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ORIGINAL ARTICLE

High-intensity interval training prevents cognitive-motor impairment and serum BDNF level reduction in parkinson mice model

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra pars compact (SNpc). Previous studies have shown that cognitive deficits and motor impairment symptoms seen in PD and that physical exercise may exert beneficial effects on PD. In most cases, brain-derived neurotrophic factor (BDNF) is involved in such effects. However, little is known on the role of BDNF in exercise, especially high-intensity interval training (HIIT)-related effects on PD. The aim of this study was to investigate the effects of 6 weeks HIIT against experimentally reserpine (RES)-induced PD in male mice, by analyzing the motor coordination, learning and serum BDNF level. Male mice received 20 (s.c) injections of 0.1 mg/kg RES or vehicle, every other day. Rotarod and spontaneous alternation tests were used for measurement of motor coordination and short-term memory, respectively, and serum levels of BDNF were also measured using the ELISA technique. All behavioral tests were performed 48 h after the RES injection. RES injection caused a significant motor coordination and cognitive deficits ($p < 0.05$) and these effects were reversed in mice after receiving exercise protocol. HIIT improved the motor coordination and cognitive performance against RES administration ($p < 0.05$). Also, serum BDNF level was decreased in mice RES-induced PD ($p < 0.05$) and HIIT restored this to control levels ($p < 0.05$). Taken together, our results suggest that HIIT shows a protective effect in a mice model of PD and may repair motor coordination and cognitive dysfunctions in PD due to increased serum levels of BDNF.

Keywords Reserpine · Parkinson's disease · Mice model · Neuroprotective effect · BDNF

Introduction

As the second most prevalent neurodegenerative disorder afflicting the human being, Parkinson's disease (PD) acts as a progressive age-related illness [1, 2]. Many factors influential on the etiology and pathogenesis of PD were identified, yet the actual cause is not revealed. The major pathological indicator of PD represents itself as the progressive degeneration of dopaminergic neurons situated within the substantia nigra pars compacta (SNpc), and the relevant direct result of dopaminergic differentiation in the striatum. The mentioned result would increase the cardinal motor symptoms including bradykinesia, muscular rigidity, resting tremor and postural instability [3, 4].

During the recent years, using PD-affected animal models induced by neurotoxins such as reserpine (RES) has been treated as a facilitating tool for the investigation of the causes for the development of PD as well as conducting research for new drugs and examining the neuroprotective symptoms and effects [5, 6]. RES can block the vesicular transporter of monoamines (VMAT2) in an irreversible way, inclusive of monoamine depletion. Administering the RES was broadly implemented in inducing severe motor [5, 7] and nonmotor [6, 8] parkinsonian disabilities in rodents. Implementing the above treatment, the understudy samples developed motor symptoms, including motor coordination, hypokinesia and bradykinesia, which is assessed by rotarod, open field and catalepsy bar test, and cognitive impairment such as short-term memory, recognition memory and spatial working memory evaluated by the Plus-maze discriminative avoidance, novel object recognition and plus-maze task. The progressive aspect of this protocol can also be helpful in the

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researches examining the neuroprotective strategies' effect on the establishment of behavioral changes [5–10].

Brain plasticity is to a great extent dependent upon the brain-derived neurotrophic factor (BDNF); this has been also recognized as the responsible factor for the regulation of neuronal survival and influencing dopamine (DA) neurons and cognitive processing [11]. In PD-affected patients [12, 13] and in animal parkinsonian samples induced by RES [6, 7], the expression of BDNF is declined.

Numerous evidences indicate that preventive strategies like performing daily exercise may be helpful in delaying the advent of Motor dysfunction and cognitive decrease and mitigate the age-related neurological illnesses. Physical activities can dampen the neurological deficiencies happening different brain injuries like cerebral ischemia, traumatic brain harms and Alzheimer [14–16]. This has been demonstrated that PD patients' capabilities for participating in exercise may be affected by both motor and non-motor signs or at least they negatively influence the exercise results, such patients still can take part in many exercise forms and frequently positively respond to physical interventions almost identical to others of the same age without PD. Hence, many studies are now focused on the subject of exercise to examine the mechanisms by which physical activities can influence the disease progression [17].

