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Pharmacological profile of YM348, a novel, potent and orally active 5-HT_{2C} receptor agonist

Yasuharu Kimura[a,*], Ken-ichi Hatanaka[a], Yuki Naitou[a], Kyoichi Maeno[b], Itsuro Shimada[b], Akiko Koakutsu[a], Fumikazu Wanibuchi[a], Tokio Yamaguchi[a]

[a] *Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan*
[b] *Chemistry Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan*

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Abstract

YM348, (*S*)-2-(7-ethyl-1*H*-furo[2,3-g]indazol-1-yl)-1-methylethylamine, showed a high affinity for cloned human 5-HT_{2C} receptors (K_i: 0.89 nM). The functional selectivity for 5-HT_{2C} receptors in the 5-HT_2 receptor family was the highest among 5-HT_{2C} receptor agonists, including *m*-chlorophenylpiperazine (mCPP) and Ro60-0175 ((*S*)-2-(6-chloro-5-fluoroindol-1-yl)-1-methylethylamine). Oral administration of YM348 induced penile erections and hypolocomotion in rats, being completely inhibited by a selective 5-HT_{2C} receptor antagonist, SB242084 (6-chloro-5-methyl-1-[6-(2-methylpyridin-3-yloxy) pyridin-3-yl carbamoyl] indoline). The dose–response curve for penile erections, unlike that for hypolocomotion, was an inverted U-shape in the dose range of 0.0677–2.03 mg/kg. A selective 5-HT_{2A} receptor antagonist, MDL100907 (*R*(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol), and a selective 5-HT_{2B} receptor antagonist, RS-127445 (2-amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine), had no effect on the decline in penile erection frequency at 2.03 mg/kg of YM348. YM348 did not affect blood pressure at 2.03 mg/kg. In conclusion, YM348 is a novel, potent and orally active 5-HT_{2C} receptor agonist, and neither the activation of 5-HT_{2A} or 5-HT_{2B} receptors nor a cardiovascular effect is likely to contribute to the inverted U-shape dose–response curve for penile erections.
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Keywords: 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{2C} receptor; Penile erection; Hypolocomotion; mCPP (*m*-chlorophenylpiperazine); Ro60-0175; SB242084; MDL100907; RS-127445

1. Introduction

5-Hydroxytryptamine (5-HT) has been implicated in a variety of physiological functions through various 5-HT receptors. At present, there are at least 14 different subtypes of 5-HT receptors, which are encoded by distinct genes. In the structural homology, pharmacology, and signal transduction system, they are classified into seven families (Barnes and Sharp, 1999). A 5-HT_2 receptor family consists of three subtypes termed 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, which are coupled to phospholipase C.

5-HT_{2C} receptors are unique in the 5-HT_2 receptor family because they are expressed little in most peripheral tissues (Ullmer et al., 1995). 5-HT_{2C} receptors are not only present at very high levels in choloid plexus, but they also occur in various other brain regions, such as hippocampus, cerebral cortex, striatum, hypothalamus and spinal cord (Abramowski et al., 1995). Activation of 5-HT_{2C} receptors has been reported to mediate various effects, including hypophagia, hypolocomotion, hyperthermia and the induction of penile erections (Kahn and Wetzler, 1991; Kennett, 1993).

Interestingly, in contrast to hypolocomotion, hypophagia and hyperthermia, the dose–response curve for penile erections has been reported to be an inverted U-shape (Martin et al., 1998; Lucki et al., 1989; Higgins et al., 2001; Klodzinska and Chojnacka-Wojcik, 1992; Berendsen et al., 1990; Millan et al., 1997). The cause remains unclear, however, because of a lack of selective 5-HT_{2C} receptor agonists and detailed investigations.

* Corresponding author. Tel.: +81-298-63-6510; fax: +81-298-56-2515.
E-mail address: kimura_y@yamanouchi.co.jp (Y. Kimura).

