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Preventive role of regular low-intensity exercise during adolescence in schizophrenia model mice with abnormal behaviors

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ABSTRACT

Schizophrenia is probably ascribed to perinatal neurodevelopmental deficits, and its onset might be affected by environmental factors. Hypofrontality with glutamatergic and dopaminergic neuronal dysfunction are known factors, but a way to mitigate abnormalities remains unfound. An early enriched environment such as a wheel running in rodents may contribute to the prevention, but its clinical applicability is very limited. From our studies, low-intensity exercise training (LET) based on physiological indices, such as lactate threshold, easily translates to humans and positively affects the brains. Hence, LET during adolescence may ameliorate abnormalities in neurodevelopment and prevent the development of schizophrenia. In the current study, LET prevented sensitization to phencyclidine (PCP) treatment, impairment of cognition, and affective behavioral abnormalities in an animal model of schizophrenia induced by prenatal PCP treatment. Further, LET increased dopamine turnover and attenuated the impairment of phosphorylation of ERK1/2 after exposure to a novel object in the prenatal PCP-treated mice. These results suggest that LET during adolescence completely improves schizophrenia-like abnormal behaviors associated with improved glutamate uptake and the dopamine-induced ERK1/2 signaling pathway in the PFC.

1. Introduction

Schizophrenia is one of the most devastating mental illnesses, affecting approximately 1% of individuals sometime in their lifetime. Growing evidence indicates that schizophrenia is ascribed to a neurodevelopmental disorder, in which disruption of the perinatal neuronal development results in psychiatric behaviors in later life [1]. However, as suggested by reports of a 50% concordance rate in monozygotic twins [2], environmental factors can influence the onset and progression of schizophrenia. Thus, postnatal development might be a critical window to invert abnormal neural functions.

Positive lifestyle, such as appropriate exercise habits, is expected to enhance neuronal plasticity and promote mental health. Voluntary wheel running improves memory function [3], increases the binding affinity to the N-methyl-D-aspartate receptor (NMDAR) antagonist in the prefrontal cortex (PFC), suggesting improving NMDAR-mediated neural transmitting [4]. Additionally, voluntary wheel running also increases locomotor activity in response to amphetamine, suggesting an enhanced dopamine (DA) response

Abbreviations: PFC, prefrontal cortex; LET, low-intensity exercise training; PCP, phencyclidine; SAL, saline; LT, lactate threshold; VT, ventilatory threshold; SED, sedentary; NMDAR, N-methyl-D-aspartate receptor; ERK1/2, extracellular-signaling-regulated kinase 1/2; DA, dopamine; D1R, dopamine D1 receptor; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 3-MT, 3-Methoxytyramine; ANOVA, analysis of variance.

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[5]. The evidence provides insight into the potential of exercise to prevent the disease by improving glutamatergic and dopaminergic neurotransmission in the PFC.

Since voluntary wheel running shows varying exercise intensity, duration, and frequency, its applicability to clinical trials is limited. Therefore, we developed an exercise model using a rodent treadmill based on physiological indices: lactate threshold (LT) and ventilatory threshold (VT). Further, we show low-intensity exercise, which is below the LT and VT, enhances hippocampal neuroplasticity, spatial memory, and PFC-dependent cognitive function in healthy animals and young adults [6,7]. These results lead us to postulate that even a light intensity of exercise has positive effects on mental health, acting not only in the hippocampus but also in the PFC. However, it remains unclear whether LET during adolescence might prevent the onset of schizophrenia.

