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Research report

Selegiline ameliorates depression-like behaviors in rodents and modulates hippocampal dopaminergic transmission and synaptic plasticity



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ABSTRACT

Selegiline, an irreversible inhibitor of monoamine oxidase (MAO)-type B, is widely prescribed for Parkinson's disease and, at higher doses, for major and atypical depression, whereby it is non-selectively inhibitory to both MAO-A and MAO-B activities. MAO inhibitors have been considered to function as antidepressants through MAO-A inhibition. We have previously reported that selegiline exerts antidepressant-like effects in the mouse forced swim test (FST) via dopamine D1 receptor activation. Our objective was to elucidate the mechanisms underlying the antidepressant-like effects of selegiline. We also tested another propargylamine MAO-B inhibitor, rasagiline. Triple subcutaneous injection (at 24, 5, and 1 h prior to behavioral testing) with selegiline (10 mg/kg/ injection), but not rasagiline (1, 3, or 10 mg/kg/injection), reduced the immobility time in the mouse FST and rat tail suspension test. In the hippocampus and prefrontal cortex of mice subjected to the FST, selegiline and rasagiline completely inhibited MAO-B activities. However, selegiline suppressed MAO-A activities and monoamine turnover rates at a lesser degree than rasagiline at the same doses, indicating that the antidepressant-like effects of selegiline are independent of MAO-A inhibition. Moreover, selegiline, but not rasagiline, increased the hippocampal dopamine content. A single subcutaneous administration of 10 mg/kg selegiline, but not of rasagiline, significantly prevented hippocampal CA1 long-term potentiation impairment, induced by low-frequency stimulation prior to high-frequency stimulation in rats. These results suggest that the antidepressant-like effects of selegiline are attributable to enhancement of dopaminergic transmission and prevention of the impairment of synaptic plasticity in the hippocampus.

1. Introduction

Depression is one of the most frequent psychiatric and potentially life-threatening disorders [1,2]. Monoamine oxidase (MAO) inhibitors had been used for treatment of depression in the late 1950's, and some of them are still prescribed today despite the introduction of new class antidepressants. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that in major depressive disorder (MDD), patients resistant to conventional treatments exhibit similar remission rates by monotherapy with the non-selective MAO inhibitor, tranylcypromine, to the rates by combination therapy with mirtazapine (a noradrenergic and specific serotonergic antidepressant) and venlafaxine [a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI)], whereas tranylcypromine is less tolerated [3]. Because of dietary tyramine restrictions, possible serious side effects, and drug interactions, MAO inhibitors are reserved exclusively for MDD patients who do not respond to several pharmacotherapies, including selective 5-HT reuptake inhibitors (SSRIs) and/or SNRIs [4]. MAO inhibitors prescribed as antidepressants can be classified into 3 types: irreversible non-selective, such as phenelzine, tranylcypromine, and isocarboxazid; irreversible selective MAO-B inhibitors, like selegiline; and reversible selective MAO-A inhibitors, like moclobemide. Selegiline is widely used

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; AUC, area under the curve; BDNF, brain-derived neurotrophic factor; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; EDTA, ethylenediaminetetraacetic acid; FST, forced swim test; HEPES, *N*-2-hydroxyethylpiperazine-*N*'-2-ethane sulfonic acid; HFS, high-frequency stimulation; HPA, hypothalamic-pituitary-adrenal; HVA, homovanillic acid; LFS, low-frequency stimulation; LTP, long-term potentiation; MAO, monoamine oxidase; MDD, major depressive disorder; NE, norepinephrine; OFT, open field test; PD, Parkinson's disease; PSA, population spike amplitude; s.c., subcutaneous; SC, Schaffer collaterals; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TST, tail suspension test

