Annals of Applied Sport Science, vol. 5, no. 4, pp. 39-47, Winter 2017

www.aassjournal.com
ISSN (Online)**: 2322 – 4479**
ISSN (Print)**: 2476–4981**

Original Article

www.AESAsport.com
Received: 25/12/2016
Accepted: 28/05/2017

The Effects of Mild Forced Treadmill Exercise and GABA-B Agonist on Locomotor Activity and Anxiety-Behavior in Rats with Striatum Dysfunction

[1]Shaghayegh Modaberi, [1]Mehdi Shabazi[*], [2]Nasser Naghdi, [1]Abolfazl Bagherzadeh

[1]Department of Motor Learning, Faculty of Sport Sciences, University of Tehran, Tehran, Iran. [2]Pasture Institute, Tehran, Iran.

ABSTRACT

Background. the basal ganglia's circuit dysfunction has a major role in a range of movement disorders. Some evidence has shown that exercise can improve performance, especially locomotor activity after brain injuries. There was currently insufficient information to define the impacts of intensity, duration, and frequency of different exercises. **Objectives.** in this study, we examine the role of mild forced treadmill exercise and GABA-B agonist on locomotor activity and anxiety-behavior dysfunction of ibotenic acid injection in striatum. **Methods.** forty male Wistar rats were randomly split into five groups. The animals received ibotenic acid infusions into striatum bilaterally. Locomotor activities of rats were assessed by open-field apparatus. **Results.** Our results showed that mild forced treadmill exercise and GABA-B could significantly increase distance in open field and decrease anxiety-behavior in treadmill and drug groups than lesion group (P=0.008 and P=0.001 respectively). **Conclusion.** There is no significant difference between treadmill and drug groups. So, mild forced treadmill exercise and baclofen could improve motor dysfunction of lesion by ibotenic acid injection in striatum and anxiety-behavior.

KEY WORDS: ***Striatum, Ibotenic Acid, Spatial Memory, Treadmill Exercise, Locomotor Activity.***

INTRODUCTION

Preparation and execution of intentional movements require activity of the motor cortex. In particular, the interaction between motor cortex and basal ganglia seems to be organized in relatively segregated cortico-striato-nigro-thalamocortical (CSNTC) loops (1). Basal ganglia comprises several interconnected nuclei in the forebrain, midbrain and diencephalon. In primates, basal ganglia includes the following: striatum (caudate and putamen), subthalamic nucleus, globus pallidus (internal and external segments), and substantia nigra (pars compacta and pars reticulata) (Figs 1 and 2) (2). Basal ganglia's output to the thalamus remains segregated into "motor" functions. Output from the motor portion of internal globus pallidus (GPi) reaches predominately the thalamus, which, in turn, projects to cortical motor areas that are closely related to the sequencing and execution of movements (3). The classical neurotransmitter of striatal, pallidal and SNr projection neurons is GABA. Basal ganglia circuits are organized anatomically to receive input from virtually all of cerebral cortex and to send inhibitory output via

*. Corresponding Author:
Mehdi Shabazi
E-mail: shahbazimehdi@ut.ac.ir

thalamus back to frontal lobe targets. The output from GPi and SNpr is inhibitory and uses GABA for its neurotransmitter (4). The pathway through the striatum to GPi and SNpr is inhibitory. Since the output of GPi and SNpr is inhibitory, the results are focused facilitation and surround inhibition of thalamocortical and brainstem target neurons (5).

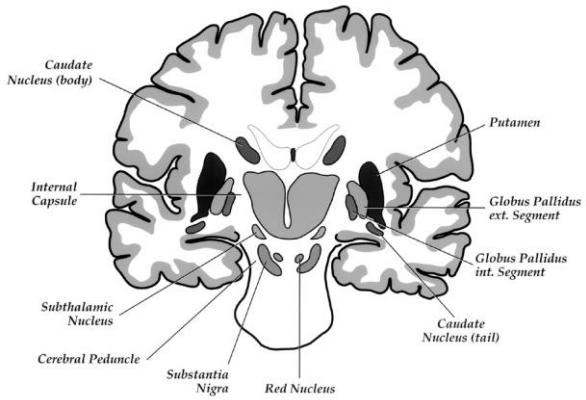


Figure 1. *Basal ganglia and adjacent structures in coronal section* [Reference by Mink, 2001 (2)].

