probably involved.

Keywords: *Maternal forced exercise, offspring, pain perception*

Introduction

Previous studies demonstrated that exercise lowers the stress and anxiety and increases endorphin secretion in brain.[1,2] Physical activity improves anxiety symptoms in healthy people and patients; chronic forced exercise shows anxiolytic-like effects in some experiments.[3] It has also been shown that exercise can counteract depression, anxiety, and pain perception and can increase the cognitive activity.[4-6] Chronic exercise in mice resulted in antidepressant-like behavioral changes that may involve a brain-derived neurotrophic factor (BDNF)-related mechanism similar to what is hypothesized for antidepressant drug treatment.[7] Exercise increases synthesis and release of dopamine and serotonin, stimulates neuroplasticity, and promotes feelings of well-being.[6] Many previous studies have shown that maternal exercise enhances neurogenesis in rat's pups, but the exact mechanism of this effect remains unclear.[8-11] Some of the studies showed that maternal exercise has beneficial effects on their offspring brain.[12,13] Furthermore, previous studies showed that offspring of the pregnant mother under treatment by regular forced exercises showed a low level of anxiety, depression, and metabolic disorder on their life. In addition, these studies demonstrated that maternal forced exercise causes increase in seizure threshold and reduces the epileptic attacks in offspring.[8,14] All of these studies showed that maternal forced and voluntary exercises can modulate the formation of dopaminergic and serotonergic systems in offspring brain; on the other hand, the role of these two neural transmission systems has been considered more powerful in mentioned studies.[15-17] It should be noted that despite all the benefits of maternal exercise during pregnancy on their offsprings and its beneficial effects on the increase of pain threshold in pups, the underlying mechanisms are unclear. Many neurotransmitters and neuromodulators can have effects on neurogenesis in fetus during development.[18,19] Some other studies have shown that dopamine and serotonin cause increase in neurogenesis and activate the neurogenesis pathways via activation of D_2 and 5-HT_2 receptors, respectively.[19-24] Many previous studies showed that D_2 and 5-HT_2 receptors, during fetal development,

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play powerful roles in the formation of neurons in reward pathways, which contribute to inhibition of anxiety and depression and enhance the cognitive function.[18-24] In addition, these two types of receptors, D_2 and 5-HT_2, have been shown to have more important roles in neurogenesis compared to μ receptors of opioid system, α_2 receptor of adrenergic system, and gamma-aminobutyric acid receptors.[25-27] According to the available data, there is no evidence about the role of maternal forced exercise on the formation of pain pathway in offspring and its mechanism of action. Furthermore, given that the D_2 and 5-HT_2 receptors have powerful roles on neurogenesis, the aim of the present study is the study of neuroprotective effects of maternal forced exercise and evaluation of the influence of two neurotransmitters, dopamine and serotonin, and their receptors, D_2 and 5-HT_2, on maternal forced exercise protective effect in offspring pain perception.

Materials and Methods

Animal

Forty-eight pregnant Wistar rats, weighing 250 ± 2 g, were used for all the experiments. All animals were obtained from Experimental Research Center of Iran University of Medical Sciences. They were divided randomly into six groups as mentioned bellow. After delivery, their offspring's were kept in the light-controlled room under a 12 h light and dark cycle with a temperature of 22 ± 2°C. Food and water were available *ad libitum*. Before the start of the tests, the animals were allowed to adapt themselves to the laboratory for at least 2 h, and they were used only once. All experimental procedures followed the guidelines on ethical standards for investigation of experimental pain in animals.

Drug

Haloperidol and trazodone were purchased from Sigma–Aldrich, Inc. (St Louis MO, USA).

Experimental design of pregnant rats

All pregnant animals were divided randomly into six groups. It should be mentioned that all pregnant rats were treated by the following protocol during the days of 5–23 of gestation.

- As the negative control, Group 1 received normal saline (0.7 ml/rat, i.p., once daily) during their pregnancy
- Group 2 was trained with forced exercise during their pregnancy
- Group 3 was treated with haloperidol (5 mg/kg, i.p., once daily) in combination with forced exercise during their pregnancy
- Group 4 was treated with trazodone (5 mg/kg, i.p., once daily) in combination with forced exercise during their pregnancy
- Group 5 was treated with haloperidol (5 mg/kg, i.p., once daily) during their pregnancy
- Group 6 was treated with trazodone (5 mg/kg, i.p., once daily) during their pregnancy.