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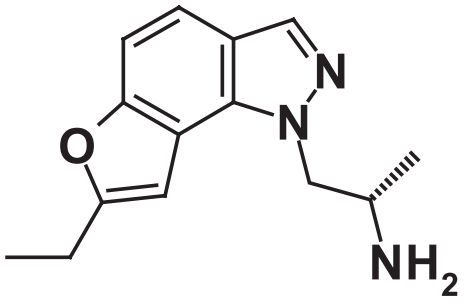

Fig. 1. Structure of YM348.

In an effort to discover a novel 5-HT_{2C} receptor agonist, we have found YM348 ((*S*)-2-(7-ethyl-1*H*-furo[2,3-*g*]indazol-1-yl)-1-methylethylamine), a novel, potent and orally active 5-HT_{2C} receptor agonist which is shown in Fig. 1. The present study provides the pharmacological profiles of YM348 and a further characterization of a 5-HT_{2C} receptor-mediated response, penile erection.

2. Materials and methods

2.1. Receptor binding assay

Experiments were performed with membranes obtained from Chinese Hamster Ovary (CHO) cells expressing human 5-HT_{2C} or 5-HT_{2A} receptors and Human Embryonic Kidney 293–Epstein–Barr virus nuclear antigen (HEK293–EBNA) cells expressing human 5-HT_{2B} receptors. Binding assays with [^{3}H] 5-HT were carried out by the method of Pazos et al. (1985) with slight modifications. The reaction medium (50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$, 10 M pargyline and 0.1 mg/ml L-(+)-ascorbic acid) containing [^{3}H] 5-HT, membrane preparation and test compounds were incubated at 37 °C for 30 min. Nonspecific binding was determined in the presence of 10 M 5-HT, and specific binding was calculated as the total binding minus the nonspecific binding. After incubation, 4 ml of 50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$ was added, and the medium was filtrated under decompression through a Whatman GF/B glass filter pretreated with 0.1% polyethyleneimine. The filter was washed with the same buffer solution (4 ml × 3). The glass filter was immersed in 6 ml of liquid scintillator (Packard, Aquasol-2), and the radioactivity was measured with a liquid scintillation counter (Packard, Tri-Carb-2500TR). The amount of protein was measured according to the method of Lowry et al. (1951). The dissociation constants (K_d values) were obtained by Scatchard analysis using SAS (ver. 6.11) (5-HT_{2C}: 1.6 nM, 5-HT_{2A}: 9.8 nM and 5-HT_{2B}: 14 nM). The concentrations of compounds showing 50% inhibition of receptor binding, IC_{50} values, were obtained by nonlinear analysis using SAS (ver. 6.11). The K_i values indicating affinity for receptors were calculated using a formula of Cheng and Prussoff (1973).

We also performed binding assays for 46 different neurotransmitter binding sites including several other 5-HT receptor subtypes (1A, 1B, 1D, 3, 4, 5A, 6, 7) at a single concentration of 1 μM. In the assays where the compound displaced more than 50% of the specific binding, the compound was retested at multiple concentrations to estimate K_i values: [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) binding to human 5-HT_{1A} receptors (Peroutka, 1986), [^{3}H] 5-carboxamidotryptamine (5-CT) binding to bovine 5-HT_{1D} receptors (Waeber et al., 1988), [^{3}H]-lysergic acid diethylamide (LSD) binding to human 5-HT_7 receptors (Shen et al., 1993), and [^{3}H]rauwolscine binding to human α_{2A} receptors (Bylund et al., 1988) with minor modifications.

