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ORIGINAL PAPER

Dopamine stimulation of the septum enhances exercise efficiency during complicated treadmill running in mice

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Abstract

We aimed to identify the neurotransmitters and brain regions involved in exercise efficiency in mice during continuous complicated exercises. Male C57BL/6J mice practiced treadmill running with intermittent obstacles on a treadmill for 8 days. Oxygen uptake (VO_2) during treadmill running was measured as exercise efficiency. After obstacle exercise training, the VO_2 measured during treadmill running with obstacles decreased significantly. Obstacle exercise-induced c-Fos expressions and dopamine turnover (DOPAC/dopamine) in the septum after obstacle exercise training were significantly higher than that before training. The dopamine turnover was correlated with exercise efficiency on the 3rd day after exercise training. Furthermore, the training effect on exercise efficiency was significantly decreased by injection of dopamine receptor antagonists into the septum and was associated with decreased c-Fos expressions in the septum and hippocampus of the mice. These results suggest that dopaminergic function in the septum is involved in exercise efficiency during continuous complicated exercises.

Keywords Exercise efficiency · Septum · Dopamine turnover · Exercise training · Oxygen uptake

Introduction

Exercise efficiency is defined as high performance with low energy expenditure [1–3] and is enhanced by relevant exercise training. Higher exercise efficiency during certain intensity movements increases enjoyment during exercise and promotes motivation for further spontaneous exercise, which is needed to prevent the development of locomotive syndrome or sarcopenia. Exercise efficiency involves adaptations of the skeletal muscle metabolism, respiratory–cardiovascular system, hemodynamics and motor skills [4–16].

Motor learning is involved in improvements in exercise techniques, which are possible after training for a certain period of time. Motor skills contribute to the ability to perform complicated exercises and are adapted earlier than other parameters [17], such as hypertrophy, hormonal sensitivity, and gene expression. Procedural memory also contributes to improvements in exercise techniques. The basal ganglia, cerebellum, and motor cortex have central roles in procedural memory [18]. Moreover, disorders of the basal ganglia in patients with Parkinson's disease and Huntington's disease hamper the ability to learn motor techniques [19]. Biomechanical mechanisms in motor skills, including somatosensory recognition both in "closed skills" and "open skills", were systematically reviewed in previous literature [20–22]. However, biochemical mechanisms in the brain for improvement of combined (closed and open skills) continuous exercises have not been understood. Biochemical neuromodulators such as dopamine and serotonin have physiological roles in physical behavior, arousal, movement, and motivation. Clarifying the brain mechanisms involved in complicated continuous exercises will provide valuable information for sports performance, rehabilitation, and movement therapy.

Although several studies have demonstrated that some exercises activated various neurons in the brains of rodents

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[23–25], no reports have indicated biochemical and physiological associations between motor skills and exercise efficiency. Therefore, the aim of the present study was to identify responsive biochemical alterations and brain regions involved in exercise efficiency during continuous complicated exercises in mice. In this study, we creatively developed a continuous complicated exercise model for mice, using a treadmill with obstacles. Moreover, we regarded oxygen consumption during continuous complicated exercise as a marker of exercise efficiency in our model.

Methods

Animals

All experiments were performed using 8-week-old male C57BL/6J mice (Slc Inc., Shizuoka, Japan). They were housed individually in plastic cages at 24 ± 1 °C with a 12-hour light/12-hour dark cycle (lights on from 0800 to 2000) and were freely fed a laboratory diet (Oriental Yeast, Tokyo, Japan) and water. This study was performed with approval from the Animal Study Committee of Tokushima University, and all regulations of our institution involving proper animal care and handling were followed during our experiments.

Measurement of oxygen uptake and treadmill running with intermittent obstacles

We used the Mousebelt-2000 (Arco System Inc., Chiba, Japan) as the belt-type treadmill chamber for mice. Oxygen uptake (VO_2) during treadmill running (15 m/min) was measured with the ARCO-2000 mass spectrometer (Arco System Inc., Chiba, Japan) to determine exercise efficiency, which defined the same exercise performance with lower oxygen cost as an efficient movement. Before and after obstacle exercising training, VO_2 during treadmill running (15 m/min) was measured to determine exercise efficiency; the same exercise performance with lower oxygen cost was defined as an efficient movement.

One trial took a total of 14 min (0 m/min for the first 2 min, 10 m/min for the next 2 min, 15 m/min for the next 10 min), and the stimulation electrode was constant at 0.7 mA. All treadmill running experiments were performed between 1300 and 1730, and we measured VO_2 on the first and last trial day. During the 1st day, mice ran on the treadmill without intermittent obstacles; the next day, they ran with intermittent obstacles. Three sponges were shaped into a regular triangular prism (length, 10 mm; height, 50 mm), and they were arranged at random intervals on the belt chamber as the intermittent obstacles (Fig. 1a). For the next 10 days, mice performed treadmill running with intermittent obstacles as motor training once per day; however, they had 2 rest days during the middle of the 10 days. During the last trial day, they performed treadmill running with intermittent obstacles. Some mice did not undergo exercise training and were part of the control group.