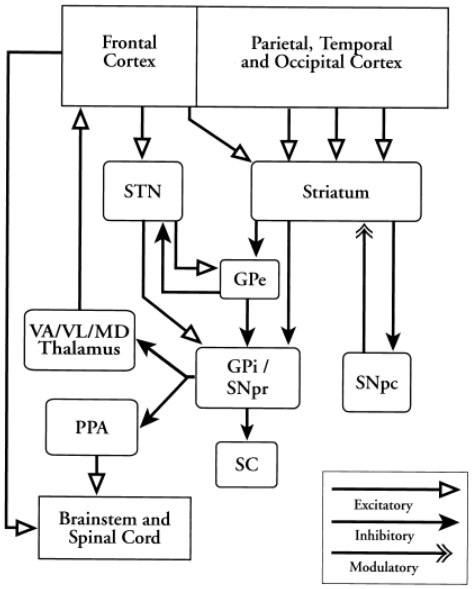


Figure 2. *Simplified schematic diagram of basal ganglia circuitry.* Excitatory connections are indicated by open arrows, inhibitory connections are indicated by filled arrows [Reference by Mink, 2001 (2)].

The spectrum of abnormal movements caused by disorders of the basal ganglia falls under the rubric of what neurologists term movement disorders. Basal ganglia dysfunction can lead to movement disorders such as dystonia, chorea, and Parkinsonism (6). Striatal lesions produced consistent deficits in tests of sensorilocomotor activity (7), skilled paw reaching (8-10), discrete trial maze and runway tasks (11) and complex visual discrimination tasks (12). Several studies have described that in nonhuman primates, large lesions of globus pallidus alone or in combination with lesions of substantia nigra cause motor deficits (5). Striatal lesions in animals would be expected to produce GABA receptor upregulation in the pallidum and SNr because of the loss of GABAergic afferents to these nuclei (6). GABA-B receptors are involved in the modulation of GABAergic transmission in GPe and GPi. It is possible that changes in the functions or localization of these receptors contribute to changes in GABAergic transmission (13). Chen et al., (2002) suggested that GABA-B receptor in globus pallidus plays an important role in the regulation of movement by modulating glutamatergic inputs at a presynaptic site (14). Galven et al., (2011) showed that injections of baclofen in GPe and GPi lead to a significant increase in the proportion of spikes in rebound bursts in parkinsonian animals, but not in normal animals (13). So, dysfunction of the striatum causes inhibitory input to the Gpi and other nucleus is disturbed.

Some studies have suggested that exercise may improve the motor manifestations of Parkinson's disease (PD) and that restricted use in rats may potentiate neuro degeneration (15). Exercise and motor training can improve the performance of balance-related activities in people with PD (16). It has been reported that exercise can protect neurons from various brain insults (17, 18). Garcia et al., (2012) in their research, concluded that acrobatic exercise induced changes in the expression of synaptic and structural proteins mainly in the motor cortex and striatum, which may underlie part of the learning of complex motor tasks. Treadmill exercise, on the other hand, promotes more robust changes of structural proteins, especially in the cerebellum, which is involved in learned and automatic tasks (19). Results of Aguiar's et al., (2009) work showed that the potential of low to moderate physical exercise (running wheel

and treadmill vehicle) is a useful tool in the prevention of motor and cognitive impairments associated with CNS monoaminergic depletion (20). The current knowledge supports physical activity (e.g. aerobic exercise) as an important preventive factor against the onset of brain injury and that physical exercise (e.g. treadmill) is crucial for the maintenance or slow decline of optimal functional ability levels in patients with striatum impairments (18). In this context, many publications have reported anxiolytic and antidepressant effects of exercise, resulting in better management of stress (21). The results obtained by different authors suggest the need to specifically investigate the time and dose-dependent relationship between aerobic fitness and cognitive performance (22).

Extensive evidence from animal and human studies (23, 24) suggests that exercise has a positive impact on cognitive and emotional aspects of behavior but there is currently insufficient information to enable a precise definition of the best exercise program for patients with brain damages. It is not clear whether forced exercise could improve movement disorders and what intensity and duration of it is needed for this purpose. As reported in previous studies, GABA-B receptor in globus pallidus plays an important role in the regulation of movement. Some studies showed that high dose of GABA-B could disturb cognition function (25-28) and there isn't enough evidence on the effects of GABA-B on anxiety-behavior. This study investigated the effects low dose of baclofen injection in internal globus pallidus on locomotor activity and anxiety-related behaviors. Also, present research focuses on the role of mild forced treadmill exercise on locomotor activity and anxiety-related behaviors after stereotaxic rats were bilaterally injected ibotenic acid in striatum.

MATERIALS AND METHODS

Participants. Forty male Wistar rats weighing 200–250 g at the time of surgery purchased from Pasteur Institute of Iran were used. They were housed in large cages (eight per cage) and kept on a 24 hour light-dark cycle (lights on at 7:00 am and off at 7:00 pm) in a room held at a temperature (25 ± 2 °C). After surgery and before testing, each animal was first handled (10 minutes) daily for a week. Declaration of Helsinki and the internationally accepted principles on procedures for animal experimentation were followed, and all efforts were made to minimize the animals' suffering (29).

