



RESEARCH ARTICLE

Aerobic Exercise Altered Locomotor Activity and Induced D1 Dopamine Receptor and Brain Derived Neurotropic Factor (BDNF) Expressions

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ABSTRACT

Exercise contributes in improving mental health and alleviates depression, anxiety, and cognitive impairment by facilitating neuronal remodeling (Park H, Poo MM. 2013). The involvement of brain derived neurotropic factor (BDNF) and D1 dopamine receptor (D1DR) has been reported. On the other hand, a limited number of information is available on the effect exercise with altered intensity on locomotor activity. This study explored the effect of altered training intensity on adult male rat locomotor activity, which may be partly regulated by neuronal remodeling through dopamine and BDNF signalling. Male adult Wistar rats were divided into 4 groups: stationary control, aerobic (sub LT), lactate threshold (LT), and anaerobic training groups (Supra LT). They were trained for 14 days followed by measuring the locomotor activity in their home cage from day 14 to 16. Rats were then sacrificed under anesthesia, and the striatum was separated for RT-PCR and Western blot analysis. We found that two-weeks training induced hyperactivity during night regardless of the training intensity. Only aerobic training group showed increased D1DR mRNA and protein levels; BDNF mRNA levels were also increased. The phosphorylation of Tropomyosin receptor kinase (Trk) A and TrkB was also altered significantly (TrkA, all training groups; TrkB, only aerobic group). In summary, two weeks training with various intensities induces hyperactivity in rats during night. Among various training protocols, only aerobic training activated D1DR and BDNF signaling pathways. These results partly revealed the mechanism how exercise with different intensity can alter behavior in rats. In addition, our study may have clinical relevance to clarify the role of exercise, particularly aerobic training, to improve mental health.

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INTRODUCTION

Exercise is known to be beneficial for mental health. Different types of exercise have been studied to determine which exercise regimen can most effectively enhance neuroplasticity (Clark *et al.*, 2016). Based on the intensity, exercise can be divided into aerobic and anaerobic exercise. While study about the correlation between anaerobic exercise and mental health was limited, many studies showed that aerobic exercise might give neuroprotective effect throughout aging (Vecchio *et al.*,

2018) and help to improve motor function in neurological disorders (Thomas *et al.*, 2012). These improvements were attributed to increase of neurotrophins and neurotransmitter receptor level in distinct brain regions (Petzinger *et al.*, 2013). However, a limited number of information is available on the effect exercise with altered intensity on locomotor activity.

The striatum is a subcortical part of forebrain. It is anatomically divided into two parts. The dorsal striatum primary facilitates voluntary movement, whereas the ventral striatum mainly involves in the motor planning,

motivation and reward cognition (Robbe, 2018). Because its strong association with motor activity, the striatum is often studied to understand how exercise can influence neuronal activity in the brain.

Animal models, particularly rat, have been used to gain our understanding of exercise-activated neuroplasticity. Interestingly, the exercise has been shown to increase neurotrophic factor such as brain derived neurotrophic factor (BDNF) (Leckie *et al.*, 2014), which promotes neuronal survival, dendritic remodeling and synaptic plasticity (Szuhany *et al.*, 2015), in the striatum. Furthermore, the exercise has been proposed as a strategy to promote neuroprotection and neurorestoration. Previous studies showed that the exercise could improve motor performance in Parkinson Disease (PD) rat model and intracerebral hemorrhage rat model by upregulating striatal dopamine receptor (DR) and BDNF, respectively (Vuckovic *et al.*, 2010; Chen *et al.*, 2012). Many studies applied exercise regimen in pathologic rat models to examine the effect of exercise on the recovery of the lesioned striatum, however, little work has been done to investigate the effect of exercise with different intensity on DR and BDNF levels in under physiological condition.