Hypofrontality induced by malfunction of N-methyl-D-aspartate receptor and dysregulation of dopaminergic neurotransmission is the potential neuropathology of schizophrenia. Consistent with the patients with schizophrenia [8], exposure to phencyclidine (PCP), a non-competitive antagonist of NMDAR, causes abnormal behaviors resembling schizophrenia and elicits decreased phosphorylation of the NR1, core subunit of the NMDAR, in the PFC of rodents [9]. DA release decreases throughout the schizophrenic patients' cortex and the PFC of chronic PCP-treated rats [10,11]. Abnormality of intracellular signaling, such as extracellular signaling-regulated kinase 1/2 (ERK1/2), also supports the dysfunction of neurotransmission in the PFC [12]. Therefore, ameliorating these neural abnormalities could be a molecular target for disease prevention. Moreover, based on the neurodevelopmental hypothesis, several studies administered NMDAR antagonists in the prenatal period to prepare a modified animal model of schizophrenia and showed validity as the disease model [13–16]. Since the neurodevelopmental disruption in the perinatal period is close to the pathogenesis of schizophrenia in humans, we assumed the prenatal PCP-treatment model is suitable to investigate the effect of LET.

We hereby aimed to investigate the hypothesis that LET during adolescence ameliorates behavioral abnormalities and neuronal dysfunction of the PFC caused by perinatal neurodevelopmental deficits. We first investigated the effect of LET on abnormal behaviors induced by prenatal PCP treatment. We then examined the effects of LET on the molecular mechanisms involved in glutamatergic and dopaminergic neuronal transmitting. Our result showed that LET ameliorated abnormal behaviors but failed to reverse the hypophosphorylation of the NR1. On the other hand, LET increased DA turnover in the PFC. Furthermore, we confirmed LET improves activation of the ERK1/2 signal pathway during the cognitive task.

2. Material and methods

For a full description of the materials and methods, see **Detailed Methods** in the Supplementary material.

2.1. Animals

Pregnant ICR dams (embryo at the 5th day [E5]) were obtained from SLC (Shizuoka, Japan) and assigned to two groups for equal weight: the saline- (SAL) treated group and PCP-treated group. After weaning on postnatal day 21, male pubs were randomly assigned to sedentary or exercise groups. Each group had litters of 2–3 to exclude the litter's influence as a confounding factor. Animal care and experiments were performed in accordance with procedures approved by the University of Tsukuba Animal Experiment Committee (animal ethical approval number 19–376).

2.2. Drug treatment

PCP hydrochloride, which synthesized according to the method of a previous report [17], was transferred from the Department of Chemical Pharmacology, Faculty of Pharmaceutical Science, Meijo University, Japan, and checked for purity. Based on previous studies [15], PCP was dissolved in SAL and the dams were administrated SAL or PCP (10 mg/kg s.c.) once per day from E6 to E18.

2.3. Exercise training

Based on the VT (Fig. S1), we defined 10 m/min for low intensity running. At the 4 weeks old, the mice were forced to run on a treadmill (LET, low-intensity exercise training, 10 m/min) and the sedentary (SED) group was kept on the treadmill for the same amount of time without running. Training continued until the mice were 8 weeks old.

2.4. Behavioral test

Behavioral tests were performed in a sound-attenuated room (AMX-3532, O'Hara & Co. Ltd., Tokyo, Japan). Different mice were used for each behavioral test and molecular analysis.

2.5. Measurement of locomotor activity

Based on a previous report [14], locomotor activity was measured. The mice were placed individually in a clear acrylic cage (L 45 x W 26 x H 40 cm) for 30 min for habituation. Subsequently, the mice were treated with SAL or PCP (3.0 mg/kg s.c.) as a pharmacological challenge, and the locomotor activity was measured for 90 min using an infrared sensor (IR Actimeter, Panlab, Barcelona, Spain).

2.6. Novel object recognition test (NORT)

Based on a previous study [14], NORT was conducted. On days 1–3, each mouse was individually habituated to the empty acrylic box (L 30 x W 30 x H 35 cm) with 10 min of exploration each day. On day 4, two novel objects were fixed to the floor of the box. Each mouse was allowed to explore for 10 min (training session). On day 5, One of the familiar objects used during training was replaced with a novel object. Mice were returned to the same box and allowed to explore for 5 min (retention session). The behaviors were recorded, and the time spent exploring each object was measured by the experimenter, who was blinded to the experimental conditions, using on-screen stopwatch software. Exploratory preference, the ratio of time spent exploring either of the two objects (training session) or the novel object (retention session) over the total amount of time, was used to recognition memory performance.

