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ORIGINAL ARTICLE

DSP-1053, a novel serotonin reuptake inhibitor with 5-HT$_{1A}$ partial agonistic activity, displays fast antidepressant effect with minimal undesirable effects in juvenile rats

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Abstract

Enhancement of serotonergic neurotransmission has been the main stream of treatment for patients with depression. However, delayed therapeutic onset and undesirable side effects are major drawbacks for conventional serotonin reuptake inhibitors. Here, we show that DSP-1053, a novel serotonin reuptake inhibitor with 5-HT$_{1A}$ partial agonistic activity, displays fast antidepressant efficacy with minimal undesirable effects, especially nausea and emesis in animal models. DSP-1053 bound human serotonin transporter and 5-HT$_{1A}$ receptor with the K_i values of 1.02 $\pm$ 0.06 and 5.05 $\pm$ 1.07 nmol/L, respectively. This compound inhibited the serotonin transporter with an IC_{50} value of 2.74 $\pm$ 0.41 nmol/L and had an intrinsic activity for 5-HT$_{1A}$ receptors of 70.0 $\pm$ 6.3%. In rat microdialysis, DSP-1053, given once at 3 and 10 mg kg^{-1}, dose-dependently increased extracellular 5-HT levels. In the rat forced swimming test, 2-week administration of DSR-1053 (1 mg kg^{-1}) significantly reduced rats immobility time after treatment, whereas paroxetine (3 and 10 mg kg^{-1}) required 3-week administration to reduce rats immobility time. In olfactory bulbectomy model, 1- and 2-week administration of DSP-1053 reduced both of emotional scores and activity in the open field, whereas paroxetine required 2 weeks to show similar beneficial effects. Although single administration of DSP-1053-induced emesis and vomiting in the rat and *Suncus murinus*, multiple treatment with this compound, but not with paroxetine, decreased the number of vomiting episodes. These results highlight the important role of 5-HT$_{1A}$ receptors in both the efficacy and tolerability of DSP-1053 as a new therapeutic option for the treatment of depression.

Abbreviations

K_d, dissociation constant; K_i, inhibition constant; i.v., intravenous; I.A., intrinsic activity; IC_{50}, half maximal inhibitory concentration; HPLC, high-performance liquid chromatography; GTPγS, guanosine 5′-(γ-thio) triphosphate, [35S]-; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; 5-HT, 5-hydroxytryptamine (serotonin).

Introduction

Major depressive disorder is a chronic, debilitating disease with a lifetime risk of approximately 15% for men and 30% for women (Kessler et al. 2005; Waraich et al. 2005). First line therapy for major depressive disorder relies on the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinepherine reuptake inhibitors (SNRIs)

(Rush et al. 2006; Gelenberg et al. 2010). Although SSRIs and SNRIs have dramatically expanded treatment options for major depressive disorder, there is still a significant unmet medical need for management of this disorder, including therapeutics delayed onset, and treatment resistance (Rush et al. 2006; Warden et al. 2007; Reeves et al. 2008; Gelenberg et al. 2010). It has been reported that pindolol, a 5-$HT_{1A/1B}$ and β adrenergic receptor partial agonist, may accelerate antidepressants onset and enhance SSRIs beneficial effects in treatment-resistant depression. (Artigas et al. 1994; Blier and Bergeron 1995; Pérez et al. 1997). This enhancement would be mediated by blockage of negative feedback inhibition in response to increased serotonin (5-HT) (Bel and Artigas 1993; Rutter et al. 1994; Kreiss and Lucki 1995; Arborelius et al. 1996). Further evidence to support the role of 5-HT_{1A} receptors in this response comes from the results of combination therapy with SSRIs and WAY-100635, a highly selective 5-HT_{1A} receptor antagonist (Gartside et al. 1995; Dawson and Nguyen 1998).

On the other hand, activation of 5-HT_{1A} receptor is also considered to shorten SSRIs onset by accelerating desensitization of 5-HT_{1A} autoreceptor (Dawson and Watson 2009). Therefore, dual-action antidepressants that can modulate 5-HT_{1A} receptor and inhibit 5-HT reuptake could be a plausible option for treatment of major depressive disorder with faster onset and higher efficacy than conventional SSRIs (see reviews, e.g., Celada et al. 2013).

Another shortcoming of the currently available armamentarium for treatment of major depressive disorder is the presence of significant side effects associated with available antidepressants, including nausea, sexual dysfunction, dizziness, sleep disorders, headache, and agitation (Gelenberg et al. 2010). Studies have actually shown that patients adherence to antidepressants is directly related to the frequency and intensity of side effects (Bull et al. 2002; Olfson et al. 2006). This highlights the need for safer treatments to manage this debilitating disorder.

Here, we report the therapeutic benefits of DSP-1053, a structurally novel 5-HT reuptake inhibitor with 5-HT_{1A} receptor partial agonistic activity, in common rodent depression models, rat forced swimming test, and olfactory bulbectomy model. We also compared DSP-1053 potential emetic effect to that of paroxetine in rats and shrews (*Suncus murinus*).

Materials and Methods

Animals

All experimental procedures for the use of animals were reviewed and approved by the Institutional Animal Care and Use Committee of Sumitomo Dainippon Pharma, Co., Ltd. Rats were purchased from Charles River Laboratories Japan, Inc. (Kanagawa, Japan) or Japan SLC, Inc. (Shizuoka, Japan). Shrews (*S. murinus*) were purchased from CLEA Japan, Inc. (Tokyo, Japan). All animals were kept in a room with controlled environmental conditions (temperature: 23 ± 3°C, humidity: 55 ± 15%, 12 h light–dark cycle with light on at 07:00 h) and used after a quarantine period of 7 days. The animals were given food (CE-2, Oriental Yeast Co., Ltd., Tokyo, Japan) and filtered tap water ad libitum.

Materials

DSP-1053 (6-(2-{4-[4-Bromo-3-(2-methoxyethoxy)benzyl]piperidin-1-yl}ethyl)-2,3-dihydro-4*H*-chromen-4-one benzenesulfonate) (Fig. 1) and paroxetine hydrochloride (paroxetine) were synthesized in our laboratories. The rout of synthesis of DSP-1053 has been described previously (Nishida et al. 2012). Clomipramine hydrochloride (clomipramine), serotonin hydrochloride (5-HT), dopamine hydrochloride (dopamine), imipramine hydrochloride (imipramine), WAY-100635, pindolol, and R-(+)-8-hydroxy-DPAT (8-OH-DPAT) were purchased from Sigma Aldrich Japan (Tokyo, Japan). All radioligands were purchased from Perkin Elmer Japan (Kanagawa, Japan). For oral (p.o.) administration in rodent models, DSP-1053 and paroxetine were dissolved in 0.5% methylcellulose. In the *S. murinus* model, DSP-1053 and paroxetine were dissolved in 40% polyethylene glycol. Dosing volume was determined based on each animal body weight measured in the morning of each administration day (5 mL kg^{-1}). Cell membranes expressing human serotonin transporter and 5-HT_{1A} receptor were purchased from Perkin Elmer Japan. Chinese hamster ovary cells expressing human serotonin transporter used for [^{3}H]5-HT uptake assay were established in our Pharmacology Research Laboratories at Sumitomo Dainippon Pharma Co., Ltd.

Preparation of rat cell membranes

Five-week-old male rats (Crl:CD(SD)) were killed by decapitation, and their brains were rapidly removed and dissected to obtain the cerebral cortex (for serotonin

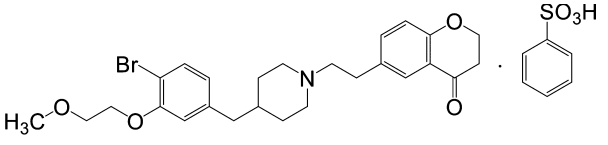

Figure 1. Chemical structure of DSP-1053.

transporter binding) and hippocampus (for 5-HT_{1A} binding), which were washed in ice-cold saline and weighed. The tissues were homogenized with a teflon-glass homogenizer in reaction buffer [50 mmol/L Tris-HCl buffer containing 120 mmol/L NaCl and 5 mmol/L KCl (for serotonin transporter) or 50 mmol/L Tris-HCl buffer containing 4 mmol/L $CaCl_2$ (for 5-HT_{1A})], and the homogenates were centrifuged at 40,000–48,000*g* for 10 min at 4°C. The obtained pellets were resuspended in the reaction buffer, and the homogenates were centrifuged again at 40,000–48,000*g* for 10 min at 4°C. The resulting pellets were resuspended in 8–10 times their volume of reaction buffer, and the protein concentrations were measured by the method of Bradford using the Bio-Rad Protein Assay (Bio-Rad Laboratories Co., Ltd., Hercules, CA, US). The cell membranes were diluted with reaction buffer to a concentration of 4 mg mL^{-1}. On the day of the experiment, the stored membranes were diluted with reaction buffer to a concentration of 447 μg mL^{-1} (200 μg/L assay).