In our previous study, by using treadmill exercise, we have established the exercise protocol to perform aerobic exercise (sub-lactate threshold, LT) and anaerobic exercise (supra-LT) trainings (Lesmana *et al.*, 2017). The present study investigated the effects of aerobic (sub-LT), LT, and anaerobic (supra-LT) exercise regimen on the expression of DR and BDNF in the striatum. Furthermore, because the dopaminergic system has been shown to influence voluntary running motivation in rats, locomotor activity of subjects was also measured. This study may have clinical relevance to understand the neurophysiological effects of exercise with different intensities on adaptive signaling pathway in the striatum.

MATERIALS AND METHODS

Animals and experimental groups: The experiments were conducted in accordance with the guidelines and protocols approved by the Animal Care and Experimentation Committee at Gunma University, Maebashi, Japan. All efforts were made to minimize the suffering and number of animals used in this study.

Twenty male Wistar rats (8 weeks old, body weight 230 ± 10 g, $n=20$) were divided into 4 groups: Stationary control, aerobic (sub lactate), Lactate threshold (LT) and anaerobic (Supra Lactate Treshold) training groups. Rats were individually housed under standard conditions (12-hr light/dark cycle, 23-24°C), with *ad libitum* access to food and water.

Treadmill habituation protocol: Treadmill habituation protocol was adopted from previous study (Soya *et al.*, 2007; Lesmana *et al.*, 2016) with minor modifications to minimize the stress. All rats were habituated for 5 days with a low-intensity exercise using flatbed treadmill machine (KN.73 Tread-Mill; Natsume Seisakusho Co., Ltd., Tokyo, Japan). On day 1, rats were put in the treadmill machine for 60 min. On day 2, rats were conditioned to run at 2 m/min for 20 min. Then on the following days, the training speed increased gradually to

11 m/min until day 5. After habituation, rats were selected based on Dishman Score (Dishman *et al.*, 1988) and only rats showing a good Dishman score were included into the experiment.

Exercise protocols: After habituation process, rats were trained to run at different speed. The speed for aerobic, LT and anaerobic exercise were 15 m/min, 20 m/min and 25 m/min for 30 min per day, respectively (Lesmana *et al.*, 2016). The speed of each group was defined by the plasma lactate levels. At 20 m/min, plasma lactate level was not altered for 20 min but weakly increased 20 min after the onset of training. Based on such results, we defined 15 m/min, 20 m/min and 25 m/min for 30 min, as aerobic (sub-LT), LT and anaerobic (supra-LT) exercise group, respectively. The exercise protocols started from day 6 until day 14.

Measurement of locomotor activity: An infrared sensor was placed over each cage to monitor locomotor activity. The infrared beam crossings were continuously recorded. The activity was measured for 72 hours (h) (day 14-16). The first and last 24 h were excluded from data analysis as a habituation period.

Tissue Harvesting: Rats were sacrificed under diethyl ether anesthesia at day 16, striatum was separated, snap frozen by liquid nitrogen and stored in -80°C until used.

Semi-quantitative RT-PCR: Total RNA was extracted from the striatum using RNeasy Kit (Qiagen, Hilden, Germany). Complementary DNA was reverse-transcribed from 500 ng total RNA as described in the PrimeScript RT reagent Kit (Takara Bio Inc., Saga, Japan), using the oligo (dT) and random primers. All experiments were repeated at least three times to confirm the results consistency. All PCR products were detected and analyzed by electrophoresis. Documentation and analysis of ethidium bromide staining was performed using Kodak 290 (Kodak, Norwalk, CT) and Image J software (Ver.1.41, NIH, Bethesda, MD). The PCR result of each sample was normalized by GAPDH mRNA level as an internal control.