2.7. Forced swimming test

Based on a previous report [16], the forced swimming test was performed. Mice were placed in a clear acrylic cylinder (25 cm high, 14 cm in diameter), which contained water at 22 ± 1 °C to a depth of 17.5 cm for 6 min. The duration of swimming was measured every minute using on-screen stopwatch software.

2.8. Western blotting

Based on a previous study [14], Western blotting was performed. Proteins (10 μg) from the left PFC were loaded on a 5–20% polyacrylamide gradient gel. The gel was then transferred to PVDF

membranes using the Trans-Blot Turbo Transfer System (Bio-Rad, California, USA). The membranes were incubated with a primary antibody for 24 h at 4 °C. After washing, the membranes were incubated with secondary antibodies for 1 h at room temperature. The immune complexes were detected using chemiluminescence analysis with the Chemi-lumi One Super Kit (02230, Nacalai Tesque, Kyoto, Japan). The density of signals was scanned by the Image Quant LAS 4000 system (GE Healthcare, Illinois, USA).

2.9. High performance liquid chromatography (HPLC)

Monoamine contents were determined using the HPLC system equipped with an electrochemical detector (HTEC500, EICOM, Kyoto, Japan). Each right PFC sample was homogenized and mixed with 10 ng of isoproterenol as a standard and was injected into the HPLC system equipped with a reversed-phase ODS column (Eicompak SC-5ODS, EICOM) and the graphite working electrode (WE-3G, EICOM).

2.10. Statistical analysis

All data are presented as mean ± standard error of the mean (SEM) and were analyzed using R software (version 4.0.0). Statistical methods are described in Table S1. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. LET attenuated abnormal behaviors induced by prenatal PCP treatment

We investigated whether exercise inhibits PCP-induced hyperlocomotion in the prenatal PCP-treated mice. After 4 weeks of LET, locomotor activity was measured. Following the 30-min habituation to the test box, mice were treated with a low dose of PCP (3 mg/kg s.c.; PCP challenge) or SAL. Time course activity showed that LET significantly decreases PCP challenge-induced hyperlocomotion induced by prenatal PCP treatment (Fig. 1A).

To investigate the effect of exercise on cognitive dysfunction induced by prenatal PCP treatment, we performed a novel object recognition test (NORT). There was no biased exploratory preference among groups in the training session (Fig. 1B). When the retention session was performed, LET reversed the decreased exploratory preference induced by the prenatal PCP treatment (Fig. 1B).

To investigate the effect of exercise on the abnormal emotional behavior induced by prenatal PCP treatment, we performed the forced swimming test. LET again reversed the extended immobility time induced by prenatal PCP treatment (Fig. 1C).

3.2. LET failed to ameliorate hypophosphorylation of the NR1 subunit of the NMDAR in the PFC of the prenatal PCP-treated mice

We investigated whether LET ameliorates the malfunction of NMDAR related to abnormal behaviors. In the PFC, although there was no difference among the groups at the level of NR1 phosphorylated at Ser^{897} (Fig. 2A), the level of NR1 protein was significantly increased in the prenatal PCP + SED mice compared with the prenatal SAL + SED mice (Fig. 2B). In addition, the ratio of phosphorylated to total protein for NR1 was significantly decreased in the prenatal PCP-treatment mice (Fig. 2C). However, LET failed to recover the decrease of ratio.

3.3. LET decreased DOPAC and HVA but increased 3-MT/DA ratio in the PFC of prenatal SAL- and prenatal PCP-treated mice

We investigated the contents of DA and its metabolites in the PFC. The results show that there was no significant difference among the groups in the DA content (Fig. 3A). However, LET decreased 3,4-dihydroxyphenylacetic acid (DOPAC, Fig. 3B) and homovanillic acid (HVA, Fig. 3C) in the prenatal SAL- and prenatal PCP-treated mice. Furthermore, LET tended to increase 3-Methoxytyramine (3-MT)/DA ratio (Fig. 3G).