Radioligand binding assay

In a total volume of 500 μL, 2.5 μL of test substance solution, clomipramine solution (2 mmol/L), 8-OH-DPAT (2 mmol/L) or dimethyl sulfoxide, 50 μL of [^{3}H]citalopram or [^{3}H]8-OH-DPAT solution, and 447.5 μL of cell membranes were mixed. Cell membranes expressing human serotonin transporter and 5-HT_{1A} receptor were diluted with the reaction buffer to a final concentration of 1 unit/447.5 μL beforehand. All samples were reacted at 25°C for 0.5 (for 5-HT_{1A}) or 1 h (for serotonin transporter) in an incubator. The reaction was terminated by addition of 4 mL ice-cold reaction buffer, and the cell membranes were collected by vacuum filtration through GF/B glass filters. The glass filters were then washed with 4 mL of ice-cold reaction buffer and placed in scintillation vials with scintillation fluid. After more than 3 h, the radioactivity in each sample was measured with a liquid scintillation counter for 2 min, and the calculated dpm value was used for data analysis. In the serotonin transporter binding assay, GF/B glass filters were soaked in 0.05% polyethylenimine solution for more than 15 min before use. The inhibition constant (K_i) was calculated in Microsoft® Office Excel 2003 (Microsoft Corporation) using the Cheng–Prusoff equation [$K_i = IC_{50}/(1 + ([L]/K_d)]$, where L is the concentration of radioligand in the assay and K_d is the dissociation constant of the radioligand for the receptor.

[^{3}H]5-HT uptake assay

Phosphate-buffered saline containing 0.1 mmol/L $CaCl_2$ and 1 mmol/L $MgCl_2$ was used as reaction buffer. One microliter of dimethyl sulfoxide or test substance and 149 μL of human serotonin transporter-expressing cells suspension were added to 96-well assay plates. The plates were preincubated at 37°C for 10 min. During that time, dimethyl sulfoxide or test substance (DSP-1053, paroxetine, or imipramine) was diluted in [^{3}H]5-HT solution in another 96-well plate. After the preincubation, the prepared [^{3}H]5-HT solution containing dimethyl sulfoxide or test substance was added to the cell suspension, and the mixture was incubated at 37°C for 10 min. Ice-cold 3% formamide in 0.9% NaCl was added to each well to stop the reaction. All reaction mixtures in the 96-well plates were then filtered through a glass fiber filter plate prewashed in 200 μL of 0.3% polyethylenimine and dried under reduced pressure with manifold (Millipore, Billerica, MA, US). To wash the glass fiber filter, 300 μL of phosphate buffered saline was added and filtrated twice. Radioactivity in each sample was measured as described in the previous section.

Guanosine 5′-(γ-thio) Triphosphate, [^{35}S]-(GTPγS) assay for 5-HT_{1A} receptor

To make up a total volume of 500 μL, 2.5 μL of test substance, 2 mmol/L GTPγS (to measure nonspecific binding), dimethyl sulfoxide (to measure basal [^{35}S]GTPγS binding), or 20 mmol/L 5-HT (to measure maximal [^{35}S]GTPγS binding), 50 μL of reaction buffer [2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES)-NaOH buffer (20 mmol/L, pH 7.4) containing 100 mmol/L NaCl, 10 mmol/L $MgCl_2$, 0.1 mmol/L dithiothreitol, and 1 μmol/L guanosine-5′-diphosphate sodium salt (GDP)] containing 20 nmol/L [^{35}S]GTPγS, and 447.5 μL of the cell membranes expressing human 5-HT_{1A} receptors (1 unit/447.5 μL) were mixed. All samples were allowed to react in an incubator set at 25°C for 20 min. The reaction was terminated by adding 4 mL of ice-cold reaction buffer, and the cell membranes were collected by vacuum filtration using GF/B glass filters. The glass filters were washed twice with 4 mL of ice-cold reaction buffer. Radioactivity in each sample was measured as described in the previous section. Intrinsic activity was expressed as relative value of the activity of 100 μmol/L 5-HT, which was considered to be 100%.

Off-target radioligand binding assays and enzyme assays

To determine DSP-1053 interaction with off-target receptors and enzymes, 29 receptor binding assays and 3 enzyme assays (catechol-*O*-methyltransferase, monoamine oxidase-A and -B) were conducted on our behalf by Sekisui Medical Co., Ltd (Tokyo, Japan). The receptor binding assays were carried out using standard techniques as summarized

in Table 3. As for the enzyme assays, pig catechol-*O*-methyltransferase, human monoamine oxidase-A, and -B activity was evaluated using *S*-adenosyl-L-[methyl-^{14}C]-methionine, 5-hydroxy[side chain-2-^{14}C]tryptamine, or beta-[ethyl-1-^{14}C]-, PKI as labeled substrate, and the amount of radioactivity was quantitated.

Pharmacokinetics of DSP-1053

Pharmacokinetic study of DSP-1053 was carries out in male rats (Crl:CD(SD)) after intravenous (i.v.) (1 mg kg^{-1}) and p.o. (10 mg kg^{-1}) administration. At appropriate time points after dosing (0.083, 0.25, 0.5, 1, 2, 4, 6, and 24 h for i.v., 0.25, 0.5, 1, 2, 4, 6, and 24 h for p.o.), blood was sampled from two (for i.v.) or three (for p.o.) different rats. Each rat was sampled 8 or 7 times in total. Plasma concentrations of DSP-1053 were determined using high-performance liquid chromatography (HPLC)/tandem mass spectrometry and analyzed by non-compartmental analysis using WinNonlin (version 6.3; Pharsight Corporation, Mountain View, CA, US).

Rat microdialysis

Surgery

This experiment was performed using 5–6-week old male rats (Crlj:WI). A vertical guide cannula (AG-04; EICOM) was implanted in the right side of the frontal cortex (3.7 mm anterior, 3.0 mm lateral, and 1.5 mm ventral from the bregma) of the rat under pentobarbital anesthesia [80 mg kg^{-1}, intraperitoneal (i.p.)]. Microdialysis was conducted on the day after surgery. A dialysis probe (A-I-4-03; EICOM) was inserted into the guide cannula under light anesthesia with isoflurane and continuously perfused by Ringer solution (147 mmol/L NaCl, 4 mmol/L KCl, 2.3 mmol/L $CaCl_2$) at 2 μL min^{-1} using a microsyringe pump. Microdialysate samples (10 μL) were continuously collected for 5 min at 20-min intervals and automatically injected into the HPLC system. DSP-1053 or vehicle was orally administered to the rats at least 3 h after the start of perfusion, that is, when stable HPLC baseline values for 5-HT and dopamine were obtained in the dialysate samples. Measurement continued for 3 h after drug or vehicle administration.

Chromatography

The collected microdialysate samples (10 μL) were separated by HPLC using a PP-ODS column (EICOM) and a mobile phase containing 0.1 mol/L phosphate buffer (pH 6.0), 1% methanol, 50 mg L^{-1} ethylenediamine tetraacetic acid disodium, and 500 mg L^{-1} sodium 1-decanesulfonate at a flow rate of 0.5 mL min^{-1}. The peaks corresponding to 5-HT and dopamine were amperometrically detected using a graphite electrode set at 400 mV with an Ag/AgCl reference electrode (RE-100; EICOM). Online data acquisition was performed using PowerChrom software (Version 2.2; AD Instruments Pty Ltd., Nagoya, Aichi, Japan). Before performing the microdialysis, the retention time of the HPLC peak for 5-HT and dopamine was determined using a standard solution. The peak height (mV) of 5-HT and dopamine at each measurement was converted into a percentage of the average of the last 4 pre-drug baseline values (percentage of baseline).