Western Blot: The dissected striatum samples were weighted, homogenized in the protein extraction reagent (RIPA Lysis buffer: 20 mM Tris-HCl (pH 7.5); 150 mM NaCl; 1 mM Na₂EDTA; 1 mM EGTA; 1% NP-40; 1% sodium deoxycholate; 2.5 mM sodium pyrophosphate; 1 mM β -glycerophosphate; 1 mM Na₃VO₄; 1 μ g/mL leupeptin) with protease inhibitors and 1 mM sodium orthovanadate (a phosphatase inhibitor). The tissue lysates were separated by centrifugation for 15 min at 15,000 rpm at 4°C and protein concentrations in the supernatant were measured (Bradford protein assay, Bio-Rad, Hercules, CA). Equal amounts of protein were resolved by SDS-PAGE, transferred to a nitrocellulose membrane and immunoblotted with D1DR or D2DR antibody (Santa Cruz Biotechnology USA); Tropomyosin receptor kinase/Tryrosin receptor kinase (Trk) A, TrkB, phosphorylated (p)-TrkA, or p-TrkB antibody (Millipore, USA); β -actin antibody (Thermoscientific, USA) for overnight at 4°C. The antigen-antibody complexes were

detected by chemiluminescence with an ECL system (GE Healthcare, UK), and visualized with a Lumi-Imager imaging analyzer (Roche, Swiss). The intensity of bands was quantified using image analysis software (Lumi Analyst, Roche, Swiss).

Statistical analysis: All data were presented as mean \pm standard error of the minimum. A two-tailed student's t-test was used for two-group comparison involving a single continuous variable and a one-way repeated measure analysis of variance (ANOVA) test was used for intra-subjects multiple comparison. Differences between the experimental groups were considered statistically significant at $P < 0.05$. All analyzed use SPSS 19 for Windows.

RESULTS

Exercise-Induced Hyperactivity: To determine the association between exercise and locomotor behavior, spontaneous locomotor activity was measured after 2-weeks exercise period (Fig. 1). The nocturnal locomotor activity increased significantly in all exercise groups compare to control (no-exercise) group ($P < 0.05$). There were no statistically significant differences in locomotor activity among aerobic, LT and anaerobic exercise groups.

Exercise-Induced Dopamine Receptor and BDNF Expression: Semiquantitative RT-PCR was performed to

assess the expression levels of D1 dopamine receptor (D1DR), D2 dopamine receptor (D2DR), and BDNF genes (Fig. 2a). Aerobic exercise group showed higher D1DR and BDNF mRNA levels in the striatum compared to control group (Fig. 2b, 2d; $P < 0.05$). On the other hand, there was no significant changes on D1DR and BDNF mRNA levels in LT and anaerobic exercise groups. Compared to control group, D2DR mRNA level increased slightly in aerobic group, but such increase was not statistically significant ($P < 0.05$) (Fig. 2C).

To examine the protein levels of DR, Western blot to for D1DR and D2DR was performed (Fig. 3a). The result was in accordance with RT-PCR results, showing that D1DR level was significantly higher only in aerobic group (Fig. 3b; $P < 0.05$). Furthermore, no significant differences in DRD2 protein were observed among groups (Fig. 3c).

BDNF exerts its action by binding to TrkB and induce autophosphorylation of TrkB. To examine the activation of BDNF signaling pathway, Western blot for phosphorylated-TrkB (pTrkB) was performed (Fig. 4a). The ratio of pTrkB to TrkB was significantly higher in aerobic exercise group compared to control group (Fig. 4b; $P < 0.05$). The level of phosphorylated TrkA, which is mainly activated by nerve growth factor (NGF) was also measured in this study. Compared to control group, all exercise groups showed an increase in the ratio of pTrkA to TrkA (Fig. 4c; $P < 0.05$).