Immunohistochemistry

We examined the brain region where the neural activity changed before and after exercise training. Immunostaining was performed to assess the differences in c-Fos expressions in several brain regions of the mice before and after obstacle exercise training. Ninety minutes after the last trial, the mice were anesthetized with a cocktail of ketamine (100 mg/kg; Daiichi-Sankyo, Tokyo, Japan) and xylazine (25 mg/kg; Sigma, St. Louis, MO, USA) and transcardially perfused with isotonic phosphate-buffered saline (PBS). This was followed by fixation with 4% paraformaldehyde in 0.1 M phosphate buffer before brain excision. The whole brain was removed and post-fixed for 24 h. For the following 4 days, the brains were soaked in a 20% sucrose solution. The tissue was embedded in the OCT compound (Sakura Fine-Technical, Tokyo, Japan), immediately frozen, and stored at − 80 °C until further analysis. Then, serial 30-µm cryosections were prepared using a cryostat (Leica CM1850, Wetzlar, Germany).

Sections received a 1-h quenching treatment at 3% H_2O_2 in methanol. For diaminobenzidine (DAB) antibody staining of c-Fos, sections were exposed for 2 h at 25 °C to 3% normal donkey serum and incubated for 3 days at 4 °C with rabbit antibodies to c-Fos (1:1000 dilution; Cell Signaling Technology, MA, USA). After washing the sections with PBS, immune complexes were detected using the Vectastain ABC HRP kit (peroxidase, rabbit IgG; Vector Laboratories, Burlingame, CA, USA). Sections were colored using a peroxidase stain DAB kit (Nacalaitesque, Kyoto, Japan) and metal enhancer for DAB staining (Nacalaitesque). Sections were finally examined with a microscope (Leica DM4000B Wetzlar, Germany or KEYENCE BZ-X700, Osaka, Japan). The c-Fos expression on one side of each brain region was manually counted in 700 × 350-pixel areas for inconsecutive three sections.

Monoamine concentration in the brain

The whole brain was removed, and 1-mm-thick coronal sections of the fresh brain were dissected from six regions (striatum, motor cortex, hypothalamus, hippocampus, septum, and cerebellum), frozen rapidly in liquid nitrogen, and stored at − 80 °C. Monoamine levels (dopamine [DA], 3,4-dihydroxyphenyl acetic acid [DOPAC], serotonin [5-HT], and 5-hydroxy indoleacetic acid [5-HIAA]) were quantified by high-performance liquid chromatography (HPLC) according