Study Design. After a week of adaptation to colony room conditions, each rat was randomly divided into six groups (n = 6).

1. Group 1 and 2 and 3. Control, intact and sham operated groups [Cpu (distilled)]; control and intact (nonoperatic rats were intact and to control for any non-exercise effects of treadmill running (handling, novel environment, noise and vibration), untrained control rats (sedentary) were placed on top of the treadmill apparatus for a time period equivalent to exercise training). Cpu (distilled) control-operated rats were infused and distilled bilaterally ICV.
2. Group 4. Cpu (IA) (lesion with ibotenic acid (IA) solution in distilled (5µg/µl) was injected bilaterally ICV).
3. Group 5. Cpu (IA) + treadmill (lesion with ibotenic acid (IA) solution in distilled (5µg/µl) was injected bilaterally ICV after one week of recovery for rats running on treadmill: rats were trained on the treadmill running for 4 meters/minutes for 10 minutes, 7 meters/minute for 10 minutes, 10 meters/minute for 10 minutes (7 days) for 4 weeks).
4. Group 6. Cpu (IA) + Gpi (Bac) (lesion with ibotenic acid (IA) solution distilled (5µg/µl) was injected bilaterally ICV, after one week of recovery baclofen (0.05 µg/ 0.5µl) was microinjected into the internal globus pallidus in the animal which was awake as the same time of treadmill program and test day) (14).

Open field tests were carried out to evaluate the capacity of locomotor activity and anxiety-behavior for each group after 4 weeks of mild treadmill exercise.

Surgical Method. Rats were anesthetized with combination of ketamine (5 mg/100 g of body weight (b.w.)) and xylazine (1 mg/100 g b.w. IP). Ibotenic acid (Sigma-Aldrich) was injected bilaterally using a 1 µl Hamilton Syringe in doses of 5 µg dissolved in 1 µl distilled into striatum at coordinates 0,35; ±3,05;

5,5 mm (anterior; lateral; ventral) relative to bregma using a stereotactic atlas for orientation (29, 30), According to a standard stereotaxic atlas (31), a guide cannula constructed from stainless steel was implanted into the internal globus pallidus (2.4 mm posterior, ±2.8 mm lateral from the bregma, 6.8 mm ventral from the skull surface), on either side. The cannula was fixed to the skull with stainless steel screws and dental acrylic. Stainless steel styles were used to keep the cannula sealed. To test the specificity of the effect of baclofen in the globus pallidus, the tip of the cannula was placed in some animals in the structures surrounding the center of the internal globus pallidus. Sham animals received bilaterally an equal volume of distilled into the striatum. Finally, the wound closed with simple sutures (14).

Microinjection Procedure. During 5 days following the surgical methods, for recovery, drug and vehicle were administrated into the internal globus pallidus bilaterally through the guide cannulas (23 gage) using injection needles (30 gage) connected by polyethylene tubing to 10.0-µl Hamilton microsyringe. 0.5µl vehicle or doses of baclofen were injected during 3–4 minutes. The needle was left in place for another 60 seconds before it was slowly withdrawn (14, 27).

Training Protocol. A six-lane motorized rodent treadmill was utilized for exercise training**.** All of the exercised rats were allowed to adapt to treadmill running for 10 minutes on 2 consecutive days (first day at 5 meters/minute; second day at 8 meters/minute) (33). Animals trained at a speed (10 minutes at 4 meters/minute, 10 minutes at 7 meters/minute, 10 minutes at 10 meters/minute) with 0° of inclination (34). After the exercise, rats were returned to their cages with free access to food and distilled water. The rats in the non-exercise groups without running on the treadmill were kept for the same period as the exercise group. Rats were subjected to locomotor activity testing beginning 24 hours after MWM. Figure 3 illustrates the experimental design of the study.