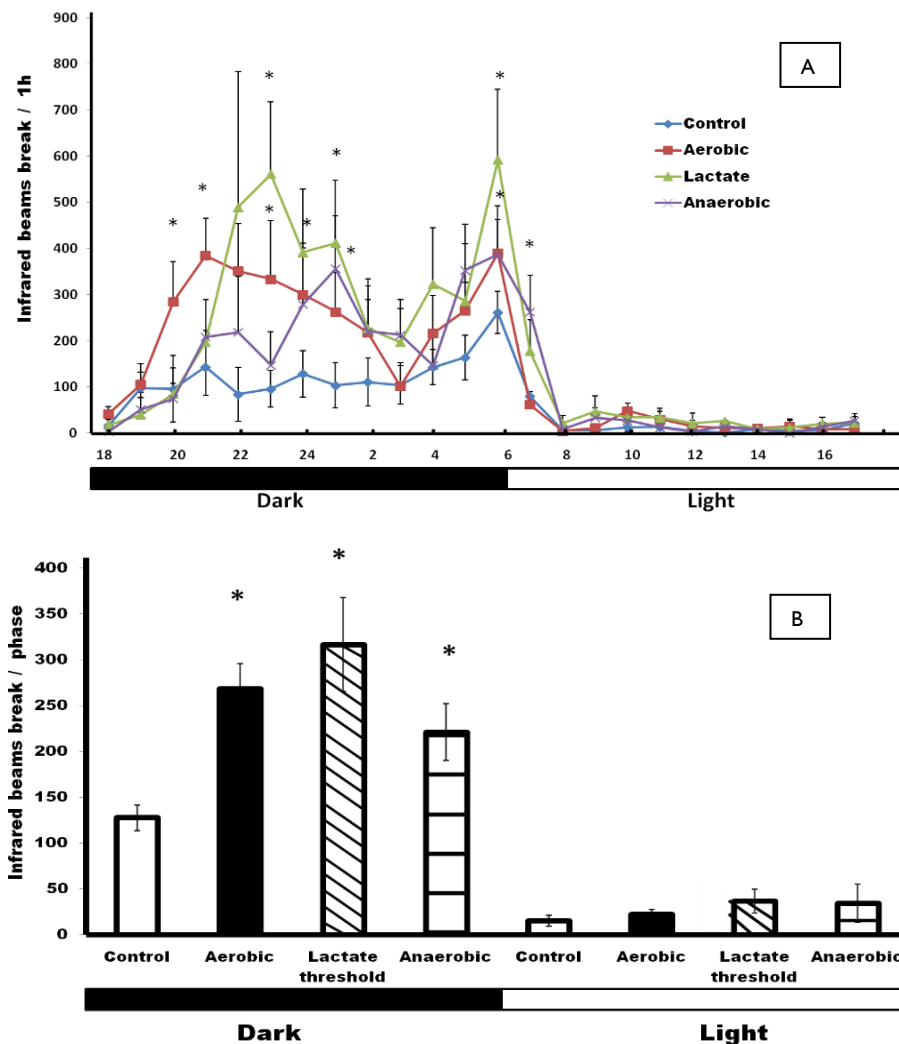


Fig. 1: Exercise with different training intensity induced hyperactivity at dark time (A) Locomotor activity was measured at days 15-17 (for 72 h). Data are expressed as mean \pm SEM for 5 rats/group exercise of hourly measurement during 24 h period. *, $P < 0.05$ compared with control group at the same phase. (B) Total locomotor activity during the dark and light phases. Data are expressed as mean \pm SEM for 5 Rats/group exercise of hourly measurement during 24 h period. *, $P < 0.05$ compared with control group at the same phase.