Rat forced swimming test

Test compounds antidepressant-like activity was assessed a previously described (Porsolt et al. 1978) with slight modifications. In the training session (Day 1), each animal (5–6-week old male rats (Crlj:WI)) was gently placed into a plastic cylinder (40 cm in height, 19 cm in diameter) containing 5.8 L of water set at 25 $\pm$ 1°C. Fifteen min after the beginning of the training session, the animal was removed from the water and returned to its home cage. Test compounds dosing suspensions were administered to animals in a blind manner 15 min after the end of the training session. From Day 2 to Day 13 or Day 20, the animals were administered the dosing suspensions once a day between 7:00AM and 7:00PM. In the test session (Day 14 or Day 21), the animals were treated with the dosing suspensions as described in the training session, and the swimming test was performed for 5 min in the same manner as in the training session. In the swimming test, the behavior of each animal was horizontally recorded onto a DVD recorder using a video camera. An animal was judged to be immobile whenever it remained floating on the water without moving its body or forepaws, except for slight movements to maintain posture. The total time the animal remained immobile was defined as immobility time. An observer blinded to test compounds doses measured the immobility time.

Olfactory bulbectomy

Surgery

The test was performed using 6–7-week-old male rats (Crlj:WI). Bilateral olfactory bulbectomy was performed on rats anesthetized with pentobarbital (50 mg kg^{-1}; i.p.), essentially as previously described (Cryan et al. 1999). The head was shaved and a midline sagittal incision was made extending at 1 cm rostral to bregma. A burr hole was drilled at points 7 mm anterior to bregma and 2 mm either side of the midline at a point corre-

sponding to the posterior margin of the orbit of the eye. The olfactory bulbs were removed by suction, and the burr holes filled with a hemostatic sponge (Spongel; Astellas Pharma Inc., Tokyo, Japan). Tetracycline powder was applied to the wound prior to closure. Sham-operated rats underwent the same procedure with the dura above the bulbs punctured, but the bulbs left intact. Following surgery, the animals were allowed 7 days recovery prior to drug administration. During recovery, the general condition of each animal was monitored.

Emotional scoring

Emotional scoring was conducted, essentially as previously reported (Cairncross et al. 1978; Gomita et al. 1983). Emotional scoring consisted of the following five tests; (1) response to a stick presented just in front of the nose, (2) response to a puff of air blown sharply onto the rat's back, (3) response to grasping the animal, (4) response to tail pinching by a forceps, (5) vocalization during scoring. In each of the tests numbered 1–4, responses were graded as follows: 0 (no response), 1 (slight response), 2 (moderate response), 3 (marked response), or 4 (extreme response). In test 5), vocalization was graded as follows: 0 (no vocalization), 1 (occasional vocalization), or 2 (extensive vocalization). Emotional scoring was performed in animals' home cages. The scores in each scoring system were added to give a single emotional score for each individual animal. The maximum emotional score was 18. Animals emotional scoring was performed just before the first drug administration (pre), and on the day after the open-field test (post).

Open-field test

The open-field test was carried out, essentially as described elsewhere (Cryan et al. 1999). Each rat was placed onto the center of the open-field apparatus, and the number of line crosses over a 5-min period was recorded.

Conditioned taste aversion test in rats

The test was performed using 10-week-old male rats (Slc: SD). Drinking water was removed overnight (from 18:00 until 09:00 h) prior to the start of the experiment. On the following 2 days, water was first given for 60 min, and then ad libitum from 12:00 until 18:00 h. On day 3, all rats had access to a 0.5% saccharin solution for 60 min instead of water. At 10:20 h of day 3, the animals were dosed with DSP-1053 or vehicle. Water was then made available ad libitum for the rest of the day and removed overnight (from 18:00 until 09:00 h). On the test day (day 4), the animals had again access to 0.5% saccharin solution for 60 min in the absence of test compound. Rats saccharin consumption was measured for each 60-min period on day 3 and 4, and saccharin intake ratio was calculated as follows.

$$(\text{Saccharin intake ratio}) = \frac{(\text{saccharin intake on day 4})}{(\text{saccharin intake on day 3})}.$$

Evaluation of emesis in *Suncus murinus*

Male Jic:SUN-Her, 5 weeks (body weight: 40–63 g) (experiment 1), or 10 weeks (body weight: 53–73 g) (experiment 2) of age at the initiation of dosing were used in this study.

Experiment 1

DSP-1053 (10, 30, 60, or 100 mg kg^{-1}) or 40% polyethylene glycol was orally administered to the animals, and the number of animals that vomited as well as the number of vomiting episodes were counted for 60 min. Paroxetine-induced emesis, as evaluated under the same protocol (Mine et al. 2013), was used as reference.

Experiment 2

On the first day of the experiment, DSP-1053 (60 mg kg^{-1}), paroxetine (60 mg kg^{-1}), or 40% polyethylene glycol was orally administered to the animals and the number of vomiting episodes was counted. Animals that showed emesis on the first day in each group (9 of 19 in DSP-1053 group, 12 of 19 in paroxetine group), and three animals in 40% polyethylene glycol group were subsequently dosed once a day for 7 days with DSP-1053 (60 mg kg^{-1}), paroxetine (60 mg kg^{-1}), or 40% polyethylene glycol, respectively, and the number of animals that vomited as well as the number of vomiting episodes was counted for 60 min after administration on each day.

Data analysis

Scatchard plots approximated by regression line with Microsoft® Office Excel 2003 (Microsoft Corporation) were used to calculate K_d value in each binding assay. The IC_{50} value in each binding assay and the maximal specific binding of each test substance [intrinsic activity (I.A.) of the test substance] as well as EC_{50} values in GTPγS assay were determined by fitting logistic curve using "Dx calculation (logistic curve fitting) with measured value input function" method in Stat Prelinica Version 1.0.3 (Takumi Information Technology Inc., Tokyo, Japan).

In rat microdialysis, data are presented as time-course changes in peak height and in cumulative values of percentage of baseline over 3 h after drug administration

[AUC (0–180 min)]. Cumulative data were analyzed with one-way analysis of variance (ANOVA) followed post hoc parametric Dunnett's multiple comparison test. Differences in immobility time in the rat forced swimming test between test compounds-treated groups and the vehicle-treated group were analyzed with one-way ANOVA followed post hoc parametric Dunnett's multiple comparison test.

In olfactory bulbectomy, the statistical significance of differences in emotional scores and the number of line crosses between each group was assessed with three-way ANOVA, and post hoc individual group comparison were made with *t*-test and parametric Dunnett's multiple comparison test.

In rat conditioned taste aversion model, differences in water or saccharin and saccharin intake ratio between DSP-1053-treated group and the vehicle-treated group were analyzed with one-way ANOVA followed post hoc parametric Tukey's multiple comparison test.

In emesis test using *S. murinus*, data analysis was conducted as previously reported (Mine et al. 2013). In experiment 1, differences in incidence of vomiting between the vehicle-treated group and compounds-treated groups were analyzed by Fisher's exact test. The number of emetic episodes was determined as average for all animals that vomited. In experiment 2, the number of emetic episodes was determined as average for all tested animals. Differences in the number of emetic episodes between Day 1 and Day 2 to Day 7 of treatment were analyzed with one-way ANOVA followed *post hoc* parametric Dunnett's multiple comparison test.

In all animal experiments, Stat Prelinica Version 1.2 was used as analysis software.

Results

DSP-1053 in vitro binding to the serotonin transporter

DSP-1053 inhibited the binding of [^{3}H]citalopram to human and rat serotonin transporter, with K_i values of 1.02 ± 0.06 and 0.489 ± 0.039 nmol/L (mean ± SEM duplicate, 3 independent experiments (n = 3)], respectively. In addition, in 5-HT uptake assay using Chinese hamster ovary cells expressing human serotonin transporter, DSP-1053 inhibited [^{3}H]5-HT uptake with an IC_{50} value of 2.47 ± 0.41 (n = 3). In both assays, DSP-1053 binding affinity for human serotonin transporter was lower than that of paroxetime, but higher than that of imipramine (Table 1).

DSP-1053 in vitro binding to the 5-HT$_{1A}$ receptor

DSP-1053 inhibited the binding of [^{3}H] 8-OH-DPAT to human and rat 5-HT$_{1A}$ receptor with K_i values of 5.05 ± 1.07 and 5.09 ± 1.03 nmol/L (mean ± SEM n = 3), respectively. In GTPγS assay using Chinese hamster ovary cell membrane expressing human 5-HT$_{1A}$ receptor, DSP-1053 displayed I.A. of 70.0 ± 6.3% [EC_{50}; 98.0 ± 34.9 nmol/L] (n = 3). DSP-1053 binding affinity for human 5-HT$_{1A}$ receptor was comparable to that of pindolol or 8-OH-DPAT, but lower than that of WAY-100635. On the other hand, DSP-1053 I.A. for 5-HT$_{1A}$ receptor was higher than that of WAY-100635 or pindolol, but lower than that of 8-OH-DPAT (Table 2).