2.2. Phosphatidylinositol hydrolysis

Phosphatidylinositol hydrolysis assay was conducted by the methods of Aramori and Nakanishi (1992) with slight modifications. CHO cells expressing human 5-HT_{2C} or 5-HT_{2A} receptors and HEK 293-EBNA cells expressing 5-HT_{2B} receptors were seeded onto a 24-well plate (approximately 1×10^5 cells/well), and cultured for 1 day. After the addition of myo-[^{3}H] inositol (3 Ci/ml), they were incubated for 24 h for labeling. After the cells were washed two times with phosphate-buffered saline (PBS), they were incubated with PBS for 20 min, and then further incubated with PBS–LiCl solution for 20 min. After 20-min incubation with PBS–LiCl solution containing the test compound, the reaction was terminated by adding 0.2 M perchloric acid, and the reaction mixture was stood at 4 °C for 1 to 3 h. After the addition of 2 N KOH and 100 mM EDTA–2Na solution, the plate was centrifuged (2000 rpm, 5 min). The supernatant (1 ml) was added to a Bio-Rad AG1-X8 column, and washed with GPI solution (5 mM disodium tetraborate, 60 mM sodium formate) (3.5 ml × 2), and eluted with 4 ml of inositol 1,4,5-triphosphate (IP_3) solution (0.1 M formate, 1 M ammonium formate). The elution was added to a liquid scintillator (Aquasol-2), and measured with a liquid scintillation counter. The EC_{50} values and E_{max} (%) were calculated by nonlinear analysis with SAS (ver.6.11). The E_{max} (%) indicated intrinsic activity, and the response produced by 10 M 5-HT was defined as 100%.

2.3. Animal and maintenance conditions

Male Wistar rats (215–350 g; Japan SLC) were used. The animals were cared for under standard maintenance conditions (lights on 0730–2030 h, 23 ± 2 °C, 55 ± 10% relative humidity) and allowed free access to laboratory chow and tap water in the home cage. All testing was done

during the lights on portion of the day–night cycle. All animal procedures were approved by the Animal Ethical Committee of Yamanouchi Pharmaceutical Co., Ltd.

2.4. Penile erection test

The rats were placed individually in transparent acrylic plastic cages (7.5 × 18 × 30 cm) for counting of the number of penile erections. A penile erection is defined as previously described (Berendsen et al., 1990): repeated pelvic thrusts immediately followed by an upright position on the hind limbs, an emerging, engorged penis and licking of the penis. The number of penile erections was observed for 60 min immediately after oral administration of YM348. SB242084 (6-chloro-5-methyl-1-[6-(2-methyl-pyridin-3-yloxy) pyridin-3-yl carbamoyl] indoline) (0.1–3 mg/kg i.p.), MDL100907 (*R*(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol) (0.1 mg/kg s.c.) and RS-127445 (2-amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine) (10 mg/kg i.p.) were administered 30 min before YM348 treatment. The doses, routs and pretreatment times employed for SB242084, MDL100907 and RS-127445 were determined based on published work on these compounds (Kennett et al., 1997; Vickers et al., 2001; Higgins et al., 2001; Bonhaus et al., 1999a,b).

2.5. Hypolocomotion

Rats were administered YM348 orally and moved again to their home cages. After 20 min, thereafter, the rats were individually placed in transparent acrylic plastic cages (35 × 30 × 18 cm), and their motor activity was measured for 40 min. The measurements were carried out using a SUPER-MEX sensor (Muromachi Kikai). SB242084 (0.1–3 mg/kg i.p.) was administered 30 min before YM348 treatment.

2.6. Wet-dog shake

Wet-dog shake was observed in a transparent acrylic plastic cage (diameter 25 cm, depth 22 cm). SB242084 (3 mg/kg i.p.) was administered 20 min prior to YM348 treatment. YM348 (2.03 mg/kg) was administered orally 10 min before the test. The number of wet-dog shakes was recorded over a 50-min period.

2.7. Cardiovascular effect

The rats were anesthetized with pentobarbital sodium (60 mg/kg i.p.), and a catheter was inserted into the carotid artery to measure the systemic arterial pressure. The rats were used in the study after a postoperative recovery period of two or more days.

After conscious animals were housed in cages for blood pressure measurement and stabilized for at least 30 min, YM348 was administrated orally at 2.03–20.3 mg/kg. Changes in blood pressure were observed for 90 min after YM348 administration.