The useful effects of moderate-intensity continuous training (MICT) on the improvement of cognitive [6, 8, 18, 19] and motor functions [8, 17, 18] and the increase in the BDNF level [6, 20] have been observed in various studies on both animal parkinsonian model and human with PD.

Researchers and physiotherapy experts are focusing on the investigations to reveal the effect of short-term exercise bouts on the patients' physiology aiming at the optimization of time consumption; for example, high-intensity interval training (HIIT) which refers to the exercise with main feature of short bursts of intense activities, followed by rest or less-intense recovery exercise [21]. Marusiak et al. showed that HIIT will cause reduction of rigidity and increase of the serum BDNF levels in patients with PD [22]. Zoladz et al. also reported that moderate-intensity interval training will produce desirable effects on the serum BDNF levels in patients with PD [20].

Nevertheless the HIIT effects on the cognitive performance and motor coordination of patients with PD and animal-induced Parkinson models have not been investigated. Considering that intervention variables in human samples can affect the study results,

Hence using animal models can be helpful due to the controllability of variables. The main aim of this study was considering the probable protective impact of HHT in a RES-induced mice model of PD, emphasizing the behavioral (short-term memory and motor coordination) and immunohistochemical (serum BDNF level) effects.

Methods

Animals

Male C57BL/6 mice (10–12 weeks old) were purchased from Laboratory of Animal Center, Kermanshah University of Medical Sciences, Kermanshah (Iran). Mice were kept in standard polycarbonate cages in a room with the controlled temperature at a constant 12-h darkness–illumination cycle (8 a.m.–8 p.m.) and free access to water and food. This condition was considered as an appropriate condition in all experimental steps.

Drug treatment, general procedures, and experimental design

RES (methyl reserpate 3,4,5-trimethoxybenzoic acid ester, Sigma Chemical Co., St. Louis, MO, USA) was dissolved in 0.2% glacial acetic acid (Sigma Aldrich, St. Louis, MO, USA) and 0.9% NaCl (saline). Vehicle consisted of 0.2% glacial acetic acid and 0.9% NaCl. The animals received 20 s.c. injections of vehicle or 0.1 mg/kg of RES every other day. All behavioral tests were performed 48 h after the RES injection [6] (Fig. 1). The present treatment schedule was designed to investigate the chronic consequences of physical exercise in the cognitive and motor deficits induced by RES [8].

Exercise protocol and experimental design

One week before the start of the treadmill exercise paradigm, 40 mice that could maintain a forward position on the 45 cm treadmill belt for 5 min at 5 m/min were randomly assigned to the four groups to ensure that all animals performed similarly on the treadmill task before reserpine administration [8]. Exercise was performed on a motored mice treadmill 5 days/week (monday–friday) for 6 weeks [23]. HIIT groups started with a warm-up at 5 m/min, where after HIIT consisted 8 bouts of 2.5 min high-intensity at 90% of the maximal running capacity (MRC) (22 m/min) intercalated by eight active rest periods (2.5 min each) at 50% of the MRC (12 m/min) [24].

The mice were randomly assigned to one of four groups: control (CTRL: $n = 10$), control with HIIT (CTRL + HIIT: $n = 10$), RES-treated (RES: $n = 10$) and RES-treated with HIIT (RES + HIIT: $n = 10$) groups.

Behavioral tasks

Spontaneous alternation test (Y-maze)

In this study, the Y-maze test was performed for the purpose of evaluating the shot-term memory. In this study a Y-maze