3.4. LET improved the hypophosphorylation of ERK1/2 in brains of the prenatal PCP-treated mice exposed to a novel object

To determine whether LET actually improved signaling transmitting, we examined the phosphorylation of ERK1/2 pathway after exposure to a novel object (Fig. 4A) because PCP impairs learning through inhibition of phosphorylation of ERK1/2 [18]. Immediately after 10 min of exposure to the novel object, the ratio of phosphorylation to total protein for ERK1/2 was significantly increased in the PFC of prenatal SAL-treated, but not PCP-treated mice (Fig. 4C). The failure of novelty-induced ERK1/2 activation in the prenatal PCP-treated mice was reversed by LET.

4. Discussion

According to the multifactorial etiology of schizophrenia, resulting from a combination of genetic and environmental factors, an early enriched environment with low stress may have an impact on the brain to mitigate the symptoms of schizophrenia. Here we tested the hypothesis that mild-exercise habits during adolescence could ameliorate abnormalities in neurodevelopment and prevent the development of schizophrenia. Our results reveal that LET during adolescence attenuates schizophrenia-like abnormal behaviors in the prenatal PCP-treated mice. Although LET failed to reverse the decreased phosphorylation of NR1 in the PFC of prenatal PCP-treated mice, LET decreased DOPAC and HVA, but tended to increase the 3-MT/DA ratio in the PFC. Furthermore, LET blocked the impairment of novelty-induced hyperphosphorylation of ERK1/2 in the PFC of the prenatal PCP-treated mice. These results suggest that LET during adolescence may ameliorate abnormal behavior in prenatal PCP-treated mice through the modulation of DA-ERK1/2 signal pathway in the PFC.

Exposure to PCP has been found to reproduce abnormal behaviors resembling schizophrenia, including positive symptoms, negative symptoms, and cognitive dysfunction in adult rodents [9,19,20]. Since the pathogenesis of schizophrenia is considered to occur at the developmental stage [21], the blockade of NMDAR in the perinatal period has been used to prepare a modified animal model of schizophrenia [13–15]. Consistent with earlier reports, we confirmed that prenatal PCP-treated mice showed not only sensitization to PCP-induced hyperlocomotion (Fig. 1A), but also cognitive impairment (Fig. 1B), and abnormal affective behavior (Fig. 1C). These results support the appropriateness of its usage in the current study as an animal model of schizophrenia based on the neurodevelopmental hypothesis.

A notable finding of the current study is that LET during adolescence prevents abnormal behaviors (Fig. 1). An early enriched environment, including voluntary wheel running, showed inhibition of schizophrenia-like abnormalities in transgenic and pharmacological model mice [22–25]. Nevertheless, because the enriched environment involves numerous factors, including social interaction and cognitive stimuli, such as novel toys, no studies have been able to extract and investigate the effects of exercise as a single intervention. The findings of the current study support the