2.8. Drugs and solution

YM348, Ro60-0175, SB242084, MDL100907 and RS-127445 were synthesized in our laboratories. In the present study, YM348 monofumarate was used as YM348. *m*-chlorophenylpiperazine (mCPP) hydrochloride was purchased from Tocris Cookson. 5-HT creatinine sulfate was purchased from Sigma. Other materials were obtained commercially in a special grade. For the in vitro experiments, all compounds were initially dissolved in dimethylsulphoxide (DMSO) to give a 10^{-2} M solution and diluted with assay buffer. For the in vivo experiments, YM348 was dissolved in distilled water. SB242084 was suspended in 0.5% methyl cellulose/saline. MDL100907 solution was prepared with 1% Tween 80/saline. RS-127445 was prepared with 5% DMSO and 5% cremophor® EL/saline. Injection volumes of 5 ml/kg were used for all administrations. All doses were expressed in terms of the free form.

2.9. Statistics

In the penile erection test and the wet-dog shake test, the results were expressed as the means ± S.E.M. of the number of penile erections and wet-dog shakes for each group of animals, respectively. In the hypolocomotion test, the results were expressed as the means ± S.E.M. of the counts of locomotion for each group of animals. Statistical analysis was performed with Student's *t*-test and Dunnett's test. With respect to the cardiovascular effects, in cases in which significant differences were observed in the interaction by Two-way repeated measurement analysis of valiance (ANOVA), statistical analysis was performed followed by Dunnett's test to compare the differences between the control group and the administration group at each point in time.

3. Results

3.1. Receptor binding profile

YM348 had high affinity for cloned human 5-HT_{2C} receptors with a K_i value of 0.89 nM and lower affinities

Table 1
Affinities of YM348, mCPP, Ro60-0175 and 5-HT for cloned human 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors

Agonists	K_i (nM)			Ratio of K_i (2A/2C)	Ratio of K_i (2B/2C)
	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}		
YM348	0.89 ± 0.05	13 ± 2	2.5 ± 0.5	15	2.8
mCPP	16 ± 1	85 ± 20	40 ± 9	5.3	2.5
Ro60-0175	19 ± 2	24 ± 6	2.4 ± 0.1	1.3	0.13
5-HT	2.4 ± 0.2	21 ± 8	19 ± 5	8.8	7.9

Table 2
Agonistic activity of YM348, mCPP and Ro60-0175 for cloned human 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors

Agonists	5-HT_{2C}		5-HT_{2A}		5-HT_{2B}		Ratio of EC_{50} (2A/2C)	Ratio of EC_{50} (2B/2C)
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)		
YM348	1.0 ± 0.2	76 ± 1	93 ± 10	97 ± 2	3.2 ± 3	110 ± 10	93	3.2
mCPP	120 ± 10	63 ± 3	150 ± 20	18 ± 2	93 ± 50	21 ± 9	1.3	0.78
Ro60-0175	52 ± 3	88 ± 20	400 ± 20	91 ± 5	2.4 ± 1	130 ± 30	7.7	0.05
5-HT	24 ± 4	100 ± 5	70 ± 8	100 ± 0.3	5.8 ± 1	97 ± 3	2.9	0.24

for human-cloned 5-HT_{2B} (K_i: 2.5 nM) and 5-HT_{2A} receptors (K_i: 13 nM), as shown in Table 1. The K_i values of mCPP and Ro60-0175 for the cloned human 5-HT_{2C} receptors were 16 and 19 nM, respectively. The affinity of mCPP for human 5-HT_{2C} receptors was higher than those for human cloned 5-HT_{2B} (K_i: 40 nM) and 5-HT_{2A} receptors (K_i: 85 nM). The affinity of Ro60-0175 for human 5-HT_{2C} receptors was lower than that for human 5-HT_{2B} receptors (K_i: 2.4 nM) and almost equivalent to that for human 5-HT_{2A} receptors (K_i: 24 nM). To assess the binding specificity of YM348, we performed a broad evaluation of an additional 46 binding sites including several other 5-HT receptor subtypes (1A, 1B, 1D, 3, 4, 5A, 6, 7). IC_{50} values of YM348 were found to be >1 μM for all of the binding sites except for the human 5-HT_{1A} receptors (K_i: 130 nM), bovine 5-HT_{1D} receptors (K_i: 481 nM), human 5-HT_7 receptors (K_i: 177 nM), and human α_{2A} receptors (K_i: 126 nM).