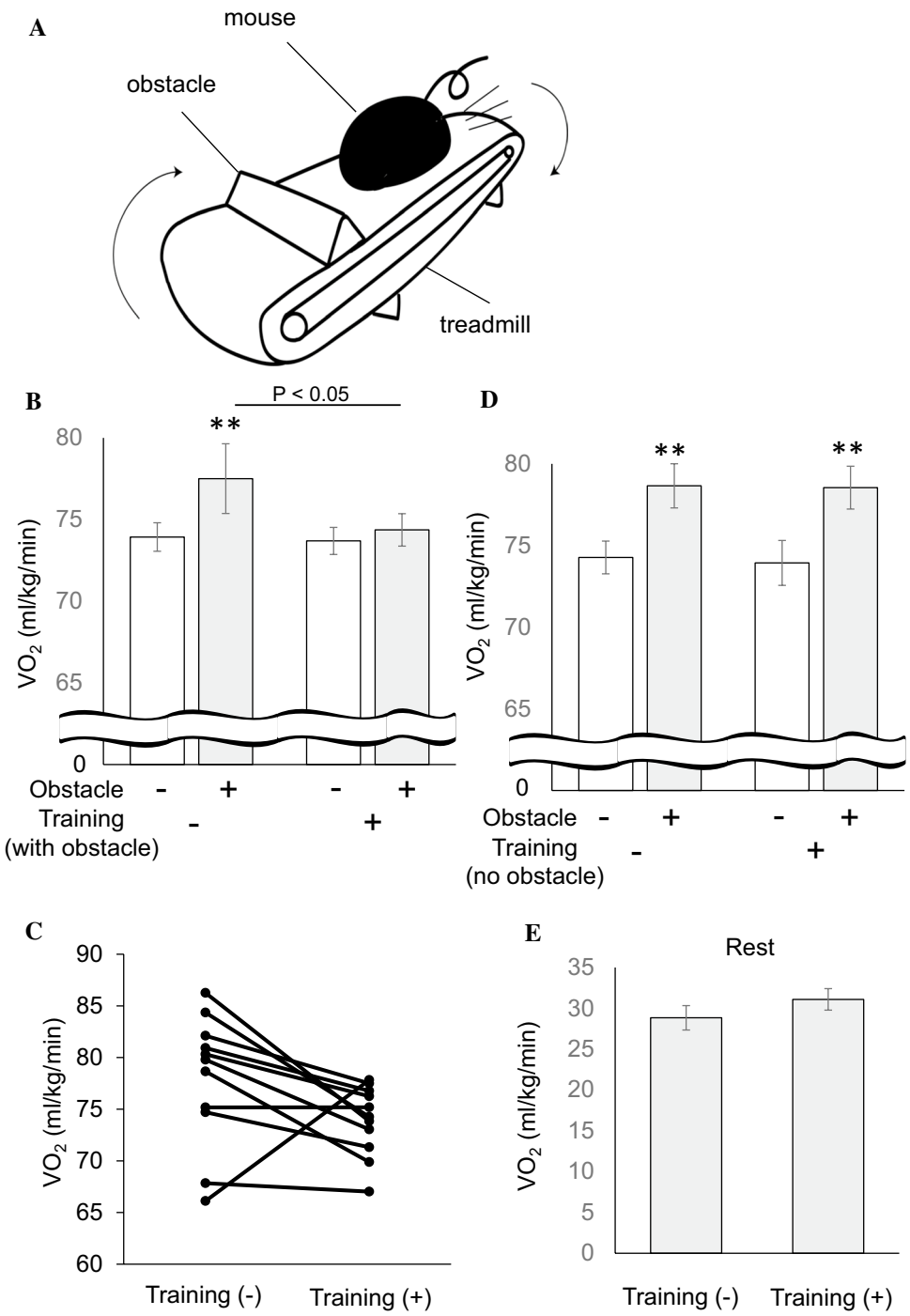

Fig. 1 Exercise efficiency before and after training of treadmill running with intermittent obstacles. **a** Model of treadmill running with intermittent obstacles. The belt-type treadmill chamber (width, 50 mm; length, 295 mm; height, 60 mm) was sealed in a rectangular parallelepiped glass case, and there were air holes in the front and rear. The rear air hole was connected to a tube used for measuring oxygen uptake (VO_2). **b** Average VO_2 during treadmill running with or without obstacles before and after training ($n = 11$). Training was performed with obstacle treadmill running. **c** Alteration of VO_2 during treadmill running with obstacles in each mouse before and after training of treadmill running with obstacles ($n = 11$). **d** Average VO_2 during treadmill running with or without obstacles before and after training ($n = 11$). Training was performed without obstacle treadmill running. **e** VO_2 at rest before and after training ($n = 11$). Data are presented as mean ± standard error. Paired *t* test was used. Asterisk indicates $p < 0.05$ vs. VO_2 during no obstacle treadmill running before training

to previously published methods with slight modifications [26]. DOPAC/DA and 5-HIAA/5-HT ratios were used to estimate the metabolic ratio.

Pharmacological treatments and injection procedure

Mice were anesthetized by intraperitoneal (ip) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg), and a double-walled stainless steel cannula (Plastics One, Roanoke, VA, USA) was stereotaxically implanted into the septum bilaterally (AP + 0.5 mm, L ± 0.5 mm, and H + 3 mm from the bregma) according to an atlas [27] (Supplemental Fig. 1). We used SCH 23,390 hydrochloride (Abcam PLC, Cambridge, UK) as a dopamine D1 receptor antagonist (D1 antagonist) and (S)-(-)-Sulpiride (Abcam PLC) as a dopamine D2 receptor antagonist (D2 antagonist). We handled mice for 10 min per day during the recovery period (10 days)

after cannula implantation. After recovery, exercise training with obstacles was performed using the same process as described above, and pharmacological administration was performed only once before the last trial on the final day. Each drug was dissolved in 10% DMSO in Ringer's solution and adjusted to 100 mM. One to two minutes before the last trial, mice were administered a 0.2-μL bilateral LS injection of vehicle (10% DMSO in Ringer's solution), SCH 23,390 hydrochloride, or (S)-(-)-Sulpiride.

Statistical analyses

The results were expressed as mean ± standard error of the mean (SE). Data from the two groups were analyzed using the Student's paired or unpaired *t* test. Data from more than two groups were analyzed using the one-way analysis of variance, followed by the Bonferroni test. p values < 0.05 were considered statistically significant.

Results

Exercise efficiency before and after treadmill training with intermittent obstacles

Before and after obstacles exercising training, VO_2 during treadmill running (15 m/min) was measured as exercise efficiency, wherein the same exercise performance with lower oxygen cost was defined as an efficient movement. First, we examined whether the treadmill with intermittent obstacles was difficult for the mice. As a result, VO_2 during obstacle treadmill running was significantly higher than that without obstacles (Fig. 1b). After the training period, VO_2 during obstacle treadmill running decreased (Fig. 1b, c), while treadmill running training without obstacle did not lead to decrease in VO_2 during obstacle treadmill running (Fig. 1d). VO_2 at rest before and after training did not change (Fig. 1e). These results demonstrated that obstacle treadmill running created difficulty for the mice, and those 8 days of training improved exercise efficiency.