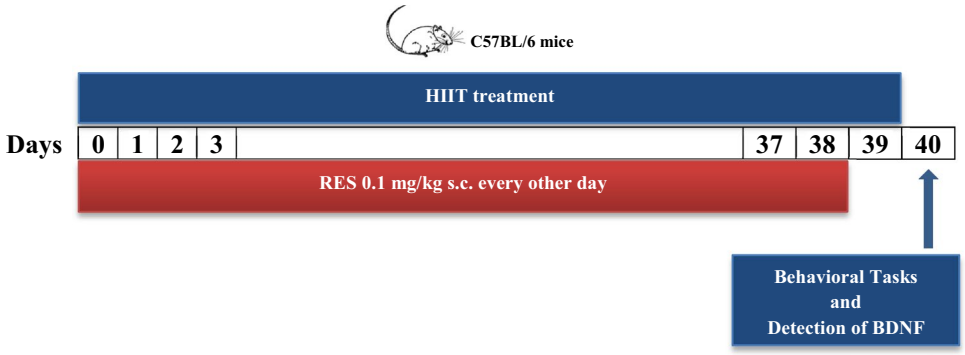

Fig. 1 Schematic representation of the experimental design: animals were treated with RES (20 s.c. injections of vehicle or 0.1 mg/kg) and HIIT. Thereafter, animals were subjected to behavioral tasks 48 h after the RES injection

consisting of three arms was used (length, 35 cm; height, 25 cm; and width, 10 cm) together with a triangular central area. The mouse at the end of one arm was able to move freely inside the maze for a period of 8 min. In case the mouse was able to climb the walls of maze, immediately it was returned back to the desolate arm. To avoid placement bias, the start arm changed between mice and visually the series of arm entries were recorded—the arm entry definition was the entry of the mouse whole body into the arm. Spontaneous alternation consists of sequential entries into all three arms. Therefore, the spontaneous alterations' percentage could be calculated through dividing the number of changes by the number of probable changes [number of alternation/(number of total arm entries-2)]. The Y-maze inside was cleansed using ethanol (70%) between each two trials and left to be dried [25].

Rotarod test

To assess motor coordination in mice, accelerating rotarod test was employed. The test was performed on 1 day and each mouse performed three attempts (an inter-trial interval of 1 h). The maximum trial time was considered as latency to fall off. The time latency to fall was recorded with a maximum trial length of 300 s and acceleration speed was from 4 to 40 rpm over a 5-min period [26].

Determination of serum BDNF level in mice

After the behavioral tests [27] 8 mice were selected from each group, anesthetized with the ether, and immediately after incision of abdomen, their heart blood samples were taken. The collected blood samples were centrifuged for 15 min at 4000 rpm. Serum samples were stored at − 80 °C until further analysis and then were measured by ELISA (ZellBio GmbH, Germany) according to company instructions.

Data analysis

Data were analyzed using the statistical software SPSS (version 22.0). Data were represented based on mean ± standard error of the mean. Normality of data was checked by Kolmogorov–Smirnov Test (K–S test). Two-way ANOVA was used to compare the motor coordination, short-term memory and serum GDNF level between groups. Tukey's post hoc test was used to determine differences between groups and $p < 0.05$ was considered to reflect significant differences.

Results

The effect of HIIT on behavioral tasks

The effect of HIIT on short-term memory

Results of two-way ANOVA proved the significant effect of RES ($F_{(1,36)} = 16.600$, $p < 0001$) and HIIT ($F_{(1,36)} = 12.923$, $p = 001$), though the interactive effect was not significant ($F_{(1,36)} = 0.511$, $p = 480$). One-way ANOVA ($F_{(3,36)} = 10.011$, $p < 0001$; Fig. 2) and Tukey's post hoc test revealed that PD induced by RES decrease short-term memory compared with CTRL, RES + HIIT ($p < 0.05$) and CTRL + HIIT groups

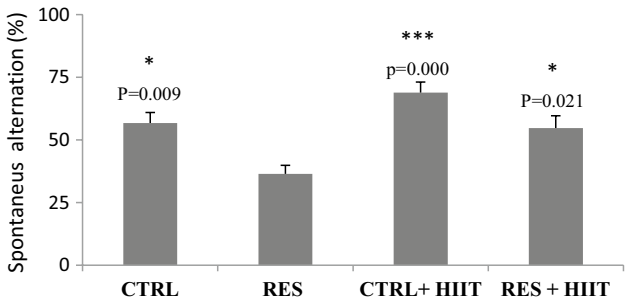

Fig. 2 Beneficial effect of HIIT on cognitive deficiency in RES-induced PD mice. Data are expressed as the mean ± standard error of the mean. *$P < 0.05$ and ***$P < 0.0001$ compared to the RES group. #$P < 0.05$ compared to the CTRL + HIIT group