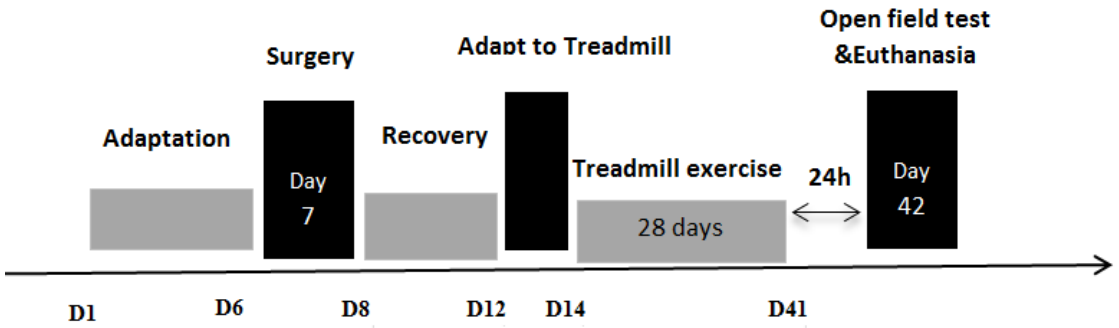


Figure 3. After one week adaptation in a standard cage and handling, on day 7, rats from lesion and sham groups underwent surgery and were allowed to recover for five days after stereotaxic surgery. Rats in the exercise (treadmill) and treadmill and ibotenic acid-induced lesion groups (IA) were subjected to 4 weeks of treadmill exercise on a treadmill for rodents. Twenty-four hours later, exercising rats were given the open field test. Finally, rats were euthanized and brain tissue was removed.

Behavioral Assessment (open field apparatus). We evaluated the effects of Ibotenic acid-induced striatum lesion and baclofen injection in internal globus pallidus on locomotors activity and rearing (frequency with which the animal stood on hind legs in open-field) according to the animals' performance in the open field (31).

Statistical Analysis. Differences within or between normally distributed data were analyzed by t-test and analysis of variance (one-way ANOVA), followed by Tukey's post hoc test. All figures were appropriate using Figure Pad Prism 6.0 (Figure Pad Software Inc.). Statistically significant differences were accepted at $p<0.05$.

RESULTS

Intact, control and sham operated groups

Open-field test (distance). There was no difference in locomotor activity between groups ($F_{(2, 21)}$ =1.87, p=0.1) (table 1).

Open-field test (rearing). There was no difference in exploratory behavior between groups ($F_{(2, 21)}$ =0.67, p=0.5) (table 2).

Table1. Showed average ***distance*** in three groups in open-field

Group	N	Mean	SD
Control	8	3.8380E3	259.1204
Cpu(distilled)	8	3.5805E3	364.8942
intact	8	3.8093E3	233.4257

Table2. Showed average ***rearing*** in three groups in open-field

Group	N	Mean	SD
Control	8	7.25	3.536
Cpu(distilled)	8	5.62	3.159
intact	8	7.38	3.378

Cpu (IA), Cpu (distilled)

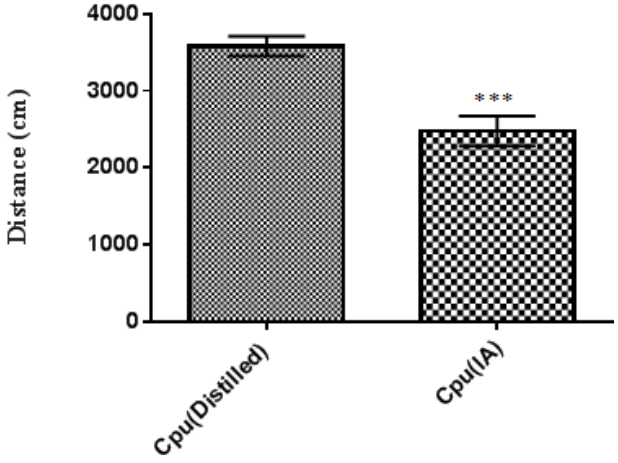
Open-field test (distance). Ibotenic acid injection in striatum significantly impaired locomotor activity in lesion group compared to control group (p=0.001) (Graph 1).

Open-field test (rearing). Ibotenic acid injection in striatum significantly impaired exploratory behavior in lesion group compared to sham group (p=0.006) (Graph 2).

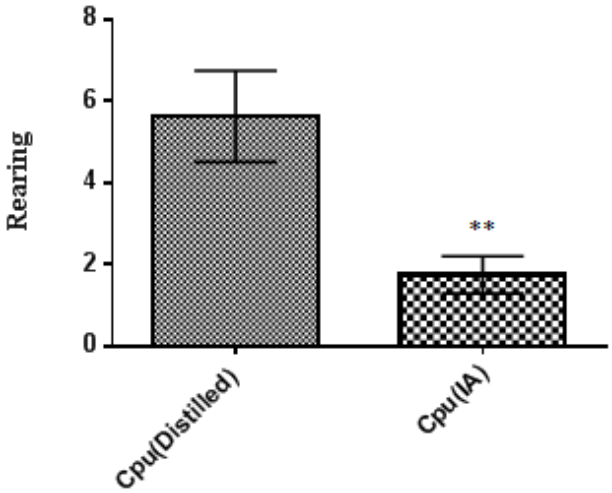
Cpu (IA), Cpu (IA) + treadmill, Cpu (IA) + Gpi (Bac)

Open-field test (distance). Mild treadmill exercise and baclofen injection in internal globus pallidus could significantly ($F_{(2, 21)}$ =10.49, P<0.01) improve locomotor activity in lesion groups than Cpu (IA) group (Graph 3).