Table 1. DSP-1053 in vitro binding to the serotonin transporter.

Drug	IC_{50} (nmol/L)	K_d (nmol/L)	K_i (nmol/L)
Human SERT binding			
DSP-1053	1.56 ± 0.09	3.45 ± 0.19	1.02 ± 0.06
Paroxetine	0.279 ± 0.014		0.183 ± 0.008
Imipramine	3.60 ± 0.07		2.36 ± 0.04
Rat SERT binding			
DSP-1053	8.84 ± 0.07	1.14 ± 0.02	0.489 ± 0.039
5-HT uptake inhibition			
DSP-1053	2.47 ± 0.41	–	–
Paroxetine	0.181 ± 0.020		
Imipramine	3.73 ± 0.27		

DSP-1053 binding to off-target receptors and enzymes

As shown in Table 3, DSP-1053 (1 μmol/L) showed affinity for histamine H_1 receptor with K_i value of 7.46 ± 1.37 nmol/L (mean ± SEM n = 3). DSP binding affinity for the other 28 tested receptors was weak (K_i values > 100 nmol/L). Moreover, DSP-1053 (1 μmol/L) did not inhibit pig catechol-*O*-methyltransferase, human monoamine oxidase-A, and -B (percent inhibition; 0.00, 5.28 and 0.19%, respectively).

Pharmacokinetics of DSP-1053

DSP-1053 reached maximum plasma levels within 1 h after p.o. administration with 7.3% bioavailability (Fig. 2). DSP-1053 clearance (CL) and volume of distribution at steady state (Vdss) after injection were 57.6 mL min^{-1} kg^{-1} and 5.1 L kg^{-1}, respectively. In all DSP-1053 in vivo studies, dosing time was selected based on the above pharmacokinetic parameters.

Effects of DSP-1053 on extracellular 5-HT and dopamine levels in the frontal cortex of rats

Basal microdialysate levels of 5-HT and DA in the rat frontal cortex were 0.355 ± 0.025 and 0.305 ± 0.019 pg/10 μL (n = 17), respectively. DSP-1053 increased 5-HT

Table 2. DSP-1053 in vitro binding to the 5-HT_{1A} receptor.

Drug	IC_{50}/EC_{50} (nmol/L)	K_d (nmol/L)	K_i (nmol/L)	I.A. (%)
Human 5-HT_{1A} binding				
DSP-1053	9.92 ± 2.11	0.313 ± 0.045	5.05 ± 1.07	–
WAY-100635	0.958 ± 0.130		0.420 ± 0.060	
Pindolol	21.6 ± 3.0		9.39 ± 1.30	
8-OH-DPAT	10.3 ± 1.5		4.47 ± 0.64	
Rat 5-HT_{1A} binding				
DSP-1053	10.7 ± 2.1	0.275 ± 0.009	5.09 ± 1.03	–
GTPγS binding				
DSP-1053	98.0 ± 34.9	–	–	70.0 ± 6.3
WAY-100635	n.d.			2.60 ± 3.88
Pindolol	n.d.			13.3 ± 3.8
8-OH-DPAT	58.0 ± 11.3			102 ± 1

Table 3. DSP-1053 (1 μmol/L) inhibition of radioligand binding to various receptors.

Target	Radioligand	Concentration (nmol/L)	Percentage inhibition at 1 μmol/L	K_i (nmol/L) (n = 3)
Human adrenergic α_{1A}	[^{125}I] HEAT	0.15	57	528 ± 45
Human adrenergic α_{1B}	[^{3}H] Prazosin	1.2	1	–
Human adrenergic α_{2A}	[^{3}H] Rawolscine	1.3	26	–
Human adrenergic α_{2B}	[^{3}H] Rawolscine	1.3	6	–
Human adrenergic α_{2C}	[^{3}H] Rawolscine	1.3	41	–
Human adrenergic β_1	[^{3}H] (-)-CGP-12177	0.21	14	–
Human adrenergic β_2	[^{3}H] (-)-CGP-12177	0.21	22	–
Human adrenergic β_3	[^{125}I] (-)-Cyanopindolol	0.060	19	–
Human dopamine D_1	[^{3}H] SCH-23390	0.48	4	–
Human dopamine D_{2L}	[^{3}H] Spiperone	2.0	35	–
Human dopamine D_3	[^{3}H] R-(+)7-OH-DPAT	0.38	65	249 ± 21
Rat $GABA_A$	[^{3}H] Flunitrazepam	0.88	8	–
Rat $GABA_B$	[^{3}H] GABA	5.2	0	–
Human histamine H_1	[^{3}H] Pyrilamine	5.2	93	7.46 ± 0.20
Human histamine H_2	[^{3}H] Tiotidine	5.1	37	–
Human musucarinic M_1	[^{3}H] *N*-Methylscopolamine	0.37	9	–
Human musucarinic M_2	[^{3}H] *N*-Methylscopolamine	0.37	21	–
Human opiate δ	[^{3}H] Naltrindole	0.88	10	–
Human opiate κ	[^{125}I] Diprenorphine	0.71	0	–
Human opiate μ	[^{125}I] Diprenorphine	0.64	2	–
guinea pig serotonin 5-HT_4	[^{3}H] GR-113808	0.55	26	–
Human serotonin 5-HT_{1B}	[^{3}H] 5-HT	8.9	47	–
Human serotonin 5-HT_{2A}	[^{3}H] Ketanserin	0.48	35	–
Human serotonin 5-HT_{2B}	[^{125}I] LSD	0.29	79	117 ± 28
Human serotonin 5-HT_{2C}	[^{3}H] Mesulergine	1.8	20	–
Human serotonin 5-HT_3	[^{3}H] GR-65630	0.47	0	–
Human serotonin 5-HT_{5A}	[^{125}I] LSD	0.020	2	–
Human serotonin 5-HT_6	[^{125}I] LSD	0.020	14	–
Human serotonin 5-HT_7	[^{125}I] LSD	0.020	73	288 ± 35

extracellular levels in the rat frontal cortex. This increase reached a maximum of 180 ± 25.9% and 264 ± 58.0% (mean ± SEM) of baseline value 100 min after DSP-1053 administration at 3 and 10 mg kg^{-1}, respectively (Fig. 3A). In addition, DSP-1053 (3 and 10 mg kg^{-1}) significantly increased cortical 5-HT cumulative value over 3 h after administration, $F(3, 13) = 30.90$, $P < 0.05$ (Fig. 3B). On the other hand, DSP-1053 did not affect dopamine extracellular levels in the rat frontal cortex at any dose, $F(3, 13) = 0.13$, $P > 0.05$ (Fig. 3C and D).

DSP-1053 antidepressant-like effect in the rat forced swimming test

As shown in Figure 4A, DSP-1053 significantly decreased immobility time following a 2-week consecutive adminis-

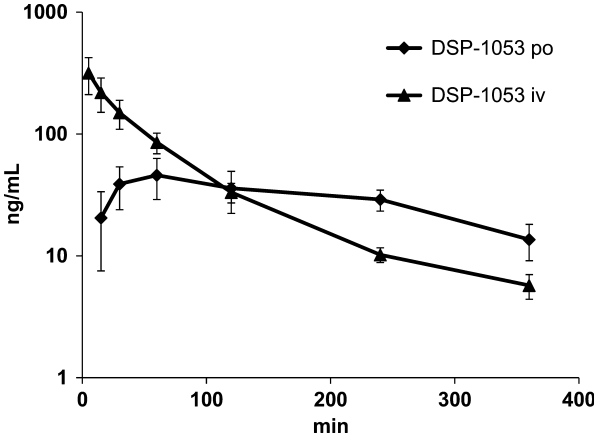

Figure 2. DSP-1053 plasma concentrations after single p.o. and i.v. administration to fed male rats. Data are the mean ± SD [n = 2 (for i.v.) or n = 3 (for p.o.)].

tration at 1 mg kg^{-1} compared to the vehicle, $F(3, 60) = 5.01$, $P < 0.05$. On the other hand, animals treated with paroxetine (3 and 10 mg kg^{-1}) for 3-week had reduced immobility time compared to the animals treated with the vehicle, $F(2, 51) = 4.64$, $P < 0.05$ (Fig. 4B). Treatment with paroxetine for 2-week had no effect on rats immobility time, $F(3, 60) = 1.59$, $P > 0.05$ (Fig. 4C).