Changes in c-Fos expression of each brain region before and after training

The immunostaining for c-Fos expressions in septum, striatum and motor cortex of the mice before and after obstacle exercise training is shown in Fig. 2a, c, e, respectively. In the septum and striatum, the c-Fos expression of mice that underwent training was significantly higher than that of mice that did not undergo training (Fig. 2b, d). In contrast, c-Fos expression in the motor cortex of mice that underwent training was significantly lower than that of mice that did not undergo training (Fig. 2f). There were no differences in other brain regions (data not shown).

Dopamine and serotonin turnover in each brain region before and after training

To identify which monoamine was involved in changes in neural activity, we next quantified monoamine and its metabolites in the brain regions that had significant differences and the other regions, including the hypothalamus, hippocampus, and cerebellum, immediately after treadmill running using HPLC. Mice that underwent training [training (+)] showed significantly higher dopamine turnover (DOPAC/DA) in the septum than training (−) mice, but there were no significant differences in the motor cortex or striatum (Fig. 3a–f). There were no significant differences involved in serotonin turnover (5-HIAA/5-HT) for any regions (Fig. 3a–f). These results indicated that dopamine action in the septum increased after obstacle treadmill running training in mice.

Relationship of dopamine turnover in brain and exercise efficiency on the 3rd day of training

Alteration of dopamine turnover in the septum and VO_2 during obstacle treadmill running was completed at 8 days of training. In contrast, these training effects had not been completed but we observed individual difference on the 3rd day of training. Therefore, we examined whether dopamine turnover in the septum was related to exercise efficiency on the 3rd day of training by checking exercise efficiency (VO_2 during complicated treadmill running). We measured dopamine turnover in the septum of the mice immediately after complicated treadmill running on the 3rd day of the training period in alternating groups. We observed that there was a significant inverse correlation between VO_2 during obstacle treadmill running and dopamine turnover in the septum but not in the motor cortex, hippocampus or striatum (Fig. 4a–d).

Change in exercise efficiency after administration of a dopamine receptor antagonist to the septum

Finally, we investigated whether increased dopamine turnover in the septum was involved in improving exercise efficiency. A dopamine receptor antagonist was administered to the septum bilaterally before the final trial. The D1 antagonist and D2 antagonist groups showed significantly higher VO_2 than the vehicle group ($F_{2,21} = 6.421$, $p = 0.0067$; Fig. 5a). This effect was not observed in no obstacle treadmill running even after training ($F_{2,21} = 0.093$, $p = 0.9118$; Fig. 5a). Additionally, c-Fos expression in the septum ($F_{2,12} = 16.751$, $p = 0.0003$; Fig. 5b, c) and in the hippocampus-CA3 in