Treadmill forced exercise protocol

Rats were allowed to run on a motor-driven leveled treadmill (ModelT408E, Diagnostic and Research Instruments Co., Taoyuan, Taiwan). The animals of Groups 2, 3, and 4 were trained with treadmill for 30 min/day during 5 days/week. The training speed was 10 m/min (for the first week) and increased to 20 and 30 m/min in the 2nd and the 3rd week, respectively. The slope and the intensity of the exercise were settled as 0° at the first 10 min, 5° for the second 10 min, and 15° for the last 25 min.[28,29]

Behavioral assay in offspring

After the treatment of pregnant rats with the mentioned drugs and the forced exercise, eight adolescent rats with the age of 2 months (60 days) including four males and four females were randomly selected from each group (one offspring from each treated mother). To consider the hormonal factors which might contribute and affect the results of our study, we selected both genders from pups and then some behavioral assays were done on offsprings according to the experimental protocol.

Writhing test

This test is based on the induction of pain by intraperitoneal injection of 10 ml/kg acetic acid (0.8%). The measurement of severity of the pain was done by counting the number of abdominal constrictions known as writhing. The total number of contractions, recorded by camera during 30 min after injection of acetic acid, was counted (number of abdominal constrictions or writhing). In addition, the onset of the first writhing was recorded as latency time.[28,30,31]

Tail flick test

This test was performed for animals before the treatment. In this test, radiant heat by tail-flick apparatus (P-162 Model, Pouyaye Armaghan Co., Iran) was used for the evaluation of pain perception in rats. Five millimeters of the tail was submitted to noxious heat. To avoid damaging the tail, trial was automatically terminated at 12 s (cutoff time). The animal reaction to remove the tail was considered as latency time.[28,30,31]

Hot plate test

In this test, analgesic activity was measured with a thermostatically heated surface which is maintained at the temperature of 55 ± 2°C. The time of reaction was considered to be the time that took the animal licking its feet or jumping out. This time of reaction considered as nociception time. The onset of the first licking reaction (latency time) on the hot plate was recorded.[28,30,31]

Statistical analysis

All data expressed as the mean ± standard error of the mean. The differences between all treatment groups were compared with one-way ANOVA and then, with a *post hoc* Tukey's test. The statistically significant values were taken as $P < 0.05$ or $P < 0.001$.

Results

The effect of maternal exercise and the role of D_2 and 5-HT_2 receptors on offspring pain response in writhing test

Figures 1 and 2 indicated the effects on offsprings of maternal forced exercise in writhing test (WT). The maternal forced exercise significantly increased the latency time in Group 2 with $P < 0.001$ compared to normal saline control group in this test. Furthermore, the number of abdominal contractions decreased in offsprings of exercise group (Group 2) compared to the control group [$P < 0.05$, Figures 1 and 2]. The treatment of mothers with forced exercise in combination with haloperidol and trazodone caused increases of abdominal contractions with $P < 0.05$ and decreased the latency time in WT with $P < 0.001$ in comparison with the group whom their mothers were treated with the exercise only [Figures 1 and 2]. In addition, the maternal treatment with haloperidol or trazodone without exercise caused the decrease of latency time and increase of abdominal contraction that was not significant in comparison to the group treated with haloperidol or trazodone concomitant with forced exercise.

The effect of maternal exercise and the role of D_2 and 5-HT_2 receptors on offspring pain perception in tail flick test

Maternal forced exercise significantly increased the latency time of tail flick test (TFT) reaction comparing to the control group [$P < 0.001$, Figure 3]. While the treatment of mothers by forced exercise in combination with haloperidol or trazodone caused decrease in latency time in comparison with the group whose mothers were treated with the exercise only [$P < 0.001$, Figure 3]. Treatment of mothers only with haloperidol or trazodone did not change the tail flick latency time, and this was not significant in comparison with group treated with forced exercise in combination with haloperidol or trazodone [Figure 3].

The effect of maternal exercise and the role of D_2 and 5-HT_2 receptors on offspring pain perception in hot plate test

Maternal forced exercise significantly increased the latency time of offspring in hot plate test (HPT) compared to control group [$P < 0.001$, Figure 4]. While the treatment of mothers by forced exercise in combination with haloperidol or trazodone caused decrease in the latency time in offspring in comparison with the group whose mothers were treated with the exercise only in HPT [$P < 0.001$, Figure 4].