DSP-1053 antidepressant-like effect in the rat olfactory bulbectomy test

Effects on emotional scores

Figure 5A and B show the effects of 1- and 2-week administration of DSP-1053 on emotional scores of sham-operated and olfactory bulbectomized animals. Three-way (drug, surgery, and dosing period) ANOVA revealed no main effect for drug × surgery × dosing period, drug × dosing period and surgery × dosing period interaction and a significant main effect for drug × surgery interaction (drug × surgery × dosing period interaction, $F(15, 144) = 1.16$, $P > 0.05$; drug × dosing period interaction, $F(15, 144) = 0.17$, $P > 0.05$; surgery × dosing period interaction, $F(15, 144) = 1.84$, $P > 0.05$; drug × surgery interaction, $F(15, 144) = 22.55$, $P < 0.05$). Olfactory bulbectomy significantly increased emotional scores, $F(15, 144) = 598.83$, $P < 0.05$. Post hoc test analysis showed that in olfactory bulbectomized animals, DSP-1053 (0.3, 1 and 3 mg/kg) produced a significant decrease in emotional scores, $F(3, 76) = 30.58$, $P < 0.05$ and no effect in the sham-operated animals, $F(3, 76) = 0.21$, $P > 0.05$. Figure 5C and D show the effects of 1- and 2-week administration of paroxetine on emotional scores of sham-operated and olfactory bulbectomized animals. Three-way ANOVA revealed a significant main effect for drug × surgery × dosing period interaction, $F(13, 125) = 5.18$, $P < 0.05$. In 1-week administration group, subeffect two-way (drug and surgery) ANOVA revealed that paroxetine did not alter emotional scores compared to the vehicle, $F(5, 54) = 0.95$, $P > 0.05$. On the other hand, olfactory bulbectomy significantly increased emotional scores, $F(5, 54) = 453.49$, $P < 0.05$, and it did not significantly affect the drug effect – drug × surgery interaction, $F(5, 54) = 1.94$, $P > 0.05$. In the 2-week administration group, subeffect two-way (drug and surgery) ANOVA revealed a significant main effect for drug × surgery interaction, $F(7, 71) = 4.16$, $P < 0.05$. Post hoc test analysis showed that in olfactory bulbectomized animals, paroxetine (3 and 10 mg/kg) produced a significant decrease in emotional scores, $F(3, 35) = 7.38$, $P < 0.05$, and no effect in the sham-operated animals, $F(3, 36) = 1.26$, $P > 0.05$.

Effects on the number of line crosses

Figure 6A and B show the effects of 1- and 2-week administration of DSP-1053 on the number of line crosses of sham-operated and olfactory bulbectomized animals. Three-way ANOVA revealed no main effect for drug × surgery × dosing period, drug × dosing period and surgery × dosing period interaction and a significant main effect for drug × surgery interaction [drug × surgery × dosing period interaction, $F(15, 144) = 0.87$, $P > 0.05$; drug × dosing period interaction, $F(15, 144) = 0.80$, $P > 0.05$; surgery × dosing period interaction, $F(15, 144) = 0.58$, $P > 0.05$; drug × surgery interaction, $F(15, 144) = 7.25$, $P < 0.05$]. Olfactory bulbectomy significantly increased the number of line crosses, $F(15, 144) = 41.65$, $P < 0.05$. Post hoc test analysis showed that in olfactory bulbectomized animals, DSP-1053 (0.3, 1 and 3 mg/kg) produced a significant decrease in the number of line crosses, $F(3, 76) = 7.85$, $P < 0.05$, and no effect in the sham-operated animals, $F(3, 76) = 1.55$, $P > 0.05$. Figure 6C and D show the effects of 1- and 2-week administration of paroxetine on the number of line crosses of sham-operated and olfactory bulbectomized animals. Three-way ANOVA revealed a significant main effect for drug × surgery × dosing period interaction, $F(13, 125) = 4.27$, $P < 0.05$. In 1-week administration group, subeffect two-way (drug and surgery) ANOVA revealed that paroxetine did not alter the number of line crosses compared to the vehicle, $F(5, 54) = 0.78$, $P > 0.05$. On the other hand, olfactory bulbectomy significantly increased the number of line crosses, $F(5, 54) = 43.03$, $P < 0.05$, and it did not significantly affect the drug effect – drug × surgery interaction, $F(5, 54) = 0.76$, $P > 0.05$. In 2-week administration group, subeffect two-way (drug and surgery) ANOVA revealed a

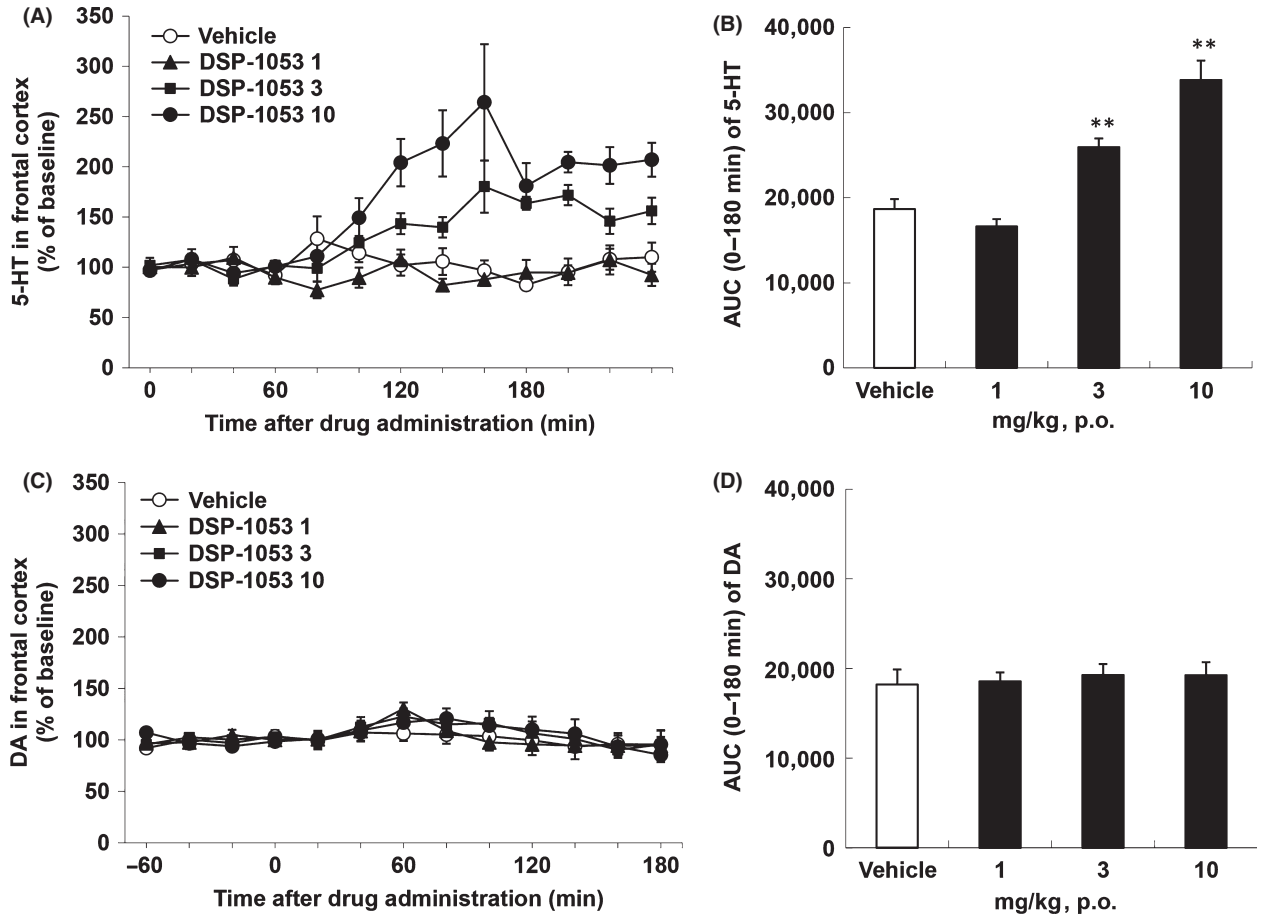

Figure 3. Effects of DSP-1053 on 5-HT and dopamine levels in rat frontal cortex. (A and C) Time-course changes in 5-HT and dopamine (DA) levels in the rat frontal cortex after DSP-1053 p.o. administration. Each point with a vertical bar represents the mean ± SEM of percentage baseline value. (B and D) Effects of DSP-1053 on extracellular 5-HT and DA levels in the rat frontal cortex. Each column with vertical bar represents the mean ± SEM of AUC of 5-HT or DA percent over 3 h. $^{**}P < 0.01$, compared to the vehicle-treated group using parametric Dunnett's multiple comparison test. Vehicle group, $n = 6$; DSP-1053 1 and 3 mg kg^{-1} groups, $n = 4$; and DSP-1053 10 mg kg^{-1}, $n = 3$.