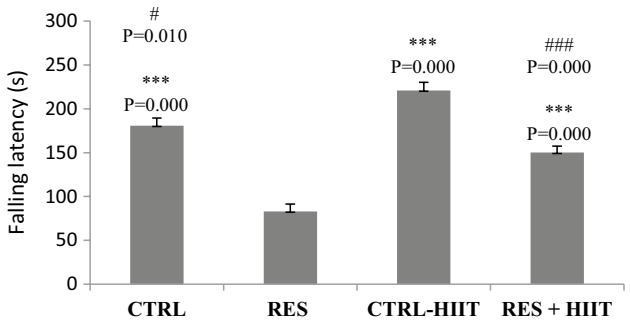

Fig. 3 Beneficial effect of HIIT on motor coordination in RES-induced PD mice. Data are expressed as the mean ± standard error of the mean. ***$P < 0.0001$ compared to the RES group. $^{\#}P < 0.05$ and $^{\#\#\#}P < 0.001$ compared to the CTRL + HIIT group

($p < 0.001$). Also, HIIT prevents memory impairment by RES injection ($p < 0.05$).

The effect of HIIT on motor coordination

Evaluation of the effects of PD induction and HIIT on motor coordination demonstrated that both effect of RES ($F_{(1,36)} = 98.711$, $p < 0001$) and effect of HIIT ($F_{(1,36)} = 39.906$, $p < 0001$) were significant. Though, the interactive effect of these variables was not significant ($F_{(1,36)} = 2.532$, $p = 120$). R esults of one-way ANOVA ($F_{(3,36)} = 47.050$, $p < 0001$; Fig. 3) and Tukey's post hoc test showed that induction of PD by RES significantly impair motor coordination compared with other groups ($p < 0.0001$). Moreover, beneficial effects of HIIT on improvement of motor coordination were observed in both experimental and control groups ($p < 0.05$).

The effect of HIIT on serum BDNF level

The mean of BDNF and Tukey's post hoc test results are shown in Table 1. Evaluation of the effects of parkinsonism induced by RES ($F_{(1,32)} = 52.678$, $p < 0001$) and HIIT ($F_{(1,32)} = 24.939$, $p < 0001$) on BDNF level demonstrated that both effects are significant. Though, the interactive effect of these variables were not significant ($F_{(1,32)} = 0.024$, $p = 879$). Results of one-way ANOVA ($F_{(3,28)} = 26.222$, $p < 0001$) and Tukey's post hoc test showed that PD induction can significantly reduce BDNF serum levels compared with other groups ($p < 0.05$). Moreover, effects of HIIT on increasing BDNF serum levels were observed in both experimental and control group ($p < 0.05$).

Discussion

In this paper a chronic experimental PD was observed resulting in cognitive performance and motor coordination deficiency in mouse that was consistent with the previous study results [6, 7, 28]. Also we witnessed the undesirable effects of injecting RES on the decrease of serum BDNF levels. However, HIIT significantly impedes the cognitive performance and motor coordination as well as reduction of serum BDNF level emanating from the injection of RES.

The reduction of BDNF expression due to RES injection which was consistent with the previous relevant study results [6, 29] can be of the reasons for the cognitive performance and motor coordination deficiencies. BDNF is assumed as a molecular mediator playing role in the performance and structure of synaptic plasticity, and acts significantly in the formation of memory and memory consolidation [11]. A simple disruption of the pathway transporting and producing BDNF can consequence the onset of clinical symptoms of memory deterioration and cognitive dysfunction [11]. The causal relation between lower levels of BDNF and cognitive reduction associated with aging, schizophrenia, and Rett syndrome has been demonstrated in the literature [30–32]. As a particular form of plasticity, Long-term potentiation (LTP) happens in the hippocampus and acts as the cellular ground of memory and learning. Also BDNF is the main regulator of the induction and LTP maintenance functioning in the hippocampus and other brain areas [11]. Studies report that neurogenesis resided in adults hippocampus is engaged in memory function and learning process [33, 34]. The signal from BDNF–TrkB affects the adult neurogenesis

Table 1 The differences among the group related with serum BDNF levels on mice

Group number	Groups	Mean (ng/ml) ± SEM	Different ($P < 0.05$) from group number	Different ($P < 0.001$) from group number
1	CTR	4.76 ± 0.29	(2; p = 0.001) (3; p = 0.001)	
2	RES	2.78 ± 0.28	(1; p = 0.001) (4; p = 0.042)	(3; p = 0.000)
3	CTR + HIIT	6.68 ± 0.21	(1; p = 0.001)	(2; p = 0.000) (4; p=0.000)
4	RES + HIIT	4.04 ± 0.43	(2; p = 0.042)	(3; p = 0.000)

through facilitating neuronal differentiation as well as the survival of new neurons [11].