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for treatment of Parkinson's disease (PD) at doses of 5–10 mg/day (oral) selectively inhibiting MAO-B activity in the brain [5]. It is also prescribed for major and atypical depression at higher doses (> 20 mg/ day, oral) inhibiting both MAO-A and -B activities [6-8]. Moreover, a transdermal formula of selegiline has been developed to bypass the first-pass metabolism and to reduce MAO-A inhibition in the gut. This formula at the minimum therapeutic dose of 6 mg/24 h for MDD does not require the limitation of dietary tyramine, whereas non-selective MAO inhibitors cause serious hypertensive reactions following the ingestion of tyramine-rich diets [9,10]. A positron emission tomography study revealed that a 28-day treatment with transdermal selegiline at 6 mg/24 h inhibits approximately 33% of brain MAO-A [9]. In contrast, administration of two other MAO inhibitors for treating MDD, tranylcypromine (10 mg/day) and moclobemide (600 mg/day), inhibits approximately 58% and 74% of MAO-A activity, respectively, in the human brain [11,12]. Treatment with oral (10 mg/day: MAO-B-selective dose) or transdermal selegiline (6 mg/24 h) has been reported to ameliorate depressive symptoms of treatment-resistant MDD patients [13,14]. Taken together, these clinical findings suggest that MAO-A inhibition may account only for part of selegiline's and other MAO inhibitors' effectiveness in MDD patients who are resistant to SSRIs or SNRIs, although it has been generally considered to mediate the function of MAO inhibitors as antidepressants by elevating the levels of 5-HT and NE [15-17]. Some monoaminergic antidepressants enhance synaptic plasticity at several levels, including hippocampal neurogenesis, brain-derived neurotrophic factor (BDNF) expression, and modulation of synaptic formation [18,19]. Several studies have shown that selegiline enhances BDNF expression in cultured mouse astrocytes and the anterior cingulate cortex of mice [20,21], and facilitates differentiation of neural stem cells isolated from the adult mouse subventricular zone into neurons, through induction of neurotrophic factors [22]. Thus, the antidepressant-like effects of selegiline might be attributable to some mechanisms other than enhancement of serotonergic and noradrenergic transmission, through MAO-A inhibition.

To elucidate the mechanisms underlying the antidepressant-like effects of selegiline, we investigated the potential effects of the drug in depression-like behaviors of rodents subjected to the forced swim test (FST) and the tail suspension test (TST). We compared these effects with those of rasagiline, because both drugs contain a propargylamine moiety that covalently interacts with the flavin N5 atom of MAO [17], thereby irreversibly inhibiting MAO activity. We also evaluated the neurochemical parameters and synaptic plasticity in depression-related brain regions. Herein, we present some evidence that selegiline exerts antidepressant-like effects, independently to MAO-A-inhibition. These effects may be attributable to the enhancement of hippocampal dopaminergic neurotransmission and prevention of the impairment of hippocampal long-term potentiation (LTP).

2. Material and methods

2.1. Animals

Male ddY mice and Wistar/ST rats (Nihon SLC, Shizuoka, Japan) were maintained in a facility with controlled humidity (50 \pm 20%) and temperature (23 \pm 3 °C), under a 12-h light/dark cycle (lights on at 7:00 a.m.), with free access to food (Oriental Yeast, Tokyo, Japan) and water. Mice and rats were housed in standard mouse plastic cages (182 \times 260 \times 128 mm) and rat plastic cages (276 \times 445 \times 204 mm, CLEA Japan Inc, Tokyo, Japan), with paper bedding (Paperclean, Nihon SLC). Animals were acclimated to their home cage for at least 6 days before experiments. This study was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and the institutional guideline for the care and use of laboratory animals.

2.2. Chemicals

Selegiline hydrochloride (Fujimoto Pharmaceutical Corporation, Osaka, Japan) and rasagiline mesylate (Sigma-Aldrich, St. Louis, MO, USA) were dissolved in saline. Drugs (1, 3, or 10 mg/kg) and saline (control) were administered to mice in a volume of 10 mL/kg and to rats in a volume of 1 mL/kg.

2.3. Forced swim test (FST)

The FST was performed according to Porsolt et al. [23] with a slight modification. Briefly, 55 mice (8-weeks-old) were placed in a black plexi glass cylinder (height 45 cm, diameter 15 cm) filled with water (25–28 °C), in a depth of 35 cm, for 6 min. The duration of immobility (s) and the swimming velocity (distance moved/mobility time, cm/s) during the last 4 min of the test were recorded by a video system, and video images were analyzed using a video tracking software (EthoVision 3.0.13, Nordus Information Technology, Wageningen, The Netherlands). Each MAO-B inhibitor (1, 3, or 10 mg/kg/injection) or saline was subcutaneously (s.c.) administered at 24, 5, and 1 h before the test.