Open-field Test (Rearing). Mild treadmill exercise and baclofen injection in internal globus pallidus could significantly ($F_{(2, 21)}$ =9.22, P<0.01) improve exploratory behavior in lesion groups compared to Cpu (IA) group (Graph 4).



Graph 1. Distance in the open field for 10 minutes was significantly decreased in lesion group compared to sham group (***p<0.001).

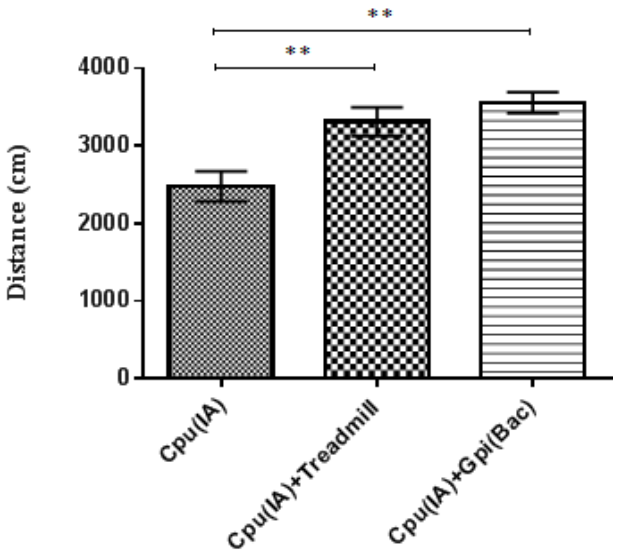


Graph 2. Rearing (frequency with which the animal stood on their hind legs in open field) for 10 minutes was significantly decreased in lesion group compared to sham group (**p<0.001).

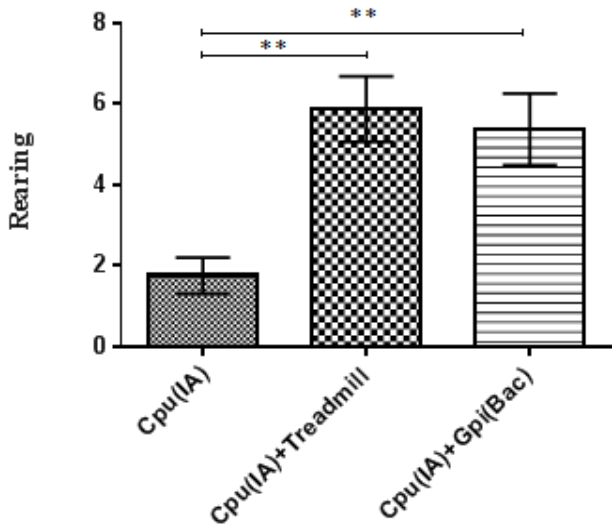
DISCUSSION

Our results showed that striatum lesion by ibotenic acid injection impaired locomotor activity in lesion group compared to other groups. This means that corpus striatum has a crucial role in motor and cognition functions. Mild forced treadmill exercise could reinforce locomotor activity in lesion groups than Cpu (IA) group. While there was no significance between Cpu (IA) + treadmill and Cpu (IA) + Gpi (Bac) groups, treadmill and baclofen had the same effect on locomotor activity disorders and

anxiety behavior in degenerated animals. Moreover, locomotor activity and anxiety-behavior degeneration in lesion group got better after injection of agonist GABA-B in internal globus pallidus.



Graph 3. Distance in open field for 10 minutes was significantly decreased in Cpu (IA) group compared to Cpu (IA)+treadmill and Cpu (IA)+Gpi (Bac) groups (**P<0.01).



Graph 4. Rearing (frequency with which the animal stood on their hind legs in open field) for 10 minutes was significantly decreased in Cpu (IA) group than Cpu (IA)+treadmill and Cpu (IA) + Gpi (Bac) groups (**P<0.01).