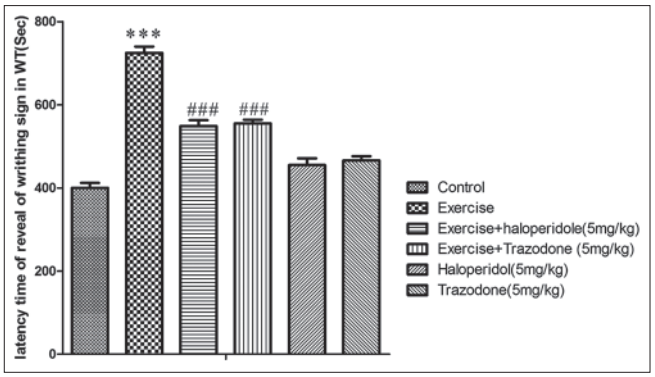

Figure 1: Latency time for expression of abdominal contractions in writhing test in the control group and group which their mother treated by exercise alone or in combination with haloperidol and trazodone and groups which their mother treated by haloperidol or trazodone alone. All data are expressed as mean ± standard error of the mean (n = 8). ***Significant differences from control group ($P < 0.001$). ###Significant differences from group which their mother was treated by exercise ($P < 0.001$)

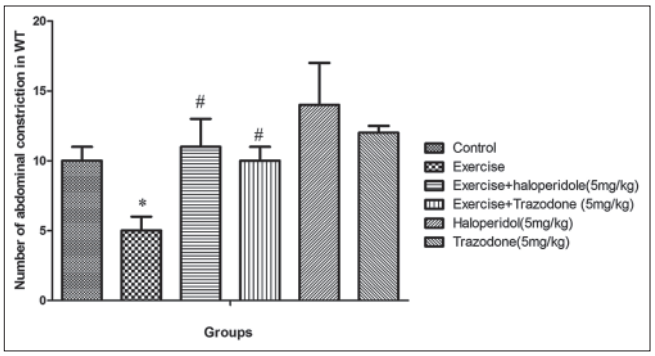

Figure 2: Number of abdominal contractions in writhing test in the control group and group which their mother treated by exercise alone or in combination with haloperidol and trazodone and groups which their mother treated by haloperidol or trazodone alone. All data are expressed as mean ± standard error of the mean (n = 8). *Significant differences from control group ($P < 0.05$). #significant differences from group which their mother was treated by exercise ($P < 0.05$)

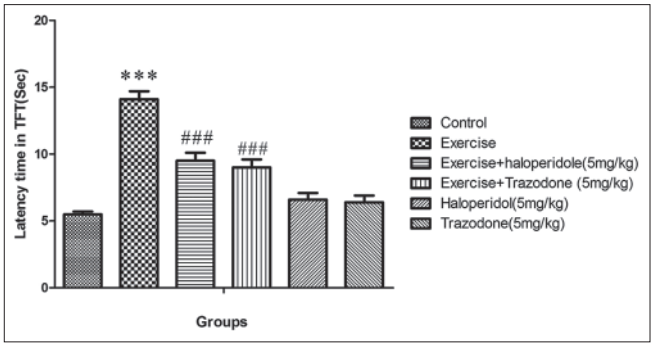

Figure 3: Latency time of tail flick test reaction in the control group and group which their mother treated by exercise alone or in combination with haloperidol and trazodone and groups which their mother treated by haloperidol or trazodone alone. All data are expressed as mean ± standard error of the mean (n = 8). ***Significant differences from control group ($P < 0.001$). ###Significant differences from group which their mother was treated by exercise ($P < 0.001$)

Treatment of mothers only with haloperidol or trazodone did not change the HPT latency time and was not significant

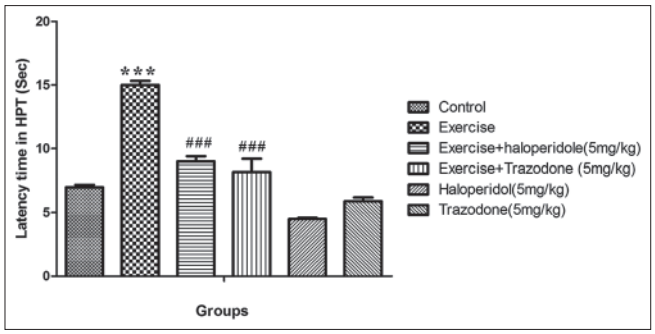

Figure 4: Latency time of hot plate test reaction in the control group and group which their mother treated by exercise alone or in combination with haloperidol and trazodone and groups which their mother treated by haloperidol or trazodone alone. All data are expressed as mean ± standard error of the mean (*n* = 8). ***Significant differences from control group (*P* < 0.001). ###Significant differences from group which their mother was treated by exercise (*P* < 0.001)

in comparison with the group treated with forced exercise in combination with haloperidol or trazodone [Figure 4].