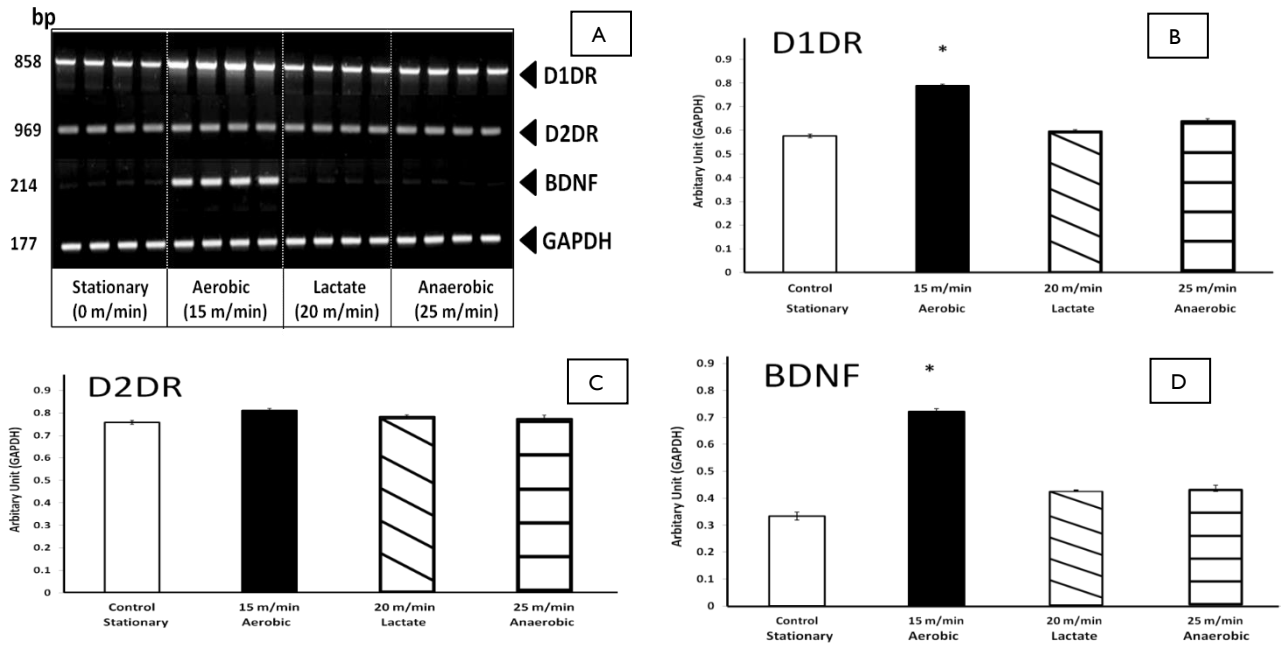


Fig. 2: Only aerobic training increased D1DR and BDNF mRNA levels in the striatum, but not D2DR levels. (A) Representative figure of gene electrophoresis results from 4 sample each groups; Relative mRNA levels of (B) D1DR, (C) D2DR, and (D) BDNF, shown as mean \pm SEM for 5 Rats/group exercise. *, $P < 0.05$ compared with control group.