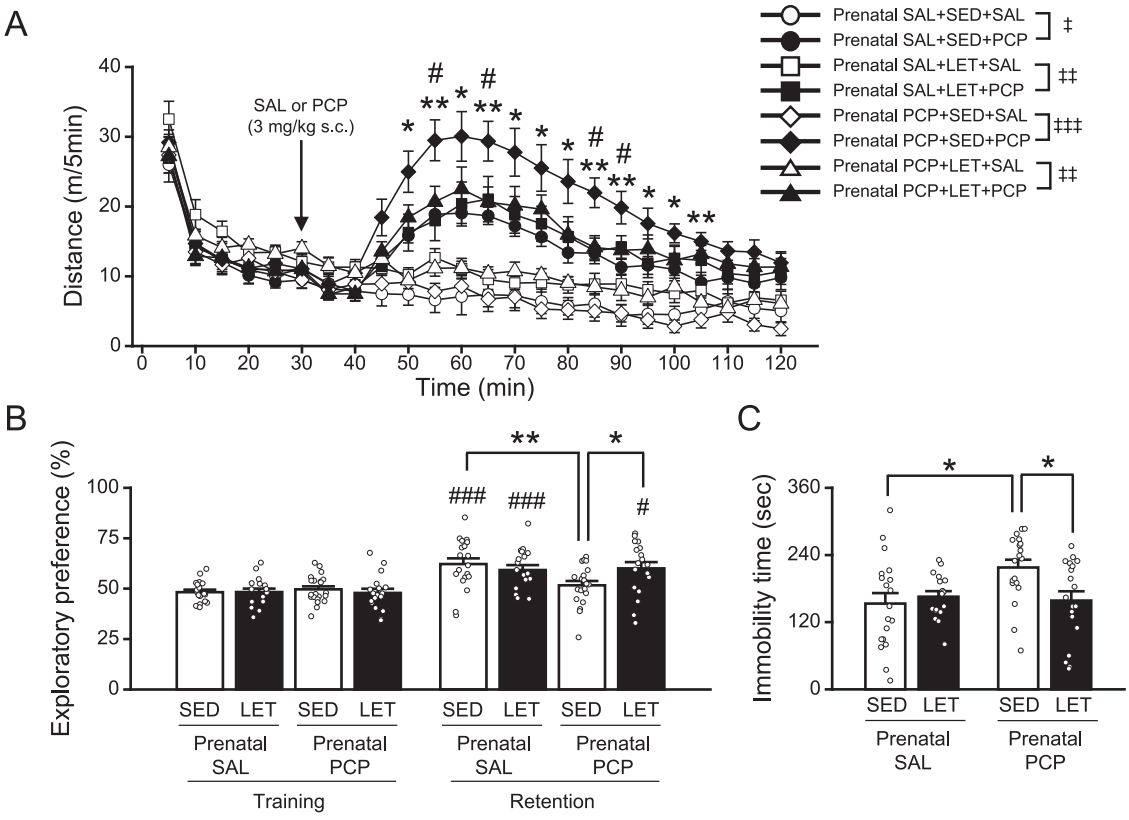

Fig. 1. LET attenuated abnormal behaviors in the prenatal PCP-treated mice. **(A)** Time course of locomotor activity. $^{*}p < 0.05$, $^{**}p < 0.01$ prenatal SAL + SED + PCP challenge vs prenatal PCP + SED + PCP challenge; $^{\#}p < 0.05$ prenatal PCP + SED + PCP challenge vs prenatal PCP + LET + PCP challenge; $^{\ddagger}p < 0.05$, $^{\ddagger\ddagger}p < 0.01$, $^{\ddagger\ddagger\ddagger}p < 0.001$ SAL vs PCP challenge. n = 8–10 per group. **(B)** Exploratory preference. $^{*}p < 0.05$, $^{**}p < 0.01$; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ training session vs retention session. n = 18–21 per group. **(C)** Immobility time. $^{*}p < 0.05$. n = 17–19 per group. SAL, saline; SED, sedentary; LET, low-intensity exercise training.