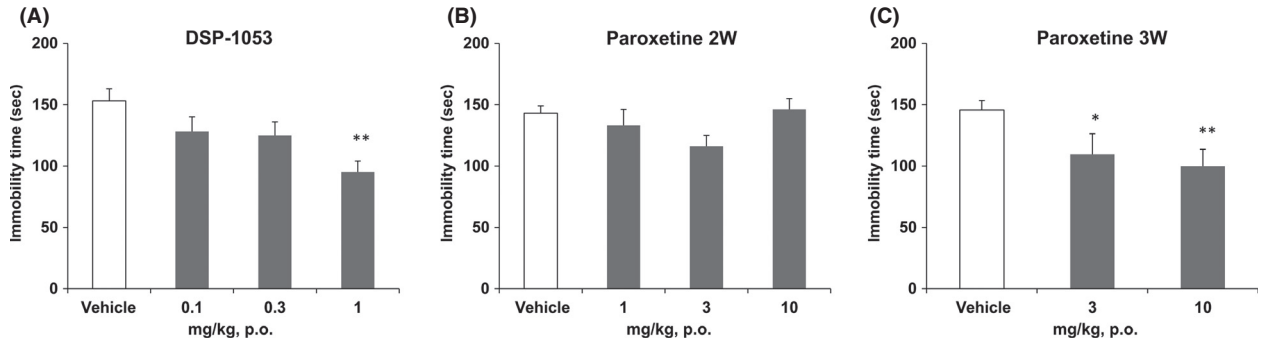

Figure 4. Effects of DSP-1053(A) and paroxetine (B and C) on immobility time in the forced swimming test in rat. Each bar represents the mean ± SEM of immobility time during a 5 min test session ($n = 16$–18 per group). $^{*}P < 0.05$, $^{**}P < 0.01$, compared to the vehicle-treated group using parametric Dunnett's multiple comparison test.

significant main effect for drug × surgery interaction, $F(7, 71) = 2.97$, $P < 0.05$. *Post hoc* test analysis showed that in olfactory bulbectomized animals, paroxetine (10 mg/kg) produced a significant decrease in the number of line crosses, $F(3, 35) = 2.92$, $P < 0.05$, and no effect in the sham-operated animals, $F(3, 36) = 2.58$, $P > 0.05$.

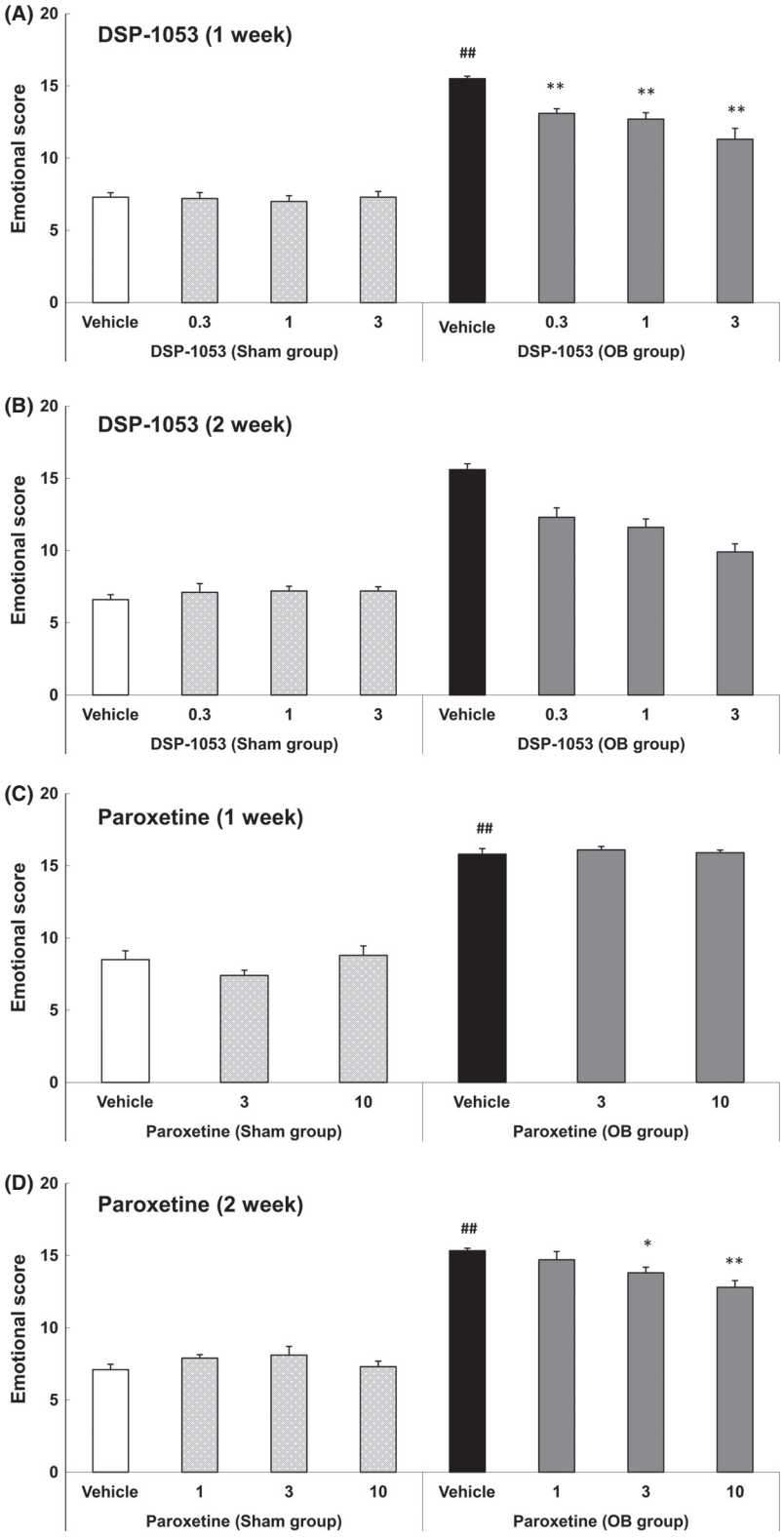

Figure 5. Effects of DSP-1053 (A and B) and paroxetine (C and D) on emotional score in sham-operated and olfactory bulbectomized (OB) rats. Each bar represents the mean ± SEM (n = 9–10 per group). $^{\#\#}P < 0.01$ OB group versus sham-operated group (t-test with two-sided significance of 5%). $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle-treated subgroup in OB group (parametric Dunnett's multiple comparison test with two-sided significance of 5%).