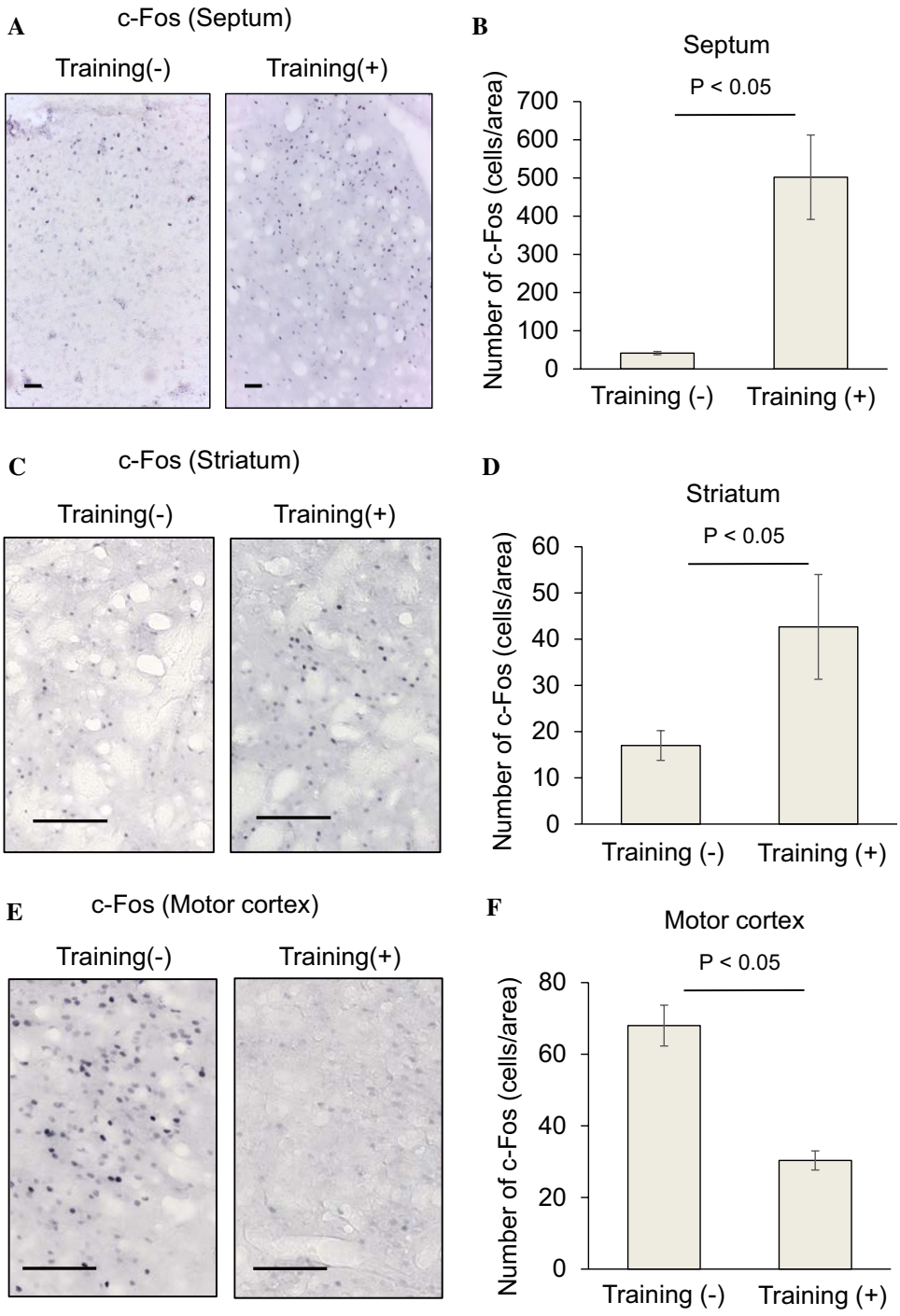

Fig. 2 Changes in c-Fos expression in each brain region before and after training. Representative image of c-Fos expression in the **a** septum, **c** striatum, and **e** motor cortex of mice before and after training. Scale bars (black) = 50 µm. The c-Fos expression values in the **b** septum, **d** striatum, and **f** motor cortex. Data are presented as mean ± standard error ($n = 5$). Unpaired *t* test was used

the D1 antagonist group ($F_{2,12} = 8.319$, $p = 0.0054$; Fig. 5d, e) significantly decreased compared to that in the vehicle group. There were no significant differences between the D2 antagonist group and vehicle group in the septum or hippocampus-CA3. No differences were observed in the c-Fos expression in other hippocampal regions (CA1, CA2, and dentate gyrus) with or without the administration of dopamine receptor antagonist (Supplemental Fig. 2).

Discussion

We hypothesized that dynamic biochemical stimulation at critical brain sites was required for continuous complicated exercises. Our results indicated that the dopaminergic function in the septum is involved in exercise efficiency during continuous complicated exercises. In this study, we used VO_2 as an indicator of exercise efficiency. VO_2 during exercise is generally used as an indicator of energy expenditure,