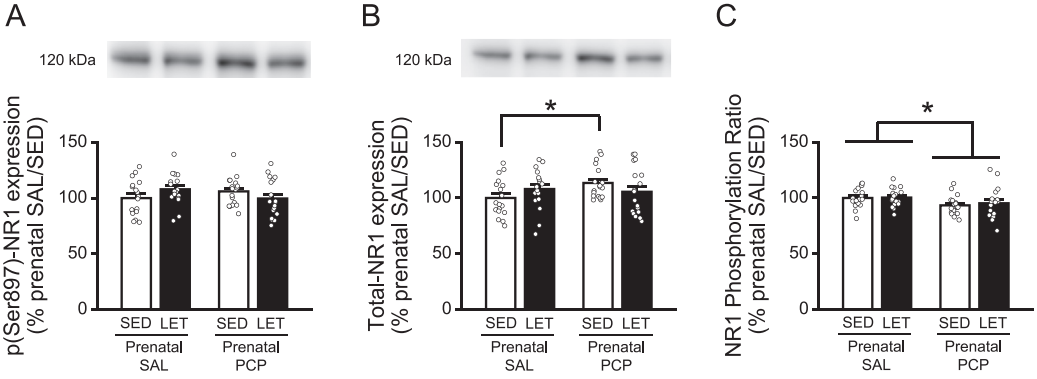

Fig. 2. LET failed to ameliorate hypophosphorylation of the NR1 in the PFC of the prenatal PCP-treated mice. **(A)** The expression level of phosphorylated (Ser897) NR1. **(B)** The expression level of Total NR1. $^{*}p < 0.05$. **(C)** NR1 phosphorylation ratio. $^{*}p < 0.05$ main effect of prenatal treatment. Data (β-actin as an internal standard) are expressed based on prenatal SAL + SED group as 100%. n = 17–18 per group.

possibility that exercise itself may contribute to the prevention of schizophrenia.

In the postmortem brain samples of patients with schizophrenia, phosphorylation of NR1 is decreased in the PFC [8]. Phosphorylation of NR1 (Ser897) modulates NMDAR function by promoting its expression on the cell surface from the endoplasmic reticulum [26]. Since LET ameliorated abnormal behavior induced by prenatal PCP treatment, we have assumed that LET improved the malfunction of the NMDAR associated with behavioral abnormalities. In the current study, we have confirmed a decrease of NMDAR phosphorylation induced by prenatal PCP treatment in the PFC; however, LET failed to recover the reduced NR1 phosphorylation (Fig. 2C). These results suggested that the effect of LET may not occur through modulation of NMDA receptor dysfunction.

Abnormalities of dopaminergic neurons are ascribed to one potential neuropathology of schizophrenia. As opposed to a state of hyperdopaminergia in the striatum, DA release decreases throughout the cortex in schizophrenic patients [10]. In an animal study, chronic PCP-treatment reduced DA release in the PFC [11]. In addition, the antipsychotic drug aripiprazole improves cognitive