Discussion

The present study indicated that the maternal forced exercise could modulate pain perception in pups. The maternal forced exercise could cause a delay in pain perception in pups that it might be modulated via D_2 (dopaminergic) receptor and 5-HT_2 (serotonergic) receptors. Previous studies have revealed that physical activity lowers stress and anxiety level and releases endorphins into the brain.[28,30] Exercise can counteract drug abuse withdrawal symptoms and cause attenuation of depression and reduction of anxiety and help to the patient well-being.[2,29] Several studies have demonstrated that exercise can affect the neural development in several disorders.[28,30] Physical activity can increase the synthesis and the release of dopamine and serotonin which stimulate neuroplasticity and promote the feelings of well-being.[8,11] The present study showed that the maternal forced exercise caused the decrease in writhing numbers in WT in offsprings; this study showed that this effect was modulated probably by dopamine D_2 and serotonin 5-HT_2 receptors since treatment with haloperidol or trazodone inhibited the protective effect of maternal forced exercise on the offspring abdominal pain perception. Previous studies demonstrated that the maternal physical activity, by mediation of dopaminergic and serotonergic system, could develop the neurogenesis in offspring[32] and change the pain perception.[33] On the other hand, previous research has shown that D_2 and 5-HT_2 receptors can modulate the pain perception, and these receptors play important roles in neuronal regeneration.[21,23] Based on these findings, it can be argued that forced exercise of mother affects offspring pain perception, and this might be probably modulated by D_2 and 5-HT_2 receptors, and probably, these two receptors have important functions in the protective effect of maternal forced exercise on offspring.[34,35] The present study showed that maternal forced exercise increases the latency time in WT in offspring and the treatment of mothers by haloperidol or trazodone in combination with forced exercise decreased the latency time in WT. Physical activity could cause inhibition of inflammatory and neuropathic pain in offspring.[36] Previous studies have shown that physical activity in mothers causes modulation of neurohormone and potentiate immunological function in child and attenuates the immunologic disorders in offsprings.[37,38] It was approved that D_2 and 5-HT_2 receptors have the main role in inflammatory pain.[39,40] Furthermore, agents which have agonistic effect on these receptors can inhibit the expression of inflammatory and acetic acid-induced pain in animal models.[30,41] Offsprings of mothers that were treated with haloperidol or trazodone increased the writhing number and decreased latency time of WT which is not significant in comparison to the group treated with forced exercise in combination with haloperidol or trazodone. This study could discuss the results based on the previous studies which showed that haloperidol and trazodone have side effects on neural development, by interaction with neuroprotective action of D_2 and 5-HT_2 receptors on neuron formation, which probably can be the reason for brain development.[42,43] They have also shown that D_2 and 5-HT_2 agonists have analgesic effect which suggests that the receptors can modulate pain perception and pathways in brain.[42,43]

In TFT for evaluation of maternal forced exercise on spinal pain perception, this research showed that forced exercise in mothers caused an increase in latency time of TFT, and this effect might probably be mediated through 5-HT_2 and D_2 receptors. While the results showed forced exercise in combination with haloperidol or trazodone caused the decrease in the latency time in comparison to the group whose mothers were treated with exercise only. Many previous studies showed that physical activity increases the tolerance of neurons against pain stimulant, especially in spinal pain. Moreover, there is growing evidence supporting the role of dopamine and serotonin in spinal pain perception.[35,44,45] The present study showed that protective role of maternal forced exercise in the management of spinal pain perception in offspring in tail flick was probably mediated by dopamine and serotonin in which 5-HT_2 and D_2 receptors were involved.

In addition, mothers which treated with haloperidol or trazodone showed a decrease in latency time of TFT. Based on this study and previous data, D_2 and 5-HT_2 receptors might be involved in brain pathways for spinal pain perception.[42,43] Furthermore, our data suggested that forced exercise protective effect on suppression of spinal pain probably was mediated by D_2 type of dopaminergic and 5-HT_2 type of serotonergic receptors which confirm some similar previous studies which confirmed the involvement of dopaminergic and serotonergic systems in the management of spinal pain.[42,43]

About the effect of forced exercise in thermal pain management similar to other researches, this study indicated that maternal activity could increase the offspring pain threshold and modulate the endogenous analgesic pathways in HPT model and thermal pain management.[46-48] Many previous studies have demonstrated that maternal physical activity can increase bioamine receptors in the brain and spinal cord, so this increase might be responsible for various protective effects of physical activity in brain disorders.[46-48] These data can be discussed with previous concepts which confirmed the involvement of D_2 and 5-HT_2 receptors in the formation of pain pathways and pain perception, especially thermal pain perception.[42,43] This research confirmed the concept that maternal forced exercise affected the thermal pain perception in HPT which might have been mediated by D_2 and 5-HT_2 receptors and it could show the role of serotonin and dopamine in maternal forced exercise neuroprotection in the formation of pain pathways in offsprings.

Conclusion

The results of the present study supported the hypothesis that the maternal physical activity is involved in the formation of inflammatory, thermal and spinal pain perception pathways in offsprings. Furthermore, this research showed that in these neuroprotective effects of maternal forced exercise, D_2 or 5-HT_2 receptors might be involved.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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