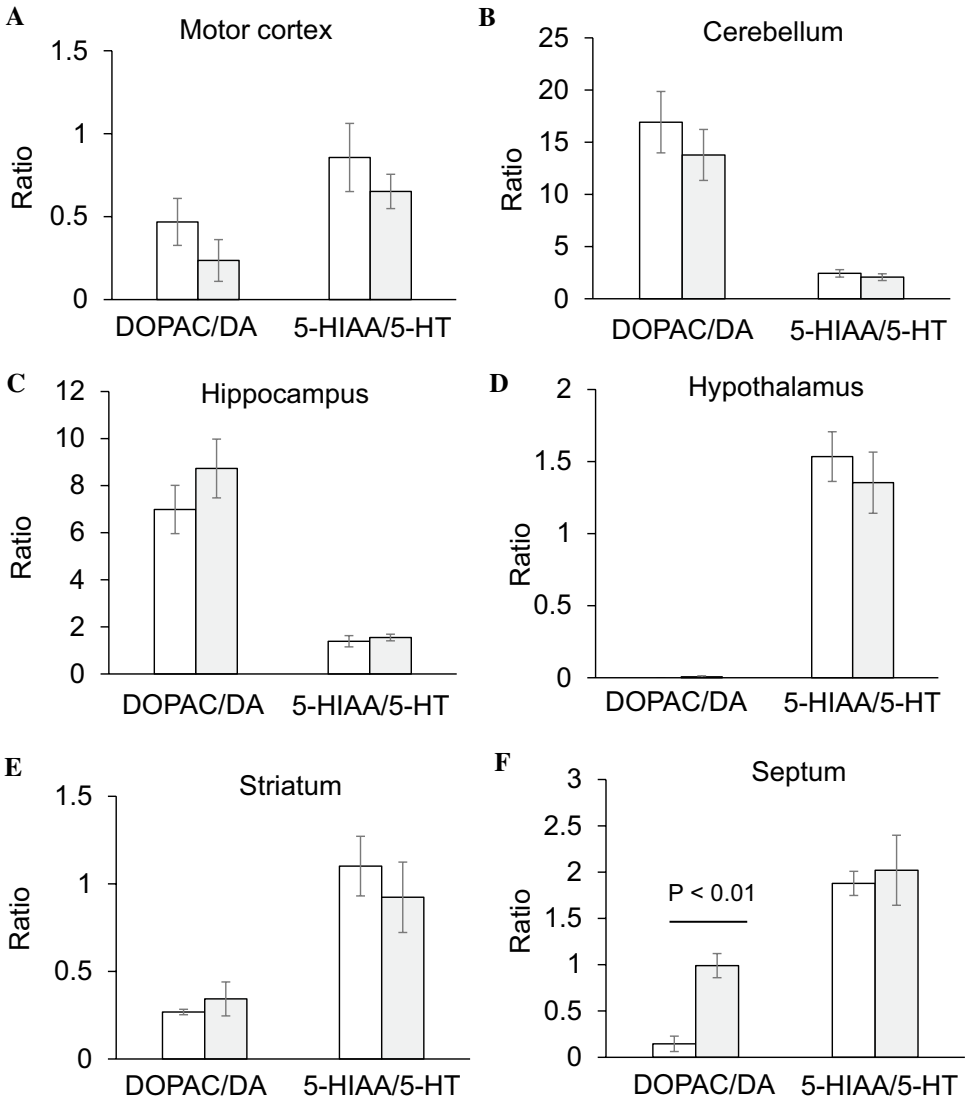

Fig. 3 Dopamine and serotonin turnover in each brain region before and after training. Dopamine turnover (DOPAC/DA) and serotonin turnover (5-HIAA/5-HT) in the **a** motor cortex, **b** cerebellum, **c** hippocampus, **d** hypothalamus, **e** striatum, and **f** septum. White bars indicate the training (−) group. Black bars indicate the training (+) group. Data are presented as mean ± standard error ($n = 5$ or $n = 6$). Unpaired t test was used

and is dependent on energy demand, nutritional status, and motor skills [28, 29]. Since VO_2 before and after training were measured at the same exercise intensity (15 m/min) and obstacle frequency, energy demand for the work load during treadmill running would be identical. Motor skill proficiency leads to efficient exercise performance without excess energy expenditure. We observed significantly lower VO_2 during the obstacle treadmill exercise after obstacle treadmill training, suggesting that exercise efficiency was increased with improved motor skills to avoid obstacles on the treadmill. VO_2 of the mice at rest did not differ by training, although we did not determine the metabolic adaptation in the contracting skeletal muscle, which was responsible for energy expenditure during exercise. In addition, a previous report demonstrated that neural factors accounted for the larger proportion of the initial strength increments with resistance training [17]. Since exercise training was performed for a short period (8 days) in this experiment, it is reasonable that motor skills, but not metabolic or respiratory–cardiovascular functions, were necessary for alterations in exercise efficiency.

The results of this study suggested that the dopaminergic function in the septum is involved in exercise efficiency. Injection of dopamine receptor antagonists into the septum did not change VO_2 during treadmill running without obstacle (Fig. 5a), suggesting that dopamine activity in the septum might not affect energy cost during running exercise. The septum is located inside the lateral ventricle in front of the anterior commissure and it communicates with the hippocampus and hypothalamus. The lateral septum is thought to be critical for processing emotional information and for modulating behavioral responses to stress [30, 31]; however, there are few reports describing the association between exercise and the septum. Regarding the relationship between the septum and dopamine, it has been reported that early social stress affects the dopamine D3 receptor of