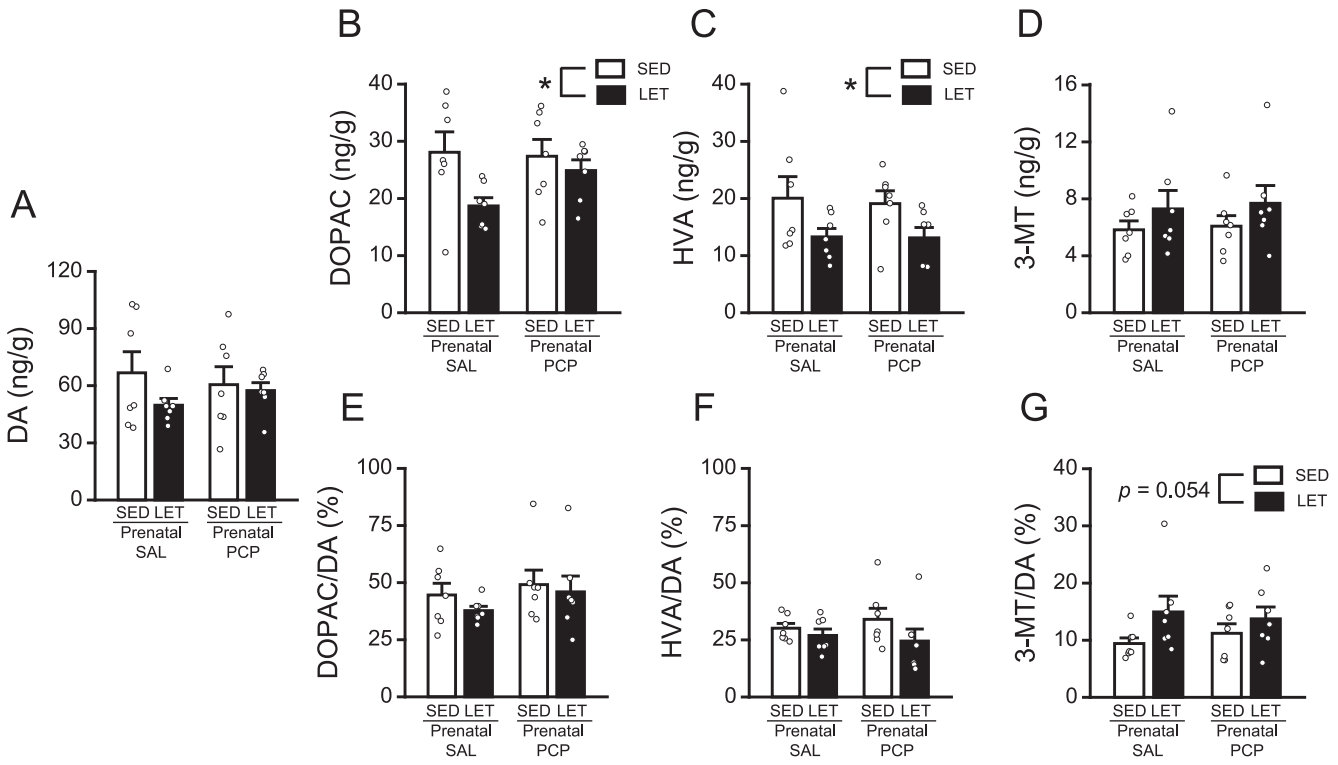

Fig. 3. LET decreased DOPAC and HVA but tended to increase 3-MT/DA ratio in the PFC of prenatal SAL- and prenatal PCP-treated mice. **(A)** Concentration of DA. **(B)** Concentration of DOPAC. *$p < 0.05$ main effect of LET. **(C)** Concentration of HVA. *$p < 0.05$ main effect of LET. **(D)** Concentration of 3-MT. **(E)** DOPAC/DA ratio. **(F)** HVE/DA ratio. **(G)** 3-MT/DA ratio. $p = 0.054$ main effect of LET. n = 7 per group.