2.4. Tail suspension test (TST)

The TST was performed according to Hinojosa et al. [24] and Chermat et al. [25] with a slight modification. Briefly, 92 rats (8-weeksold) were suspended at 20 cm above the floor, using an adhesive tape placed at approximately 5 cm from the tip of the tail. Two smooth slopes forming a V-shape were positioned below the bench, just under the rat's forepaws, in such a way that the rat could not touch the platform. The duration of immobility (s) was defined as the time spent without any limb movement during a 6-min video recording period and was manually measured with a stop watch by an observer in a singleblinded manner. Rats were grouped based on their immobility time during the 6-min recording period in the first TST (pre-test session). Six days following pre-test session of the TST, MAO-B inhibitors (1, 3, 7, or 10 mg/kg/injection) or saline were administered s.c. at 24, 5, and 1 h before the test session.

2.5. Open field test (OFT)

The OFT was performed according to Tsunekawa et al. [26] with a slight modification. Briefly, 6–8 days following the pre-TST session, 67 rats (8-weeks-old) received triple s.c. injection of MAO-B inhibitors or saline at 24, 5, and 1 h before the OFT and were placed individually in the center of an open field apparatus ($600 \times 600 \times 450$ mm). Spontaneous motor activities were measured for 10 min using a video system and tracking software (EthoVision 3.0.13).

2.6. Measurement of MAO activities in mouse hippocampus and prefrontal cortex

One hour after the FST, mice were sacrificed by cervical dislocation, and their brains were rapidly removed after decapitation. The hippocampus and prefrontal cortex were dissected out and stored at -80 °C until measurement; the right side was used for measuring MAO activities and the left for determining the monoamine content (see paragraph 2.8). The right hippocampus and prefrontal cortex were individually homogenized in 10 mM of ice-cold *N*-2-hydroxyethylpiperazine-*N'*-2-ethane sulfonic acid (HEPES; pH 7.4), containing 5 mM ethylenediaminetetraacetic acid (EDTA) and 0.32 M sucrose. Homogenates were centrifuged at 1,000 × g for 10 min at 4 °C, and the resulting supernatants were recentrifuged at 17,000 × g for 20 min at 4 °C to obtain crude mitochondrial fractions. The precipitates were resuspended in 5 mM HEPES (pH 7.4) and stored at -80 °C until use [27]. MAO-A and MAO-B activities were measured by using 1 mM 5-HT and 4 mM benzylamine, respectively, as substrates, together with EnzyChrom[™] Monoamine Oxidase Assay Kit (BioAssay Systems, Hayward, CA, USA), according to the manufacturer's instructions with a slight modification (substrate alteration). Protein concentrations were determined by Lowry's method [28] (DC Protein Assay, Bio-Rad, Hercules, CA, USA).

2.7. Plasma corticosterone concentration in rats subjected to the TST

Blood samples were collected into EDTA-containing tubes from the inferior vena cava of isoflurane-anesthetized rats 15 min after exposure to TST. Blood samples were centrifuged at $1,000 \times g$ for 15 min at 4 °C, and plasma fractions were stored at -80 °C until use. Plasma corticosterone concentration was measured using a corticosterone ELISA kit (Enzo Lifesciences, Farmingdale, NY, USA), according to the manufacturer's instructions.

2.8. Determination of monoamine and monoamine metabolites content in mouse hippocampus and prefrontal cortex

The content of each monoamine and its metabolites was measured as described previously [29]. The left hippocampus and prefrontal cortex of mice subjected to FST were individually homogenized in 0.2 M perchloric acid containing 10 pg/µL isoproterenol as an internal standard. The homogenates were kept on ice for 30 min, centrifuged for 20 min at 15,000 × g at 4 °C, and the supernatants were filtered through a 0.45-µm filter membrane. Filtered supernatants were stored at -80 °C until measurement.

The tissue content of dopamine (DA) and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) and that of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were measured in a high performance liquid chromatography-electrochemical detector system (ECD-70, Eicom Corporation., Kyoto, Japan). Each 10-µL sample was injected into a C18 reverse-phase column (Eicompak SC-50DS: 3.0 mm × 150 mm, Eicom), pre-conditioned at 25 °C. The mobile phase, consisting of 0.1 M acetic acid-citric acid buffer (pH 3.5) containing 15% methanol, 190 mg/L sodium 1-octanesulfonate, and 5 mg/L EDTA, was delivered at a flow rate of 0.5 mL/ min. The applied potential was set at + 750 mV vs Ag/AgCl. The content of monoamines and their metabolites was calculated by using standard curves and expressed as μ g/g of wet tissue.