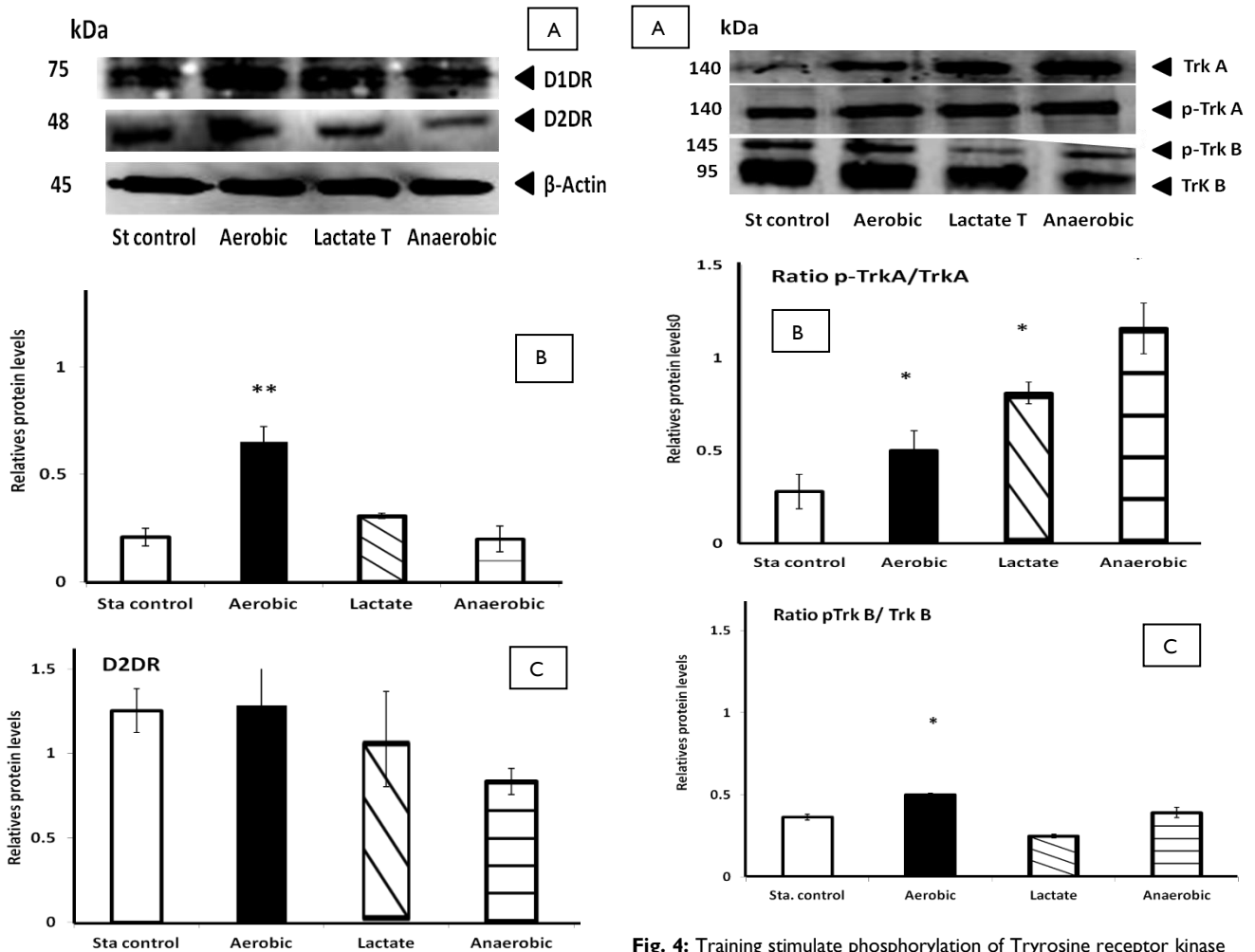


Fig. 3: Only aerobic exercise increased D1DR, whereas only anaerobic group decreased D2DR protein levels. (A) Representative Western blot result for D1DR, D2DR and b-actin. Relative protein levels of (B) D1DR and (C) D2DR. Data are expressed as mean \pm SEM for 5 Rats/group exercise. *, $P < 0.05$ compared with control group.