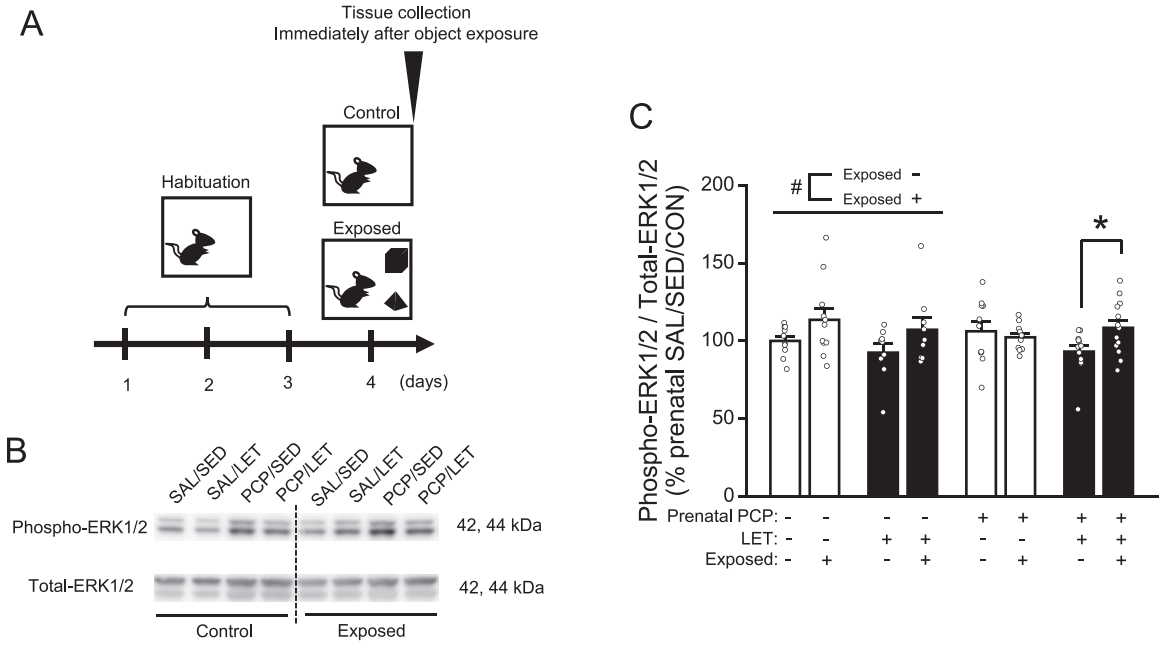

Fig. 4. LET improved the hypophosphorylation of ERK1/2 in brains of the prenatal PCP-treated mice exposed to a novel object. **(A)** Experimental design. **(B)** A representative immunoblot image. **(C)** ERK1/2 phosphorylation ratio in the PFC. #$p < 0.05$ main effect of exposure. *$p < 0.05$. n = 9–13 per group. Data are expressed based on prenatal SAL + SED group as 100%.

dysfunction induced by PCP through activation of the DA receptor D1 (D1R) [27]. Therefore, we have hypothesized that LET improves dopaminergic neural function. Results show that LET decreased DOPAC and HVA contents but tended to increase the 3-MT/DA ratio (Fig. 3B, C, 3G). Since 3-MT is an index of DA release into the synaptic cleft [28], LET may increase DA release, then extracellular DA levels, and finally facilities of dopaminergic signaling.

To investigate whether LET actually improves signal

transmission, we examined the effects of LET on the intracellular signal pathways that take place after synaptic transmission. ERK1/2 has been shown to play an important role in learning and memory [29,30]. In the case of NORT, ERK1/2 hyperphosphorylation in the PFC occurred immediately after novel object exposure. Moreover, inhibition of ERK1/2 phosphorylation reduces object recognition memory [31,32]. Furthermore, ERK1/2 is not only activated by the NMDAR-mediated signal pathway [33], but also by the D1R, and indeed the D1R antagonist impairs object recognition memory [31]. We have found that LET improves the impairment of novelty-induced ERK1/2 phosphorylation in the PFC of prenatal PCP-treated mice (Fig. 4C). Therefore, it is assumed that LET ameliorates cognitive impairment through modulating the D1R-ERK1/2 pathway in the PFC.

The current study has several limitations. First, the molecular mechanism for ameliorating effects of LET on PCP-induced sensitization and prolonged immobility time should be investigated, since the ERK1/2 pathway examined in the current study is less relevant to these behaviors. Second, we should verify whether the LET increases DA release and dopaminergic neuronal activity during novel object exposure by using *in vivo* microanalysis and immunohistochemistry. Third, the possibility of compensatory effects of other brain regions on cognitive improvement cannot be excluded. In particular, the hippocampus is a brain region that is believed to be responsible for cognitive enhancement through exercise, and further investigation is needed.

Collectively, our results that show LET during adolescence prevented abnormal behaviors in prenatal PCP-treated schizophrenia model mice, suggesting for the first time that mild exercise habits during development could be a strong preventing strategy for schizophrenia probably by masking/improving neurodevelopmental abnormalities. Although exact mechanism remains uncovered, LET increased DA turnover and improved dysfunction of ERK1/2 signaling during cognitive tasks, which suggests that LET during adolescence could prevent behavioral abnormalities in the model mice associated with improvements of DA-ERK1/2 pathway.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bbrc.2020.11.032.

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