2.9. In vivo electrophysiological experiment

In vivo electrophysiological experiments were performed as described previously [30]. Under urethane anesthesia (1.5 g/kg, intraperitoneally), 16 rats (8-10-weeks-old) were fixed in a stereotaxic frame. According to the atlas of Paxinos and Watson [31], a bipolar stimulating and a monopolar recording electrode (stainless steel) were placed in the Schaffer collaterals (SC; from bregma: anteroposterior, -3.0 mm; mediolateral, +1.5 mm; dorsoventral, -2.8 mm) and the CA1 region (from bregma: anteroposterior, -5.0 mm; mediolateral, +3.0 mm; dorsoventral, -2.0 to -2.5 mm), respectively. The population spike amplitude (PSA) in the CA1 region was obtained from seven stimuli at a 30-s interval, using an electrical stimulation system (stimulator: SEN-3301, isolator: SS-104J; Nihon Kohden, Tokyo, Japan), and recorded every 5 min, using an electrical recording system (preamplifier: AVB-21, Nihon Kohden; A/D converter: PowerLab 4/25, ADInstruments, Sydney, Australia; data analysis software: Scope 3.7.6, ADInstruments). The intensity of stimulation (pulse duration: 250 µs, stimulus interval: 30 s) was adjusted for each rat to elicit a PSA of approximately 50% of the maximum amplitude. At 45 min following a single s.c. injection of saline or MAO-B inhibitors (10 mg/kg), a lowfrequency stimulation (LFS: 1 Hz, pulse duration: 250 µs, interpulse interval: 1 s, train: 30 pulses, intertrain interval: 30 s, cycle: 30 trains) was applied for 15 min, followed by a high-frequency stimulation (HFS: 100 Hz, pulse duration: 250 µs, interpulse interval: 10 ms, train: 10 pulses, intertrain interval: 10 s, cycle: 10 trains). The PSA was expressed as a percentage of the baseline value for 5 min prior to application of the LFS. The area under the curve (AUC) of the time-course changes in PSA for 60 min after HFS was also calculated.

2.10. Statistical analyses

Statistical analyses were performed in SPSS 23.0 (IBM, Armonk, NY, USA). Data are expressed as means \pm standard error of the mean (SEM). Comparison analysis between the saline-treated and drug-treated groups was performed using Dunnett's test (behavioral and neurochemical studies) or Tukey's test (*in vivo* electrophysiological experiments), and differences between two groups were evaluated using Student's *t*-test (plasma corticosterone concentration). Any possible correlation between immobility time in FST and the monoamine content was analyzed using Pearson's correlation test. Results were considered statistically significant at a *P* value < 0.05.

3. Results

We have previously demonstrated that a single and triple s.c. administration of selegiline exerts antidepressant-like effects in the mouse FST via activation of D1 receptors, and that these effects are not attributable to the effects of *l*-methamphetamine, one of its metabolites [32]. At first, to clarify whether selegiline's action takes place through inhibition of brain MAO-A, we compared its effects on depression-like behaviors and brain MAO-A activities with those of another MAO-B inhibitor, rasagiline, since both MAO-B inhibitors have a propargylamine moiety in their chemical structure and similar activity profiles regarding MAO inhibition [33,34]. Repeated s.c. administration of selegiline at 10 mg/kg/injection but not at 1 or 3 mg/kg/injection at 24, 5, and 1 h before the FST led to a significant reduction in the immobility time (10 mg/kg/injection selegiline vs. saline, P < 0.05), without accelerating the swimming velocity (Fig. 1A). This result indicates that the antidepressant-like effects of selegiline are not elicited through motor activation, as previously described [29,32]. In contrast, repeated s.c. administration of rasagiline (1, 3 or $10 \text{ mg/kg/injection} \times 3$) did not reduce the immobility time, compared with the saline-treated group. Repeated injections of selegiline or rasagiline completely inhibited MAO-B activities in the hippocampus and prefrontal cortex of mice 1 h after the FST. There was no difference in MAO-B inhibition levels between the two drug-treatment groups (Fig. 1B). Both MAO-B inhibitors suppressed MAO-A activities in the hippocampus and prefrontal cortex in a dose-dependent manner. The MAO-A inhibitory activity of selegiline at 10 mg/kg/injection, a dose exerting antidepressant-like effects in the FST, was comparable to that of rasagiline at 3 mg/kg/injection but weaker than that of rasagiline at the same dose (10 mg/kg/injection selegiline vs. 10 mg/kg/injection rasagiline, P < 0.01).