Our results showed that ibotenic acid injection in striatum impaired locomotor activity and anxiety-behavior in the animal model. Basal ganglia are components of circuits that include cerebral cortex and thalamus and the motor circuit is particularly important in the pathophysiology of movement disorders (32). Another study says that the neocortex and striatum are linked (33). Pathological inclusions are associated with reduced concentration of hippocampal dopamine and striatum that caused a progressive reduction in dopamine-dependent learning and spontaneous locomotion (34). Previous studies showed that injection of quinolinic acid (QA) into the striatum of rats is known to produce deficit in locomotor activity and in spatial learning similar to those observed in Huntington's disease (HD) (35). Taken together, the qualitative ratings suggest that cell damage to the caudate-putamen in the rat does produces abnormalities in skilled movement and these abnormalities can be reflected in reduced performance scores. Since the caudate-putamen and the motor cortex are connected (36-38), the motoric deficits possibly result from disruption of some or all of these pathways. Whishaw, Zeeb, Erickson and McDonald (2007), showed which rats, trained to reach for single food pellets with one forelimb, received contralateral quinolinic acid or ibotenic acid lesions of the medial and lateral caudate-putamen. Their study confirmed findings that lateral caudate-putamen neurotoxic lesions in the rat impair success when the contralateral limb is used to reach for food. Their findings showed that these behavioral changes of sensorimotor neglect, motoric abnormalities and changes in success are discussed in relation to the complex contributions of the caudate-putamen to skilled reaching (33). Their results were confirmed by our observations. The aim of Marques et al.,'s study was to verify whether enriched environment is able to prevent the establishment of motor impairment in a cerebral palsy rat model. The animals were divided into four groups: control group (without CP in a standard environment), CP group (CP model in a standard environment), EE group (without CP in an

enriched environment) and CP-EE (CP model in an enriched environment). Their results demonstrated that the stimulus increment provided by EE can prevent the onset of motor deficits and histological changes in a CP rat model (39-41). So, they funded the enriched environment like exercise in our study which could improve movement disorders produced by striatum lesion.

Previous studies showed that mild forced physical training improves blood volume in key regions for movement without inducing edema in old mice (40). De Senna et al., (2015) concluded that forced treadmill training could improve short-term memory and enhances motor performance in diabetic rats (41). Several studies have reported that different types of treadmill exercise induce an improvement in cognitive and movement dysfunction of brain injury (25, 42-44). Therefore, mild forced treadmill exercise is a prepare way to improve movement disorders. Very few studies analyzed the relationship between exercise and anxiety in human and animal models. The results were controversial. Burghardt et al., (2004) demonstrated that the wheel running produced anxiogenic effects in the open-field test, whereas treadmill running had no significant effect (45). Another paper by García-Capdevila et al., (2009) investigated the effects of exercise on anxiety-related behavior in young rats (2 months) and showed that after 1 month of training with voluntary wheel running some indicators of emotional reactivity in the open-field increased, regardless of the level of exercise. These results suggest that the type of exercise and duration of its application also appear to be important factors when evaluating data in the open-field (46). As mentioned in the present study, anxiety-behavior after exercise innovation improved, like previous studies. Consistent with our findings, Pietrelli, Lopez-Costa, Goni, Brusco, Basso (2012) indicated that regular and chronic aerobic exercise has time and dose-dependent neuroprotective and restorative effects on physiological brain aging and reduces anxiety-related behaviors (47).

Our results showed that GABA-B agonist (Baclofen) injection in internal Globus Pallidus could improve movement degeneration in lesion group compared to the Cpu (IA) group. Also, Baclofen caused anxiety-behavior in lesion groups that are better than Cpu (IA) group. So, Baclofen has the same effect as mild treadmill exercise on anxiety-behavior and locomotor activity. More recent studies using small chemically-induced lesions have demonstrated clearly that lesions of GPi or SNpr cause abnormal involuntary postures and movement (48). Lesions restricted to GPi results in slowness of movement of the contralateral limbs with abnormal muscle activity (48). Baclofen ameliorates motor deficit and reduces latency in the rotarod test and number of crossings in open-field test. This is similar to our findings (49). In consistent with our findings, Kim and Seo (2014) showed that baclofen administration showed tendency to decrease locomotive activities of the crossing (50). This opposition could relate to the animal models, and in our study, all of experiments were done on rats. Also, a variety of baclofen dosages might be the main factor in this conflicting scenario. In summary, functional GABAergic stimulation via a GABA-B receptor enhances survival of striatal cells and proteasome activity in vitro and reduces ubiquitin and consequently induces restoration of locomotor activity in vivo. Applying another type of physical training such as wheel running or voluntary exercise and variation of intensity and duration of exercise regimen to test this paradigm may be needed for future experiments. Moreover, injection of GABA-B antagonist in Gpi can create a different effect so far as striatum damage is concerned. Further studies can investigate GABA-B agonist and antagonist effects on anxiety-behavior.

CONCLUSION

Our findings suggest that striatum has a major effect on motor learning and behavior. Mild forced treadmill exercise and GABA-B agonist improve motor dysfunction and reduce anxiety-behavior in animals with striatum damage by ibotenic acid injection.

APPLICABLE REMARKS

- Combination of exercise and drug could improve motor function and stress behavior in animal models with brain impairment.