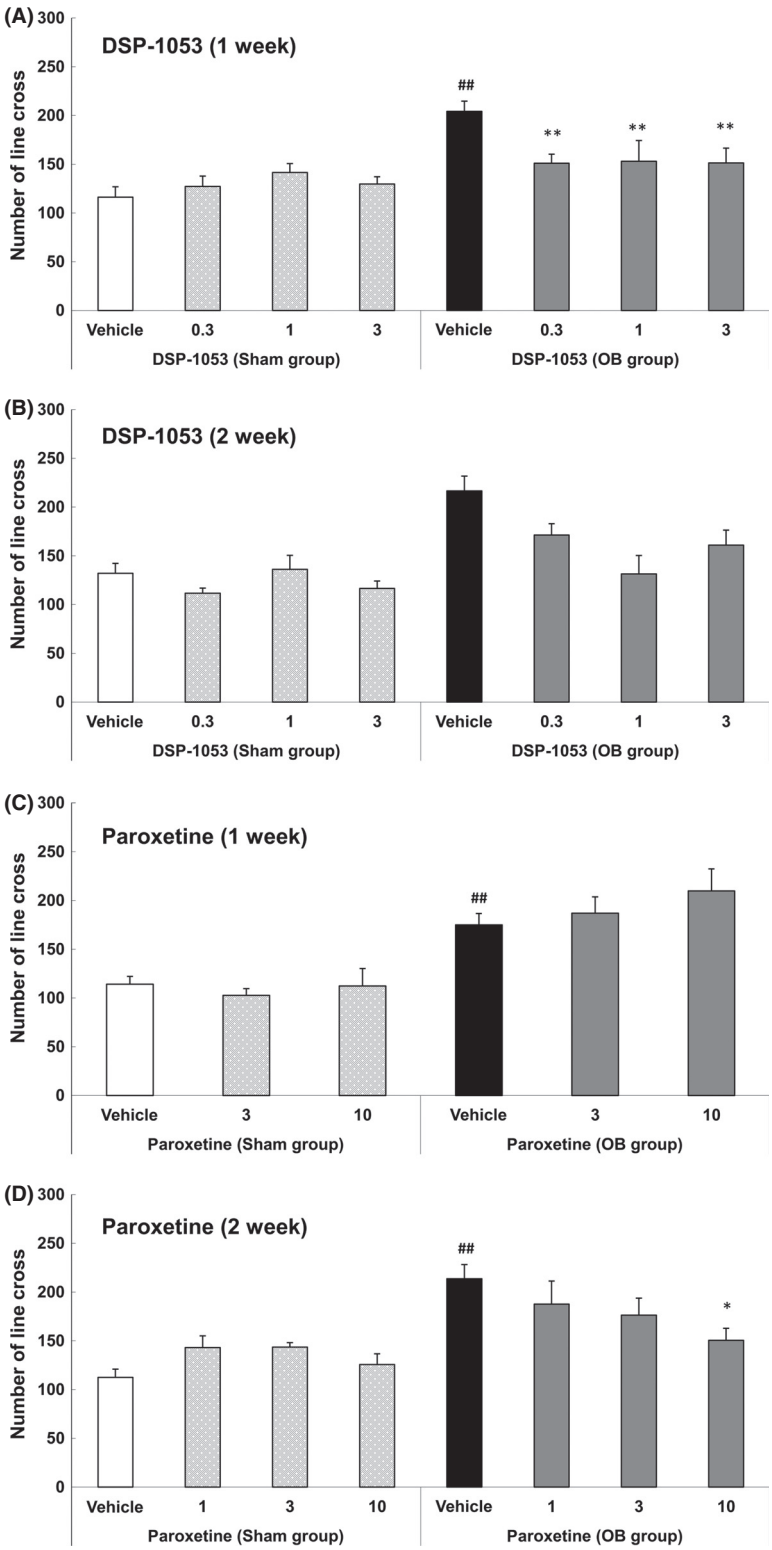

Figure 6. Effects of DSP-1053 (A and B) and paroxetine (C and D) on the number of line crosses in sham-operated and OB rats. Each bar represents the mean ± SEM (n = 9–10 per group). $^{\#\#}P < 0.01$ OB group versus sham-operated group with vehicle treatment (t-test with two-sided significance of 5%). $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle-treated subgroup in OB group (parametric Dunnett's multiple comparison test with two-sided significance of 5%).

DSP-1053 potential to induce emesis in rats conditioned taste aversion test

On Day 4, DSP-1053 (100 mg kg^{-1}) significantly inhibited saccharin consumption 24 h after administration compared to the vehicle, $F(2, 15) = 4.73$, $P < 0.05$ (Fig. 7A). Saccharine intake ratio was significantly inhibited at the doses of 60 and 100 mg kg^{-1}, $F(2, 15) = 22.77$, $P < 0.05$ (Fig. 7B).

DSP-1053 potential to induce emesis in *Suncus murinus*

In experiment 1, DSP-1053 at the dose of 10, 30, or 60 mg kg^{-1} induced emesis in 0, 1, or 3 of 6 animals, respectively, whereas, as shown in Table 4, paroxetine at 10, 30, or 60 mg kg^{-1} induced emesis in 0, 2, or 6 of 6 animals, respectively (Mine et al. 2013). In experiment 2, both DSP-1053 (60 mg kg^{-1}) and paroxetine (60 mg kg^{-1}) induced emesis in 9 and 12 of 19 animals, respectively. Figure 8 shows the incidence of vomiting and the number of vomiting episodes during a 60-min period in each day of a 7-day consecutive administration of DSP-1053 or paroxetine. A significant reduction in the number of vomiting episodes was observed from Day 2 in DSP-1053-treated group, $F(6, 56) = 5.60$, $P < 0.05$. On the other hand, repeated administration of paroxetine did not have significant effect on the number of vomiting episodes throughout the 7-day administration period, $F(6, 77) = 1.64$, $P > 0.05$.

Discussion

In this study, we evaluated the in vitro and in vivo profile of DSP-1053, a structurally novel 5-HT reuptake inhibitor with 5-HT_{1A} partial agonistic activity. Our results show that DSP-1053 exhibits a potent fast antidepressant-like effect with minimal undesirable effects in animal models.

Our in vitro experiments demonstrate that DSP-1053 works as a serotonin reuptake inhibitor with relatively high partial agonistic activity for 5-HT_{1A} receptor (70.0 ± 6.3%). It is well reported that SSRIs enhancement of 5-HT neurotransmission is dampened by activation of somatodendritic or postsynaptic 5-HT_{1A} receptors (Artigas et al. 1996; Casanovas et al. 1999). However, acute increase in 5-HT levels in the rat frontal cortex has also been achieved when antidepressants are used in combination with pindolol, a weak 5-HT_{1A} receptor partial agonist or WAY-100635, a 5-HT_{1A} receptor antagonist (Pauwels et al. 1997; Watson et al. 2000; Jerning et al. 2002; Papp et al. 2006; Hughes et al. 2007). On the other hand, acute treatment with DSP-1053, which has a relatively high 5-HT_{1A} partial agonistic activity, enhanced 5-HT neurotransmission in the rat prefrontal cortex without affecting dopamine neurotransmission. It has been suggested that stimulation of 5-HT_{1A} receptors enhances dopamine neurotransmission via activation of presynaptic 5-HT_{1A} receptors expressed in the ventral tegmental area (Lejeune et al. 1997; Millan et al. 1997). This indicates that DSP-1053 may act as antagonist for presynaptic 5-HT_{1A} receptors. On the other hand, the prolonged stimulation of 5-HT neurotransmission that occurs during chronic SSRI treatment has been reported to desensitize raphe 5-HT_{1A} autoreceptors, as assessed by single unit recordings and brain microdialysis (Blier and de Montigny 1994; Invernizzi et al. 1994; Arborelius et al. 1995; Le Poul et al. 1995). These findings suggest that DSP-1053 acute enhancement of 5-HT release may be attributed to early desensitization of 5-HT_{1A} receptors.

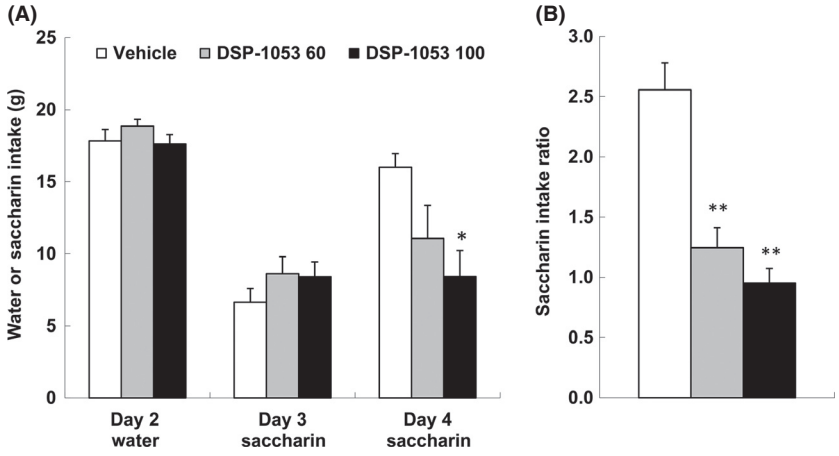

Figure 7. Effect of DSP-1053 on saccharin consumption in rat conditioned taste aversion test. (A) Each bar represents the mean ± SEM of water or saccharin consumption (g) on each day ($n = 6$). (B) Each bar represents the mean ± SEM of saccharin consumption ratio of day 4/day 3. *$P < 0.05$, **$P < 0.01$, compared with the vehicle-treated group using Tukey's test.

Table 4. Incidence of vomiting and total emetic episode.

Drugs	Dose (mg kg^{-1}, po)	Number of animals vomited/tested	Total emetic episode
Vehicle	–	0/6	–
DSP-1053	10	0/6	–
	30	1/6	2
	60	3/6	5.3 ± 1.0
Paroxetine[1]	10	0/6	–
	30	2/6	6.8
	60	6/6*	6.7 ± 0.5

Incidence of vomiting is shown as the number of shrews that vomited/the number of shrews tested. Total emetic episodes during the 1 h observation period were calculated for animals that vomited and expressed as mean ± SEM.