Furthermore, we evaluated the effects of the two MAO-B inhibitors on the 5-HT and DA content and their turnover rates in the hippocampus and prefrontal cortex of mice subjected to the FST (Fig. 2). Treatment with rasagiline at a dose of 10 mg/kg/injection (× 3) resulted in a higher increase in the hippocampal 5-HT content than the one observed with the same dose of selegiline (rasagiline vs. saline, P < 0.001; selegiline vs. saline, P < 0.05; rasagiline vs. selegiline, P < 0.05). Administration of selegiline at 10 mg/kg/injection and rasagiline at 3 or 10 mg/kg/injection increased the cortical 5-HT content (3 mg/kg/injection rasagiline vs. saline, P < 0.01; 10 mg/kg/injectionrasagiline or selegiline vs. saline, P < 0.001), and both MAO-B inhibitors at 10 mg/kg/injection suppressed the 5-HT turnover rates in the hippocampus and prefrontal cortex (rasagiline or selegiline vs. saline, P < 0.001). Rasagiline at 10 mg/kg/injection more strongly suppressed the 5-HT turnover rates than the same dose of selegiline (hippocampus: P < 0.001, prefrontal cortex: P < 0.05). Repeated treatment with selegiline (10 mg/kg/injection) led to an increase in the

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Fig. 1. Effects of monoamine oxidase (MAO)-B inhibitors on depression-like behavior in the forced swim test (FST) and on brain MAO activities in mice. (A) Repeated subcutaneous treatment with selegiline at 10 mg/kg/injection at 24, 5, and 1 h prior to the FST reduced the immobility time without increasing the swimming velocity. In contrast, rasagiline (1-10 mg/ kg/injection) did not. Saline, n = 8; selegiline, n = 8; and rasagiline, n = 7-8. Data represent means + SEM. * P < 0.05 vs. saline-treated mice (Dunnett's test). (B) Both inhibitors markedly inhibited MAO-B activity and dosedependently inhibited MAO-A activity in the hippocampus and prefrontal cortex of mice subjected to the FST. Rasagiline (blue circles) at a dose of 10 mg/kg/injection (repeated 3 times as above) was more potent in inhibiting MAO-A activity than selegiline (red circles) at the same dose. Saline, n = 8; selegiline, n = 8; and rasagiline, n = 7-8. Data represent means \pm SEM. \$\$ *P* < 0.01 vs. selegiline (10 mg/kg/ injection)-treated mice (Dunnett's test).

DA content in the hippocampus (selegiline vs. saline, P < 0.05), but not in the prefrontal cortex, whereas rasagiline did not have any effect on DA content in either brain region. Both MAO-B inhibitors at 10 mg/kg/ injection reduced DA turnover rates in the hippocampus (DOPAC/DA: rasagiline or selegiline vs. saline, P < 0.01; DOPAC + HVA/DA: rasagiline vs. saline, P < 0.05) and prefrontal cortex (rasagiline or selegiline vs. saline, P < 0.001), although selegiline's effect on the hippocampal (DOPAC + HVA)/DA rate was not significant (selegiline vs. saline, P = 0.26). These results suggest that the antidepressant-like effects of selegiline were not generated through enhancement of serotonergic and dopaminergic transmission via MAO-A inhibitory activity.

Hippocampal synaptic plasticity is modulated by stresses, including despair, fear, and anxiety [35-39], and by the action of neurotransmitters, including DA, 5-HT, and corticosterone [38,40,41]. We found a negative correlation between the hippocampal DA content and the FST immobility time in saline- and selegiline-treated mice (r = -0.485, P = 0.006); thus, we decided to evaluate the effects of selegiline on the synaptic plasticity in the hippocampal SC-CA1 pathway in rats. Prior to in vivo electrophysiological testing, we determined the effective dose of selegiline on a rat depression-like behavioral test, the TST. Similar to our FST results in mice (Fig. 1A), repeated treatment with 10 mg/kg/injection of selegiline at 24, 5, and 1 h before behavioral testing caused a significant reduction in the immobility time of rats in the TST (selegiline vs. saline, P < 0.001) without increasing their spontaneous locomotor activity in the OFT (Fig. 3A and B), confirming the antidepressant-like effects of selegiline in rats, as in mice. Administration of selegiline at 1, 3, or 7 mg/kg/ injection (\times 3), or rasagiline at 1, 3, or 10 mg/kg/injection (\times 3) did not affect the immobility time in TST or the spontaneous locomotor activity in OFT, compared with administration of saline (Fig. 3A and 3B).