3.2. Phosphatidylinositol hydrolysis assay

YM348 exhibited a concentration-related increase in IP_3 formation that achieved a maximal effect on human 5-HT_{2C}

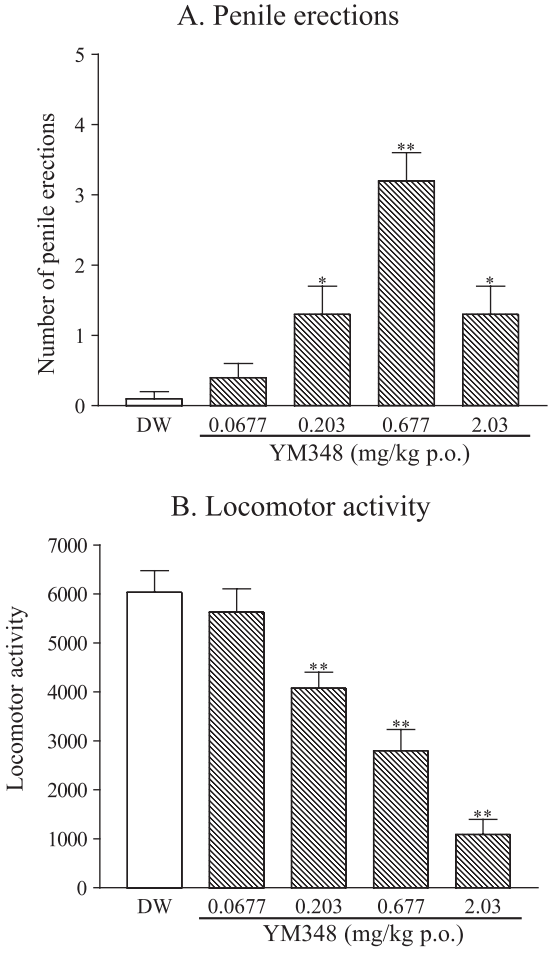

Fig. 2. Effects of YM348 on penile erections (A) and hypolocomotion (B) in rats. All columns represent the means ± S.E.M., $n = 8–12$ per group. Significantly different from the DW group, $^{*}p < 0.05$, $^{**}p < 0.01$ by Dunnett's test. DW = distilled water.

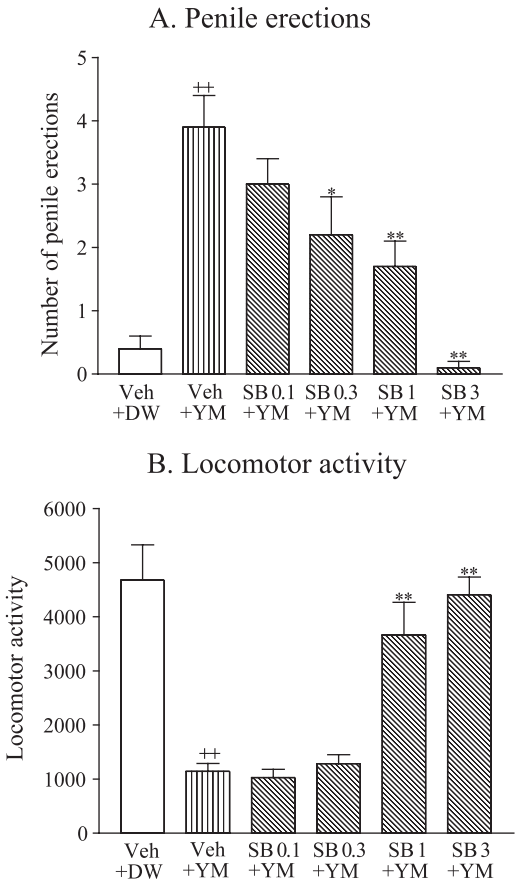

Fig. 3. Effects of a selective 5-HT_{2C} receptor antagonist, SB 242084, on YM348-induced penile erections (A) and hypolocomotion (B) in rats. 0.677 and 2.03 mg/kg of YM348 were used in (A) and (B), respectively. All columns represent the means ± S.E.M., $n = 8–10$ per group. Significantly different from the (Veh + DW)-treated group, $^{++}p < 0.01$ by Student's *t*-test and from the (Veh + YM348)-treated group, $^{*}p < 0.05$, $^{**}p < 0.01$ by Dunnett's test. DW = distilled water, Veh = vehicle, SB = SB 242084 (mg/kg i.p.), YM = YM348.