[1]Mine et al. 2013.

*$P < 0.01$ versus vehicle treatment, as analyzed by Fisher's exact test.

Like DSP-1053, vilazodone, and vortioxetine, which inhibit the serotonin transporter with 5-HT_{1A} partial or full agonistic activity, have been reported to enhance 5-HT neurotransmission by acute treatment (Hughes et al. 2005; Pehrson et al. 2013). Although further studies are needed to clarify the exact contribution of 5-HT_{1A} partial activation in DSP-1053 beneficial effects, evidence highlighting the involvement of this receptor in antidepressants early onset suggests that both inhibition and activation of 5-HT_{1A} receptors would fasten SSRI efficacy.

In the rat forced swimming test, which is the most commonly used behavioral test to assess potential antidepressants efficacy (see reviews, e.g., Cryan and Mombereau 2004; Pollak et al. 2004), DSP-1053 decreased rats immobility time after 2 weeks treatment, whereas treatment with paroxetine, a representative SSRI, required 3 weeks for comparable efficacy. These results indicate that DSP-1053 would have earlier onset of efficacy than SSRIs. Next, we evaluated the efficacy and onset of DSP-1053 in the rat olfactory bulbectomy model. The rat olfactory bulbectomy model is a suitable tool for investigating antidepressants onset, because olfactory bulbectomy-induced behavioral abnormalities can be reversed by chronic, but not acute, antidepressants treatment (Kelly et al. 1997; Roche et al. 2007, 2008). As shown in Figures 5, 6, DSP-1053 exerted significant antidepressant-like effects after 1-week administration, whereas paroxetine required 2-week treatment to show similar efficacy. This indicates that DSP-1053 has early onset of action compared to paroxetine. On the other hand, DSP-1053 improvement of hyperemotional behavior may reflect an anxiolytic-like effect as rats muricidal behavior has been reported to be improved by anxiolytics (Takaoka et al. 1988). In the rat forced swimming test and olfactory bulbectomy model, DSP-1053 showed efficacy at a lower dose range than the doses that increased 5-HT level in the rat frontal cortex. The following two reasons might explain this discrepancy. One major difference between the olfactory bulbectomy test and rat microdialysis is the duration of drug administration. That is, chronic treatment with DSP-1053 is considered to induce further desensitization of 5-HT_{1A} receptors and enhancement of 5-HT neurotransmission compared to single administration. As for the second reason, it is believed that activation of postsynaptic 5-HT_{1A} receptors contributes to DSP-1053 low dose antidepressant-like effect. This

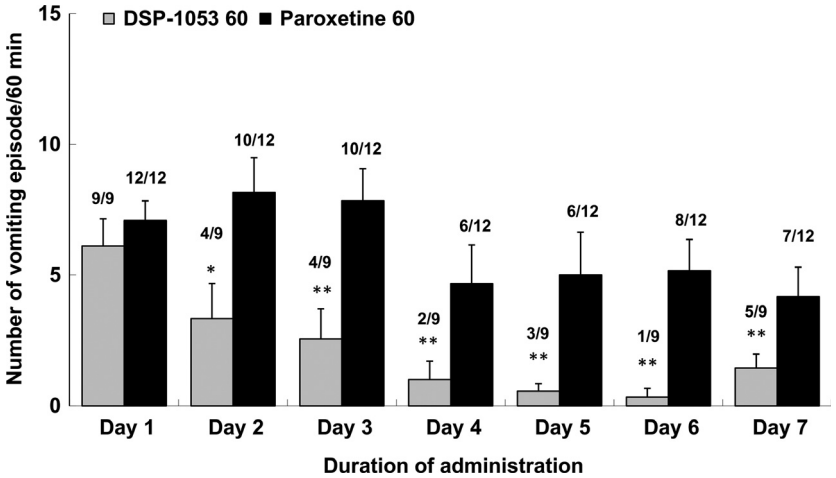

Figure 8. Effects of 7-day treatment with DSP-1053 or paroxetine on the number of vomiting episodes in *Suncus murinus*. Each column represents the mean ± SEM of the number of emetic episodes. The number above each column represents the incidence of vomiting as the number of animals that vomited/the number of animals tested. *$P < 0.05$, **$P < 0.01$, significantly different from the number of vomiting episodes observed in Day 1 using Dunnett's multiple comparison test.

hypothesis may be supported by evidence showing that postsynaptic 5-HT_{1A} receptors are particularly important in antidepressant response (Blier and Ward 2003). However, further investigation of changes in neurotransmission after chronic administration of DSP-1053 as well as evaluation of DSP-1053 effects at the efficacy pre and postsynaptic regions would be necessary to confirm the above hypothesis.

Next, we investigated DSP-1053 potential for inducing emesis in experimental animals, because emesis is one of the common side effects of SSRIs (Brambilla et al. 2005; Gelenberg et al. 2010). As emesis is uncommon in rodents, we used the conditioned taste aversion test, which is recognized as a highly reliable tool for evaluation of behavioral alterations induced by radiation or other environmental agents that cause emesis and nausea (Rabin and Hunt 1986). DSP-1053 significantly inhibited saccharin consumption compared to vehicle treatment, indicating this compound potential for nausea or feeling of vomiting. On Day 3, the lower saccharine consumption was observed in vehicle-treated rats than Day 2. This phenomenon was also reported in previous study (Hatcher et al. 1998). Although the reason of this lower saccharine intake is not clear, the first experiment for new taste might defeat the appetite for water. In addition, we used shrews (*S. murinus)* which can positively respond to various emetic stimuli including motion, X-radiation, and emetogenic substances such as cisplatin and SSRI (Matsuki et al. 1992; Okada et al. 1995; Mine et al. 2013) to further evaluate DSP-1053 potential for emesis. As a result, single administration of DSP-1053-induced emesis in a dose-dependent manner, suggesting that acute treatment with DSP-1053 can produce emesis. This undesirable effect may be due to acute increase in 5-HT level following inhibition of serotonin transporter. On the other hand, the number of vomiting episodes decreased following multiple dosing with DSP-1053, but not paroxetine. This finding indicates that repeated treatment with DSP-1053 results in a fast adaptation to the feeling of nausea and therefore reduction in emetic episodes. It has been reported that enhancement of 5-HT_{1A} receptors activation can reduce vomiting and nausea in animals (Wolff and Leander 1997; Rock et al. 2014). This beneficial effect is believed to be trigged by attenuation of 5-HT neurotransmission following somatodendritic 5-HT_{1A} receptors activation. On the other hand, DSP-1053 enhanced 5-HT neurotransmission in rat microdialysis, indicating fast desensitization of the serotonergic system play an important role in the fast adaptation to the feeling of nausea and therefore emesis. It is reported that SSRI-induced nausea typically ceases as treatment continues (Peretti et al., 2000). Although the precise mechanism of SSRI-induced nausea is still unclear, 5-HT_3 receptors in the chemoreceptor trigger zone are considered to have an important role, as 5-HT_3 antagonists, including cisapride and ondansetron, are reported to reduce SSRI-induced gastrointestinal side effects (Bergeron and Blier 1994). In addition, HTR3B gene polymorphisms are considered as significant predictors of paroxetine-induced nausea (Sugai et al. 2006). Moreover, chronic activation of ionotropic 5-HT_3 receptors is believed to produce significant desensitization of 5-HT_3 receptors (see review, e.g., Jackson and Yakel 1995). Taken together, these findings indicate that DSP-1053 fast onset enhancement of 5-HT neurotransmission induces fast desensitization of 5-HT_3 receptors, resulting in fast adaptation to the feeling of nausea and emesis. However, further work is needed to confirm this hypothesis.

In conclusion, this study shows that DSP-1053, a novel serotonin reuptake inhibitor with 5-HT_{1A} receptor partial agonistic activity, shows fast antidepressant-like effect and fast adaptation to the feeling of nausea and emesis in rodent and shrew models. These results highlight the important role of 5-HT_{1A} receptors in both the efficacy and tolerability of DSP-1053 as a new therapeutic option for the treatment of depression.

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Author Contribution

T. K. and K. Y. participated in research design and wrote or contributed to the writing of the manuscript. T. K., Y. M., M. Y., K. M., S. B, K. N, H. M., and H. N. conducted the experiments. T. K., M. Y., K. M., and S. B. performed data analysis.

Disclosures

All authors are employees of Sumitomo Dainippon Pharma Co., Ltd.

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