REFERENCES

1. Romanelli P, Esposito V, Schaal DW, Heit G. Somatotopy in the basal ganglia: experimental and clinical evidence for segregated sensorimotor channels. Brain research reviews. 2005;48(1):112-28.
2. Mink JW. Basal ganglia motor function in relation to Hallervorden-Spatz syndrome. Pediatric neurology. 2001;25(2):112-7.
3. Ilinsky I, Jouandet M, Goldman-Rakic P. Organization of the nigrothalamocortical system in the rhesus monkey. Journal of Comparative Neurology. 1985;236(3):315-30.
4. Penney J, Young A. Speculations on the functional anatomy of basal ganglia disorders. Annual review of neuroscience. 1983;6(1):73-94.
5. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Progress in neurobiology. 1996;50(4):381-425.
6. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends in neurosciences. 1989;12(10):366-75.
7. Dunnett SB, Iversen SD. Sensorimotor impairments following localized kainic acid and 6-hydroxydopamine lesions of the neostriatum. Brain research. 1982;248(1):121-7.
8. Montoya C, Astell S, Dunnett S. Effects of nigral and striatal grafts on skilled forelimb use in the rat. Progress in brain research. 1990;82:459-66.
9. Pisa M. Motor functions of the striatum in the rat: critical role of the lateral region in tongue and forelimb reaching. Neuroscience. 1988;24(2):453-63.
10. Pisa M, Schranz JA. Dissociable motor roles of the rat's striatum conform to a somatotopic model. Behavioral neuroscience. 1988;102(3):429.
11. Divac I, Markowitsch HJ, Pritzel M. Behavioral and anatomical consequences of small intrastriatal injections of kainic acid in the rat. Brain research. 1978;151(3):523-32.
12. Reading PJ, Dunnett SB, Robbins TW. Dissociable roles of the ventral, medial and lateral striatum on the acquisition and performance of a complex visual stimulus-response habit. Behavioural brain research. 1991;45(2):147-61.
13. Galvan A, Hu X, Smith Y, Wichmann T. Localization and pharmacological modulation of GABA-B receptors in the globus pallidus of parkinsonian monkeys. Experimental neurology. 2011;229(2):429-39.
14. Chen L, Chan S, Yung W. Rotational behavior and electrophysiological effects induced by GABA B receptor activation in rat globus pallidus. Neuroscience. 2002;114(2):417-25.
15. Tillerson J, Caudle W, Reveron M, Miller G. Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. Neuroscience. 2003;119(3):899-911.
16. Allen NE, Sherrington C, Paul SS, Canning CG. Balance and falls in Parkinson's disease: A meta-analysis of the effect of exercise and motor training. Movement disorders. 2011;26(9):1605-15.
17. Murray DK, Sacheli MA, Eng JJ, Stoessl AJ. The effects of exercise on cognition in Parkinson's disease: a systematic review. Translational neurodegeneration. 2014;3(1):1.
18. Paillard T, Rolland Y, de Souto Barreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. Journal of clinical neurology. 2015;11(3):212-9.
19. Garcia PC, Real CC, Ferreira AF, Alouche SR, Britto LR, Pires RS. Different protocols of physical exercise produce different effects on synaptic and structural proteins in motor areas of the rat brain. Brain research. 2012;1456:36-48.
20. Aguiar AS, Araújo AL, da-Cunha TR, Speck AE, Ignácio ZM, De-Mello N, et al. Physical exercise improves motor and short-term social memory deficits in reserpinized rats. Brain research bulletin. 2009;79(6):452-7.
21. Dishman RK, Berthoud HR, Booth FW, Cotman CW, Edgerton VR, Fleshner MR, et al. Neurobiology of exercise. Obesity. 2006;14(3):345-56.
22. Etnier JL, Nowell PM, Landers DM, Sibley BA. A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain research reviews. 2006;52(1):119-30.
23. Cotman CW, Engesser-Cesar C. Exercise enhances and protects brain function. Exercise and sport sciences reviews. 2002;30(2):75-9.
24. Markham JA, Greenough WT. Experience-driven brain plasticity: beyond the synapse. Neuron glia biology. 2004;1(04):351-63.
25. Stackman RW, Walsh TJ. Baclofen produces dose-related working memory impairments after intraseptal injection. Behavioral and neural biology. 1994;61(2):181-5.
26. Sandyk R, Gillman M. Baclofen-induced memory impairment. Clinical neuropharmacology. 1985;8(3):294-5.
27. Nourjah P., Rostami P., BarzegarM.H. a. The role of GABA- B receptors of NBM in learning