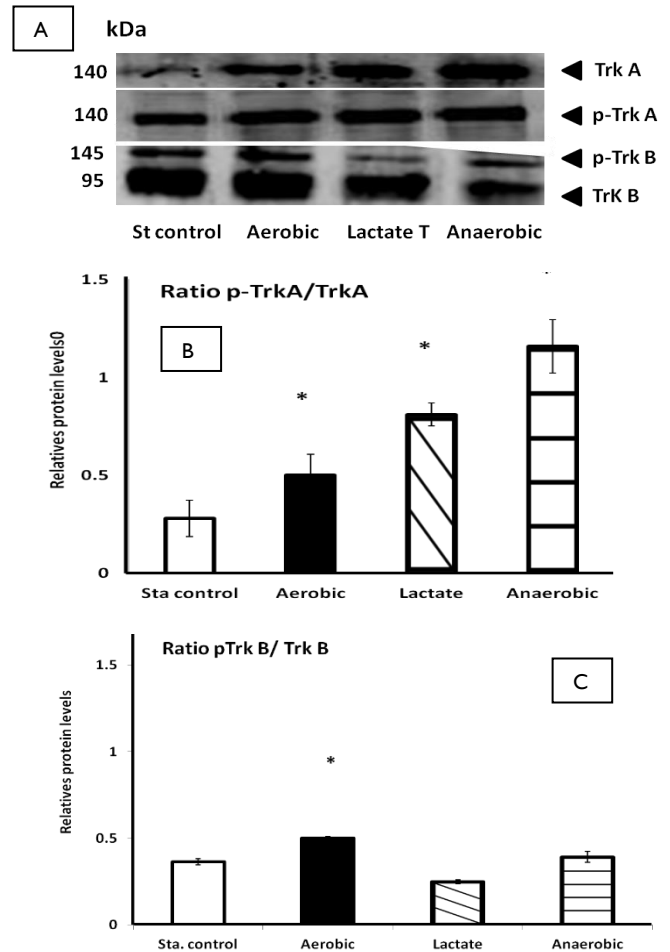


Fig. 4: Training stimulate phosphorylation of Tyrosine receptor kinase (Trk) A by an intensity-dependent manner, whereas only aerobic exercise stimulated phosphorylation of TrkB protein. (A) Representative Western blot result showing TrkA and B phosphorylation, (B) The ratio of p-TrkA/TrkA, and (C) The ratio of p-TrkB/TrkB. Data are expressed as mean \pm SEM for 5 Rats/group exercise. *, $P < 0.05$ compared with control group.

DISCUSSION

The present study showed that 2-weeks exercise training with different intensity altered locomotor activity of adult male rat. The expression of D1DR and BDNF was altered only by aerobic exercise. These results indicate that repeated training may influence the behavioral patterns and aerobic training may be effective in activating dopaminergic and BDNF-mediated signaling in the striatum (de Assis and de Almondes, 2017.).

In rats, locomotor activity assessment has proven useful in differentiating the effects of a variety of dopaminergic agents (Schindler and Carmona, 2002; Heyn *et al.*, 2004.). Administration of dopamine agonist increased the locomotor activity and the administration of dopamine antagonist gave the opposite effect. In our study, locomotor activity increased in all exercise groups (Fig. 1), whereas D1DR expression was upregulated only in aerobic group. Therefore, we cannot solely attribute the increase of locomotor activity to the increase of D1DR. The increment of locomotor activity in this study may be induced by several factors such as exercise-mediated anxiolytic or a stress response or learn process to a new environment (Lett *et al.*, 2002; Wassum *et al.*, 2011).

Mazur *et al.* (2017) had reported that physical exercise on a treadmill could decrease anxiety-like behavior and increase locomotor activity in rats. Furthermore, the exercise-induced increase in cardiovascular fitness or muscular endurance may facilitate better locomotor capability. Further study is needed to confirm the possible other related mechanisms including involvement of dopamine signaling which may be responsible in controlling the behavior of rats.

D1DR are exclusively expressed in post synaptic terminals. Their activation in the dorsal striatum stimulates the direct pathway to activate locomotor activity (Beaulieu and Gainetdinov, 2011). On the other hand, DRD2s are expressed in pre and post synaptic terminals and its activation inhibits striatal neurons through the indirect pathway, which inhibits activation of locomotion stimulated by the direct pathway. Thus, motor activity is finely tuned by these systems. In the present study, aerobic exercise induced an increase in D1DR levels but not D2DR levels. Such increased may have attributed to the increased locomotor activity. However, the increase in D1DR was not observed in other training conditions. Furthermore, our finding was not fully consistent with previous study showing that the aerobic exercise increased D2DR expression (Vuckovic *et al.*, 2010). This discrepancy may be caused by the shorter training period in our study, in which we conducted only for 2 weeks training, whereas previous study conducted for 1.5-6 months. A distinct differential response in subcortical circuits by altered training duration has been observed previously (Real *et al.*, 2015). Crude extract of striatum sample was homogenized without dividing dorsal and ventral regions. Thus, the possibility that the upregulation of D1DR observed in the present study may not exclusively associated with the direct pathway in the dorsal striatum, may need to be considered (Fig. 3). The ventral striatum, which is more aligned with reward and motivation, may be activated during aerobic exercise (Threlfell and Cragg, 2011). Rats may have considered