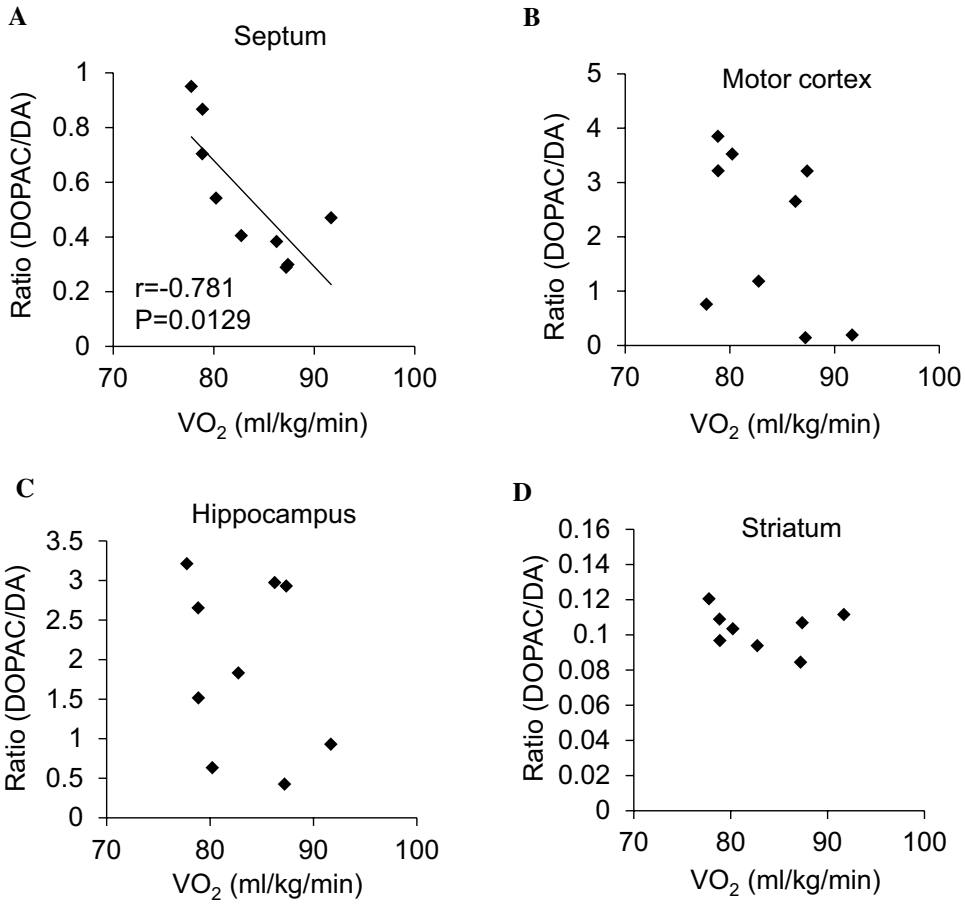

Fig. 4 Correlation between dopamine turnover in each brain region and oxygen uptake (VO_2) in the middle of training. Dopamine turnover (DOPAC/DA) in the **a** septum, **b** motor cortex, **c** hippocampus, and **d** striatum on the 3rd day after the beginning of training ($n=9$). Data are presented as mean ± standard error. Regression analysis was performed

the lateral septum and is a risk factor for social dysfunction [32]. In addition, it has been reported that activation of glutamate and the gamma-aminobutyric acid (GABA) system in the septum during treadmill running and wheel running increases brain wave θ power in the hippocampus [33, 34]. However, the effect of the dopamine system on motor function in the septum has not yet been clarified. When we injected a dopamine receptor antagonist into the bilateral septum, VO_2 did not change during simple treadmill running (without obstacles) even after training (Fig. 5a), suggesting that dopamine stimulation in the septum was not involved in energy expenditure during exercise.

In addition to the septum, significant differences in c-Fos expression were confirmed in the striatum and motor cortex after training. The motor cortex comprises a "motion loop" that is involved in motor control with strong consciousness during exercise [35]. We considered that the decrease in c-Fos expression in the motor cortex after training compared with before training was due to motor control stabilization attributable to training. On the other hand, it was clinically reported that exercise has a beneficial effect on reactivity and movement behavior in Parkinson's disease following administration of levodopa, a dopamine precursor, indicating that augmented synthesis and release of endogenous dopamine occurred in some brain regions [36]. The striatum is involved in motor learning and the formation of habitual movement patterns, i.e., procedural memory. Moreover, motor skills are mediated by the dopaminergic system in the striatum; the deletion is involved in the development of the Parkinson's disease. However, this was not a concern in this study because dopamine turnover in the striatum was not altered.

In this experiment, administration of the dopamine D1 receptor antagonist to the bilateral septum decreased c-Fos expression in the CA3 area of the hippocampus with increased VO_2, suggesting that dopamine stimulation via the D1 receptor in the septum is involved in exercise efficiency through the CA3 area of the hippocampus. Exercise increased brain-derived neurotrophic factors in CA3 neurons in the hippocampus [37–40]. Dopaminergic input to the septum has been implicated in modulating the pathway from the septum to the hippocampus and involved in learning spatial recognition ability. This pathway might be required to hurdle continuing obstacles in complicated running. Dopaminergic neuron is in the ventral tegmental area (VTA) and substantia nigra. The lateral septum receives dopaminergic projections primarily from the VTA [41]. This dopaminergic input has been implicated in modulating the pathway from the septum to the hippocampus [42–44]. However, in this study, we were