and memory. Iranian biology journal. 2006;3(20):278-87.
28. McNamara RK, Skelton RW. Baclofen, a selective GABA B receptor agonist, dose-dependently impairs spatial learning in rats. Pharmacology Biochemistry and Behavior. 1996;53(2):303-8.
29. Zeman A, Hoefeijzers S, Milton F, Dewar M, Carr M, Streatfield C. The GABA B receptor agonist, baclofen, contributes to three distinct varieties of amnesia in the human brain–A detailed case report. Cortex. 2016;74:9-19.
30. Paxinos G, Watson CR, Emson PC. AChE-stained horizontal sections of the rat brain in stereotaxic coordinates. Journal of neuroscience methods. 2004;3(2):129-49.
31. Walsh RN, Cummins RA. The open-field test: A critical review. Psychological bulletin. 1976;83(3):482.
32. Tarsy D, Vitek JL, Lozano AM. Surgical treatment of Parkinson's disease and other movement disorders: Springer Science & Business Media; 2002.
33. Whishaw I, Zeeb F, Erickson C, McDonald R. Neurotoxic lesions of the caudate-putamen on a reaching for food task in the rat: acute sensorimotor neglect and chronic qualitative motor impairment follow lateral lesions and improved success follows medial lesions. Neuroscience. 2007;146(1):86-97.
34. Costa C, Sgobio C, Siliquini S, Tozzi A, Tantucci M, Ghiglieri V, et al. Mechanisms underlying the impairment of hippocampal long-term potentiation and memory in experimental Parkinson's disease. Brain. 2012:aws101.
35. Block F, Kunkel M, Schwarz M. Quinolinic acid lesion of the striatum induces impairment in spatial learning and motor performance in rats. Neuroscience letters. 1993;149(2):126-8.
36. Cheatwood J, Corwin J, Reep R. Overlap and interdigitation of cortical and thalamic afferents to dorsocentral striatum in the rat. Brain research. 2005;1036(1):90-100.
37. Cheatwood J, Reep R, Corwin J. The associative striatum: cortical and thalamic projections to the dorsocentral striatum in rats. Brain research. 2003;968(1):1-14.
38. Gabrieli JD, Stebbins GT, Singh J, Willingham DB, Goetz CG. Intact mirror-tracing and impaired rotary-pursuit skill learning in patients with Huntington's disease: evidence for dissociable memory systems in skill learning. Neuropsychology. 1997;11(2):272.
39. Ang E-T, Dawe GS, Wong PT, Moochhala S, Ng Y-K. Alterations in spatial learning and memory after forced exercise. Brain research. 2006;1113(1):186-93.
40. Mariotti R, Fattoretti P, Malatesta M, Nicolato E, Sandri M, Zancanaro C. Forced mild physical training improves blood volume in the motor and hippocampal cortex of old mice. The journal of nutrition, health & aging. 2014;18(2):178-83.
41. Marques MR, Stigger F, Segabinazi E, Augustin OA, Barbosa S, Piazza FV, et al. Beneficial effects of early environmental enrichment on motor development and spinal cord plasticity in a rat model of cerebral palsy. Behavioural brain research. 2014;263:149-57.
42. Döbrössy MD, Dunnett SB. Motor training effects on recovery of function after striatal lesions and striatal grafts. Experimental neurology. 2003;184(1):274-84.
43. Hoveida R, Alaei H, Oryan S, Parivar K, Reisi P. Treadmill running improves spatial memory in an animal model of Alzheimer's disease. Behavioural brain research. 2011;216(1):270-4.
44. Kim S-H, Kim H-B, Jang M-H, Lim B-V, Kim Y-J, Kim Y-P, et al. Treadmill exercise increases cell proliferation without altering of apoptosis in dentate gyrus of Sprague-Dawley rats. Life sciences. 2002;71(11):1331-40.
45. Burghardt PR, Fulk LJ, Hand GA, Wilson MA. The effects of chronic treadmill and wheel running on behavior in rats. Brain research. 2004;1019(1):84-96.
46. García-Capdevila S, Portell-Cortés I, Torras-Garcia M, Coll-Andreu M, Costa-Miserachs D. Effects of long-term voluntary exercise on learning and memory processes: dependency of the task and level of exercise. Behavioural brain research. 2009;202(2):162-70.
47. Pietrelli A, Lopez-Costa J, Goni R, Brusco A, Basso N. Aerobic exercise prevents age-dependent cognitive decline and reduces anxiety-related behaviors in middle-aged and old rats. Neuroscience. 2012;202:252-66.
48. Mink J, Thach W. Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. Journal of neurophysiology. 1991;65(2):330-51.
49. Slow EJ, Van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, et al. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. Human molecular genetics. 2003;12(13):1555-67.
50. Kim W, Seo H. Baclofen, a GABA B receptor agonist, enhances ubiquitin-proteasome system functioning and neuronal survival in Huntington's disease model mice. Biochemical and biophysical research communications. 2014;443(2):706-11.