Depression and stress are associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and high blood glucocorticoid levels, which influence behavior and synapse number and function [19,38,42]. Antagonists of glucocorticoid receptor ameliorate depression-like behavior [38,43] and prevent hippocampal LTP impairment [44] in rodents exposed to inescapable stress. Following the TST, there were no differences in plasma corticosterone concentrations between saline- and selegiline-treated rats [Saline: 522.3 ± 32.3 ng/mL, Selegiline (10 mg/kg/injection × 3): 518.3 ± 20.7 ng/mL (mean \pm SEM, n = 10), P = 0.917], indicating that selegiline does not suppress plasma corticosterone levels after the TST.

In addition to stressful events, application of LFS prior to LTP-inducing HFS has been reported to result in hippocampal LTP impairment and affect the HPA axis [35,39]. We, therefore, evaluated the effects of an acute treatment with selegiline on hippocampal synaptic plasticity, by using a simplified experimental design that included a single drug treatment and application of LFS prior to LTP induction by HFS, as an experimental model of LTP impairment. As shown in Fig. 3C, application of HFS produced a sustained increase in the PSA in the hippocampus of control rats, indicating LTP induction. Exposure to LFS before application of HFS resulted in abolishment of HFS-induced LTP induction in the hippocampal CA1 region (LFS + saline vs. control, P < 0.001), suggesting the elicitation of LFS-induced LTP impairment. A single administration of 10 mg/kg selegiline 60 min prior to HFS significantly prevented LTP impairment in the hippocampal CA1 region (LFS + selegiline vs. LFS + saline, P < 0.001), whereas a single



Fig. 2. Changes in monoamine content and turnover rates in the hippocampus and prefrontal cortex of mice treated with monoamine oxidase (MAO)-B inhibitors. In mice subjected to the forced swim test (FST), repeated treatment with selegiline (10 mg/kg/injection, 3 times: at 24, 5, and 1 h prior to testing) increased dopamine (DA) content in the hippocampus but not in the prefrontal cortex, whereas rasagiline did not have the same effect. Both MAO-B inhibitors at a dose of 10 mg/kg/injection (× 3) reduced DA turnover rates in the hippocampus and prefrontal cortex. At that dose, rasagiline resulted in a higher increase in hippocampal serotonin (5-HT) content and more potent reduction in hippocampal and cortical 5-HT turnover ratio than selegiline. Data from top to bottom show the 5-HT content (μ g/g wet tissue), ratio of the 5-HT metabolite 5-HIAA to 5-HT, DA content (ng/g wet tissue), and ratio of the DA metabolites DOPAC and HVA to DA in the hippocampus (left panels) and prefrontal cortex (right panels) of mice subjected to the FST. DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HIAA, 5-hydro-xyindoleacetic acid. Saline, *n* = 8; selegiline, *n* = 8; and rasagiline, *n* = 7–8. Data represent means + SEM. **P* < 0.05, ** *P* < 0.01, *** *P* < 0.001 vs. saline-treated mice; \$*P* < 0.05, \$\$\$ *P* < 0.001 vs. selegiline (10 mg/kg/injection)-treated mice (Dunnett's test).

administration of rasagiline at 10 mg/kg did not. A single administration of neither selegiline nor rasagiline significantly influenced the baseline PSA prior to LFS application, in comparison with the control group. Selegiline increased the AUC of the time-course changes in PSA during the application of LFS compared with LFS + saline (P < 0.05), but not with control group (Supplementary Figure). These data suggest that selegiline prevents elicitation of LTP impairment in the hippocampal CA1 region of rats, and that its antidepressant-like effects may

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be attributable to the enhancement of dopaminergic neurotransmission and to prevention of synaptic plasticity impairment in the hippocampus.