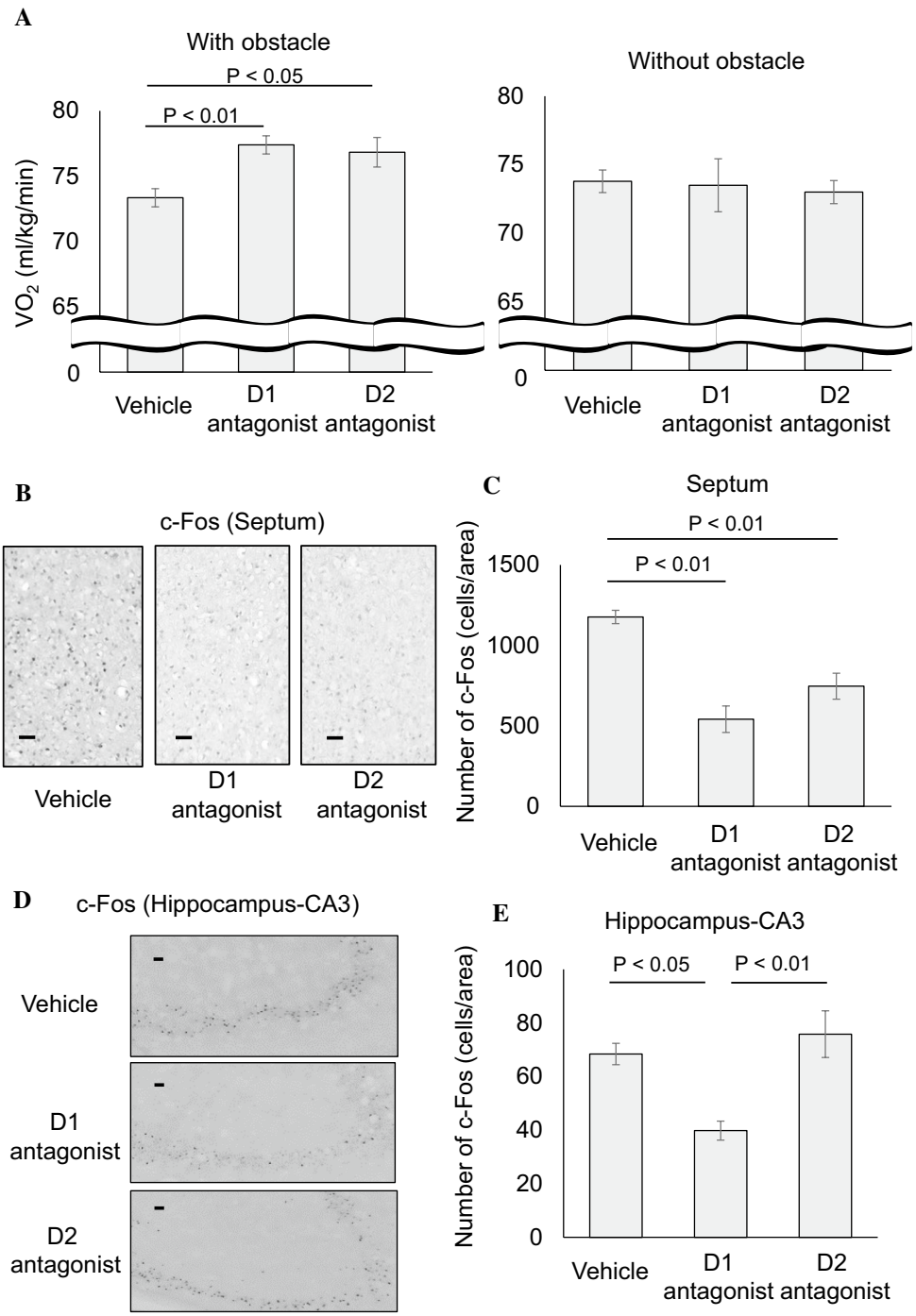

Fig. 5 Change in exercise efficiency caused by bilateral administration of a dopamine receptor antagonist to the septum. **a** Oxygen uptake (VO_2) during obstacle treadmill running after training with or without injection of dopamine receptor antagonists into bilateral septum ($n=8$). The left panel shows VO_2 during obstacle treadmill running after training, while the right panel shows VO_2 during normal treadmill running after training. Representative image of c-Fos expressions in the **b** septum and **d** hippocampus-CA3. Scale bars = 50 µm. The c-Fos expression values in the **c** septum ($n=5$) and **e** hippocampus-CA3 ($n=5$). Data are presented as mean ± standard error. One-way analysis of variance, followed by the Bonferroni test, was used

unable to identify the dopaminergic neurons from the VTA or substantia nigra involved in exercise efficiency or verify which molecule stimulated the dopaminergic neurons projecting into the septum.

This study has some limitations. First, we could not clarify the significance of increase in c-Fos expression in the striatum after training. Dopaminergic system in the striatum is involved in motor skill and reward similar with septum although dopamine turnover was not altered in striatum. Second, we also could not uncover the role of dopamine D2 receptor in septum during obstacle treadmill exercise though the injection of D2 receptor antagonist into the septum significantly decreased exercise efficiency. Further investigation is needed.

These results provide valuable information for sports performance, rehabilitation, and movement therapy. However, our findings apply only to improving exercise efficiency during forced complicated exercise and cannot be applied

to spontaneous complicated exercise. Therefore, it will be necessary to investigate whether the dopaminergic system in the septum is involved in improvement in exercise efficiency during spontaneous complicated exercise.

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Author contributions TS and TM contributed to experimental design, data collection, analysis, and manuscript preparation. NS and SC contributed to data collection and analysis. HS contributed to experimental design and manuscript preparation.

Compliance with ethical standards

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

Statement on the welfare of animals All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted.

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