Regarding the BDNF effects on the motor coordination, it has been observed that BDNF over-expression dramatically enhanced the performance while performing the rotarod test [35, 36]. BDNF is required for the survival and differentiation of striatal neurons [37, 38] and deficiency in BDNF-mediated signaling alone is sufficient to cause dendritic abnormalities and neuronal loss in the cerebral cortex and striatum [11, 39]. The above findings empower the probability that the decreased provision of striatal BDNF can dramatically involve in motor dysfunction [40, 41]. Guo et al. (2012) demonstrated that damage in striatum involved particularly in motor deficiency and dysfunction [42]. Moreover, expressing BDNF in both the striatum and midbrain or either of them would increase striatal DA levels and tyrosine hydroxylase activity [37, 43], dampens the 6-hydroxydopamine-induced (6-OHDA–induced) damage of nigrostriatal neurons, which would result in behavioral improvements [44].

Also we witnessed the useful effects of HIIT on the behavioral performance of chronic experimental PD. According to the literature, the physical exercise would enhance the cognitive performance and motor symptoms in PD rodents [6, 15, 17]. Additionally, the regular physical exercise is related to greater brain plasticity [7], neurogenesis [45] and generation of neurotrophic factors [21]. Some studies have proposed a role of neurotrophic factors as involved in exercise-induced alterations. Despite the fact that the MICT produces neuroprotective effects on PD model of rodents [6, 46], in the present study we observed the useful effects of HIIT on prevention from the decrease of BDNF neurotrophic factor in the Parkinson-induced model. On the other hand, some studies have shown evidences of long-term effects of HIIT on BDNF synthesis in healthy rodents [47, 48]. Thirty HIIT sessions considerably escalated the BDNF levels (protein) in the brain as compared to the control group [47]. The researchers proposed that HIIT heightened the amount of hydrogen peroxide (H2O2) and Tumor Necrosis Factor Alpha (TNFα) concentration in the brain; and that the mentioned molecules were able to activate the BDNF synthesis [49] or CREB [50] which they considered it a transcription factor positively performing the regulation of BDNF synthesis [21].

Although many study the shown the benefits of MICT on health-related factors in human being [51, 52]; the society, however, maintains the shortage of time as the main obstacle to regularly doing aerobic exercise [51, 53]. On the whole the HIIT is executed on a training session lasting ≤ 30-min, inclusive of warming-up and cooling down steps [53–55]. Moreover, the HIIT could be performed on cyclical exercises like bicycling, swimming, running and whole bodily exercise [21]. Also, previous studies have reported that HIIT was considered an exercise modality, and inferred higher exhaustion compared with MICT [56]. HIIT on the other hand is assumed more enjoyable than MICT [57]. In addition, it has been reported in previous studies that 73% of the study samples preferred the HIIT protocol [58]. Also, Chapman et al. stated that HIIT was preferable, acceptable and feasible as MICT for the adults with mental illness [59]. Consistently, the HIIT has been suggested as an excellent strategy aiming at increasing the adherence to exercise programs in people with disability [57].

Conclusion

In sum, the present study results illustrated that the RES-induced Parkinson through the decrease of BDNF serum level can cause motor coordination and cognitive performance. Also the useful effects of HIIT activity on the improvement of behavioral performances and BDNF nortrophic factor levels were observed and that the HIIT due to the increased BDNF serum levels can be considered an effective treatment approach in reducing the behavioral disorders resulting from the PD. Due to limited possibilities, we were unable to measure other factors associated with the possible effects of physical activity, including brain plasticity, neurogenesis, and changes in other neurotrophic factors. Therefore, the effects of HIIT on these variables and the comparison with the MICT can be interesting topics in future research.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval All procedures performed in this study involving animal participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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