aerobic exercise as a rewarding and reinforcing activity (Trost and Hauber, 2014). Herrera *et al.* (2016) have reported that voluntary exercise and forced exercise activated circuits implicated in reward; the dopaminergic neuron projection from ventral tegmental area to nucleus accumbens. Furthermore, LT exercise and anaerobic exercise may be interpreted as a stressor or negative experiences which might not enhance DR levels in the striatum.

In the present study, aerobic exercise has been shown to enhance BDNF expression (Marais *et al.*, 2009; Marlat *et al.* 2012). This finding is in accordance with previous study in which treadmill training increased BDNF protein levels in the striatum (Szuhany *et al.*, 2016; Mackay *et al.*, 2017). BDNF promotes survival and proper function of neuronal population. This neurotrophin also increases the number of dendritic spine. Such increase is important to improve the chance of dendritic filopodium encounter nearby axon and establish a connection (Baydyuk and Xu, 2014). Thus, the upregulation of BDNF induced by aerobic exercise in our study may be beneficial to promote neuronal plasticity.

BDNF expression was not altered in LT exercise and anaerobic exercise groups. This finding may be due to the possibility of LT and anaerobic exercises to induce glucocorticoid secretion. In a previous study, an intense exercise regimen on a treadmill (20 m/min for 30 min/day) in a brain ischemia rat model increased plasma corticosterone up to three times higher than the normal level and diminish exercise-induced BDNF expression in the striatum (Ke *et al.*, 2011). The exercise regimen for LT group was the same condition as their study also. However, because our subjects are healthy rats, further study is needed to examine the effect of LT and anaerobic exercise regimen on plasma corticosterone levels under our experimental conditions. BDNF stimulate target neurons by binding to TrkB. This binding induces receptor dimerization and auto-phosphorylation of its tyrosine residues, resulting in activation of downstream signaling pathways. In the present study, an increase in pTrkB/TrkB ratio in aerobic exercise group together with an increase in BDNF levels. These results indicate that aerobic exercise activates BDNF pathway in the striatum and may give beneficial effect to the mental health (Leckie *et al.*, 2014). A previous study showed that Tropomyosin receptor kinase (Trk) B is not equally distributed throughout the striatum (Baydyuk *et al.*, 2013). Instead, it is preferentially expressed in the medium spiny neurons, which also express D2DR, of the indirect pathway. In Huntington Disease model rats, in which the indirect pathway was affected, decreased BDNF mRNA levels in the striatum was improved by voluntary exercise (Pang *et al.*, 2006). It may be interesting to investigate the physiological importance of the activation of indirect pathway by BDNF upregulation by aerobic exercise.

Interestingly, the pTrkA/TrkA ratio was significantly increased in all exercised group (Fig. 4). TrkA is a receptor for nerve growth factor (NGF). Its activation promotes neuronal survival and differentiation. Chen *et al.* (2012) showed that treadmill exercise rehabilitation after intracerebral hemorrhage improved neurorestoration partly through BDNF-TrkB signaling, but not NGF-TrkA signaling. Our finding showed that the normal striatum

showed different responses. The activation of NGF-TrkA signaling may have contributed to exercise-induced neuroprotection in nigrostriatal pathway.

Conclusions: Different exercise intensity may induce different neurophysiological responses. Aerobic exercise may be the most significant regimen to enhance neuroplasticity at least in part by inducing D1DR and BDNF expression in the striatum.

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Authors contribution: RL and NK designed the project. RL, HG, YP and NS executed the experiment and analyzed the tissue samples. RL, EH, VT, IS, US and AP analyzed the data. All authors critically revised the manuscript and approved the final version.

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