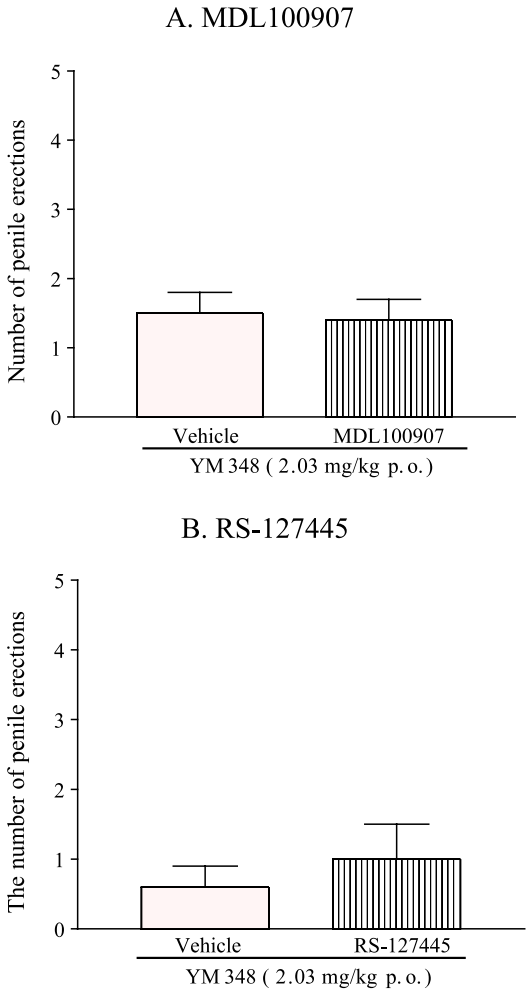

Fig. 4. Effects of a selective 5-HT_{2A} receptor antagonist, MDL100907, (A) and a selective 5-HT_{2B} receptor antagonist, RS-127445, (B) on the decline in penile erection frequency induced by 2.03 mg/kg of YM348. All columns represent the means ± S.E.M., $n = 8$ per group. No significant difference was observed between the (vehicle + YM348)-treated group and the (MDL100907 + YM348)-treated group or the (RS-127445 + YM348)-treated group by Student's *t*-test.

receptors similar to that of 5-HT itself. YM348 also exhibited a full-agonistic activity on human 5-HT_{2A} and 5-HT_{2B} receptors. The EC_{50} values of YM348 for 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors were 1.0, 93 and 3.2 nM, respectively (Table 2). Ro60-0175 showed full-agonistic activity on 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors. Its EC_{50} values for 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors were 52, 400 and 2.4 nM, respectively. mCPP showed partial-agonistic activity on 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors. Its EC_{50} values for 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors were 120, 150 and 93 nM, respectively.

3.3. Penile erection test

Oral administration of YM348 induced penile erections in rats (Fig. 2A). The dose–response curve of YM348 for penile erections was an inverted U-shape in the dose range between 0.0677 and 2.03 mg/kg. The minimum and maximal effective doses of YM348 were 0.203 and 0.677 mg/kg, respectively. A selective 5-HT_{2C} receptor antagonist, SB242084, inhibited the penile erections elicited by the maximal effective dose (0.677 mg/kg) of YM348 in a dose-dependent manner (Fig. 3A). Neither a selective 5-HT_{2A} antagonist, MDL100907, nor a selective 5-HT_{2B} receptor antagonist, RS-127445, recovered the decline in penile erection frequency at 2.03 mg/kg of YM348 (Fig. 4A and B).