4. Discussion

The antidepressant effects of non-selective MAO inhibitors for treating MDD have been considered to be attributable to the enhancement of serotonergic and noradrenergic transmission mediated by the inhibition of MAO-A activity, because 5-HT and NE are associated with mood, and are targets for most antidepressants [15-17]. However, in the present study, repeated s.c. administration of selegiline ameliorated depression-like behaviors in rodents at 10 mg/kg/injection. Even though the effects of rasagiline, at the same dose, on MAO-A activity and 5-HT content were stronger than those of selegiline, rasagiline did not produce any antidepressant-like effects. Thus, our findings suggest that MAO-A inhibition and the resulting enhancement of serotonergic transmission do not entirely account for the antidepressant-like effects of selegiline. Consistent with our results, there are no reports to our knowledge regarding the effectiveness of rasagiline in animal models of depression or in MDD patients, although rasagiline was reported to somewhat improve the depressive symptoms in PD patients [45] and depression-like behavior in mice lacking the CD157/BST1 gene, a risk factor for PD [29]. Moreover, only selegiline at 10 mg/kg/injection resulted in a significant increase in hippocampal DA content in mice subjected to the FST. A single administration of selegiline at 10 mg/kg prevented the LFS-induced LTP impairment in the SC-CA1 pathway,

Fig. 3. Effects of monoamine oxidase (MAO)-B inhibitors on depression-like behavior in the tail suspension test (TST) and hippocampal long-term potentiation (LTP) impairment in rats. (A) Repeated subcutaneous treatment with selegiline at 10 mg/kg/injection at 24, 5, and 1 h prior to the TST reduced the immobility time, whereas rasagiline (1-10 mg/kg/injection) did not. Saline, n = 22; selegiline, n = 7-19; and rasagiline, n = 8-9. Data represent means + SEM. *** P < 0.001 vs. saline-treated rats (Dunnett's test). (B) Neither selegiline nor rasagiline increased spontaneous locomotor activities of rats in the open field test. Saline, n = 16, selegiline, n = 6-14, and rasagiline, n = 6-7.Data represent means + SEM. (C) Effects of MAO-B inhibitors on the low-frequency stimulation (LFS)-induced suppression of LTP induction. Upper panel: representative electrograms obtained before a single injection of saline or MAO-B inhibitors (black line) and after high-frequency stimulation (HFS) (red line). Ctrl, control; Sal, saline; Sel, selegiline; Ras, rasagiline. Left panel: changes in population spike amplitude (PSA). Right panel: quantification of the area under the curve (AUC; %60 min/1000) of the time-course changes in PSA for 60 min after the HFS. Application of LFS suppressed HFS-induced sustained increases in PSA in the hippocampal CA1 region. A single injection of selegiline, but not of rasagiline, at a dose of 10 mg/ kg, prevented the LFS-induced suppression of LTP induction. Ctrl (closed circles or column), n = 4; LFS + Sal (open circles or column), n = 4; LFS + Sel (red circles or column), n = 4; and LFS + Ras (blue circles or column), n = 4. Data represent means + SEM. ### P < 0.001vs. the Ctrl group, *** P < 0.001 vs. LFS + Sal group (Tukey's test).

whereas rasagiline at the same dose did not. Because DA is a substrate for both forms of MAO, and both drugs at 10 mg/kg/injection suppressed hippocampal DA turnover rates comparably, the increasing effects of selegiline on hippocampal DA content may correlate with enhanced dopaminergic transmission by other mechanisms, such as DA reuptake inhibition, in addition to MAO inhibition. Selegiline and rasagiline exhibit some pharmacological differences in DA reuptake inhibition [46] and enhancement of impulse-mediated release of DA [47]. Although *l*-methamphetamine, a metabolite of selegiline, enhances dopaminergic transmission via DA reuptake inhibition, the effects of selegiline on LTP impairment cannot be mediated through this metabolite, as it was reported that *d*-methamphetamine, which exerts more potent pharmacological effects than the *l*-enantiomer [32], reduces HFS-induced LTP in the hippocampal CA1 region [48]. Moreover, our previous study also did not support *l*-methamphetamine effects as the origin of the antidepressant-like effects of selegiline [32].

Stressful situations, like those experienced during the forced swimming, tail suspension, and chronic unpredictable mild stress tests, cause impairments in LTP induction in the hippocampal CA1 region and affect the HPA axis [35–38,49]. In addition, DA and dopaminergic agents, such as DA receptor agonists and DA reuptake inhibitors, modulate hippocampal synaptic plasticity [40,50–52]. DA also regulates the expression of proteins, such as BDNF, that are essential for the establishment of durable neuronal plasticity [53,54]. Selegiline at 10 mg/kg ameliorated depressive-like behavior, increased hippocampal DA content, and prevented LFS-induced LTP impairment without decreasing plasma corticosterone concentration. It has been reported that

a single and repeated administration of selegiline ameliorates depression-like behaviors via activation of D1 receptors [32,55], and that D1/ D5 receptor modulates SC-CA1 synaptic plasticity [51]. Therefore, these findings suggest that the selegiline may exert its antidepressantlike effects by preventing LTP-induction impairment through enhancement of hippocampal dopaminergic transmission. Some antidepressants, such as imipramine, milnacipran, and moclobemide, require chronic administration to restore the impaired LTP in the hippocampus in stress-exposed rats or in transgenic mice with impaired glucocorticoid receptor function [56-58]. However, a single administration of a multimodal antidepressant, vortioxetine, was recently reported to prevent LTP impairment without suppressing the increased plasma corticosterone levels in rats exposed to elevated-platform stress and to increase rapidly hippocampal cell proliferation [59]. Moreover, treatment with rasagiline (10 μ M) and selegiline (30 μ M) were reported to restore DA release in the striatum; however, only selegiline treatment restored striatal LTP deficits in mice carrying a heterozygous mutation in PTEN-induced kinase 1 gene, which causes PD with Lewy body pathology [60]. Further investigation is required to clarify the dopaminergic and non-dopaminergic mechanisms underlying the rapid effects of selegiline on LTP impairment.

Hippocampal synaptic plasticity contributes not only to the pathophysiology of anxiety and depressive disorder, but also to the neural basis of learning and memory [19,61]. Depression is frequently associated with cognitive disturbances [62], and some antidepressants have been shown to reverse stress-induced hippocampal LTP impairment and to improve cognitive dysfunction [58,59]. Selegiline was reported to ameliorate learning and memory impairments in rats administered with the vesicular monoamine transporter inhibitor, tetrabenazine, when tested in a shuttle box [63], as well as in those co-treated with a muscarinic receptor antagonist, scopolamine, and a 5-HT synthesis inhibitor, *p*-chlorophenylalanine, when tested in Morris water maze [64]. Thus, the preventing effects of selegiline on hippocampal LTP impairment, observed in the present study, suggest that selegiline may have the potential to ameliorate stress-associated cognitive dysfunction. It was reported that s.c. treatment with selegiline (3 mg/kg for 3 days) restores CA1 synaptic plasticity, dendritic spine density, and memory deficits in the Tg2576 mouse model of Alzheimer's disease, possibly by restoring dopaminergic drive in the hippocampus [65]. Further studies are required to elucidate how the preventing effects of selegiline against hippocampal LTP impairment contribute to cognitive function and depressive behavior amelioration in stressed rodents.

The present study has some limitations; (1) the antidepressant-like activity of selegiline was evaluated using a triple (not chronic) administration treatment design in acute (not chronic) stress models of depression; (2) the effect of selegiline on LTP impairment was evaluated by LFS-induced LTP impairment, but not by using animal models of depression; (3) we only determined changes in monoaminergic transmission following the administration of selegiline or rasagiline, but not those in other neurotransmission such as the glutamatergic system. Further analyses using chronic rodent models of depression may clarify the effects of chronic administration of selegiline on behavior, brain non-monoaminergic systems, and synaptic plasticity impairment. Moreover, because of a triple administration design and acute stress models, we cannot exclude the possibility that the effective dose (10 mg/kg) of selegiline required in mouse FST and rat TST was higher than the therapeutic doses in MDD patients (> 20 mg/day, oral). This difference in effective doses may reflect different physiological roles of brain MAO-A and MAO-B between rodents and humans, and pathological differences between acute stress-exposed rodents and MDD patients. Extrapolation to chronic clinical doses of selegiline requires the use of chronic stress-exposed primates, in which MAO-B distribution in the brain is similar to that in humans.

5. Conclusions

In conclusion, antidepressant-like effects of selegiline are not a consequence of MAO-A or MAO-B inhibition but may be attributable to enhancement of dopaminergic transmission and prevention of synaptic plasticity impairment in the hippocampus. Elucidating the significance of MAO-A-independent and hippocampal neuroplastic mechanisms underlying the therapeutic effects of selegiline will lead to a further understanding of neurobiology of patients with atypical or treatment-resistant depression who respond to selegiline.

Declarations of interest

All authors are employees of Fujimoto Pharmaceutical Corporation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2018.10.032.

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