3.4. Hypolocomotion

YM348 inhibited spontaneous activity in a dose-dependent manner with a minimum effective dose of 0.203 mg/kg (Fig. 2B). A selective 5-HT_{2C} receptor antagonist, SB242084 inhibited YM348 (2.03 mg/kg p.o.)-induced hypolocomotion in a dose-dependent manner (Fig. 3B).

3.5. Wet-dog shake

YM348 (2.03 mg/kg p.o.) had no effect on wet-dog shake, one of the typical 5-HT_{2A} receptor-mediated behaviors, in the presence of SB242084 (3 mg/kg i.p.): The numbers of wet-dog shakes were 0.5 ± 0.3 and 0.2 ± 0.2 in the (distilled water and SB242084)-treated group and the (YM348 and SB242084)-treated group, respectively ($P > 0.05$, $n = 6$).

3.6. Cardiovascular effect

YM348 had little effect on mean arterial blood pressure (MAP) for 90 min at a dose of 2.03 mg/kg p.o. YM348 increased MAP slightly and dramatically at doses of 6.77 and 20.3 mg/kg p.o., respectively (Fig. 5). The between-subjects and within-subjects effects and interaction differed significantly with two-way repeated measurement ANOVA.

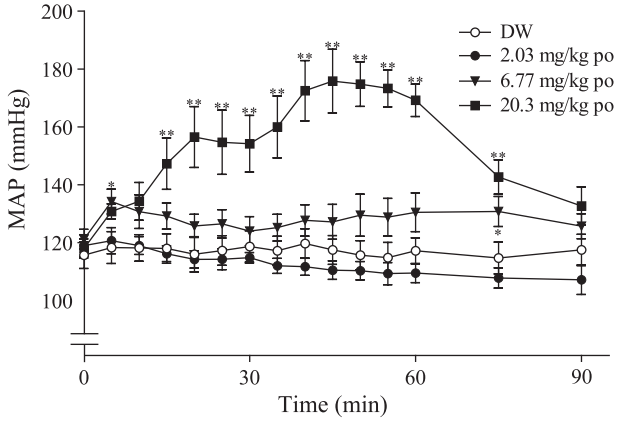

Fig. 5. Effect of YM348 on mean arterial blood pressure (MAP) in rats. All points represent the means ± S.E.M., $n = 6$ per group. Significant difference from the DW group, $^{*}p < 0.05$, $^{**}p < 0.01$ (two-way repeated measurement ANOVA followed by Dunnett's test). DW = distilled water.

4. Discussion

Receptor binding studies (Table 1) demonstrated that YM348 had a high affinity for 5-HT_{2C} receptors which was 15 and 3 times higher than those for cloned human 5-HT_{2A} and 5-HT_{2B} receptors, respectively, and at least 100-fold selectivity over 46 different neurotransmitter binding sites including several other 5-HT receptor subtypes (1A, 1B, 1D, 3, 4, 5A, 6, 7).

In studies of phosphatidylinositol hydrolysis (Table 2), the potency of YM348 for 5-HT_{2C} receptors was 93 and 3 times higher than those for 5-HT_{2A} and 5-HT_{2B} receptors, respectively. The functional selectivity of YM348 for 5-HT_{2C} receptors in the 5-HT_2 receptor family was the highest among 5-HT_{2C} receptor agonists, including mCPP and Ro60-0175.

Oral administration of YM348 induced penile erections and hypolocomotion in rats (Fig. 2A and B), as did other 5-HT_{2C} receptor agonists (Berendsen et al., 1990; Millan et al., 1997). These effects were completely inhibited by a selective 5-HT_{2C} receptor antagonist, SB242084 (Fig. 3A and B). These results suggest that YM348 is a potent and orally active 5-HT_{2C} receptor agonist.

Interestingly, YM348 showed quite different dose–response curves for penile erections and hypolocomotion in the dose range between 0.0677 and 2.03 mg/kg p.o. (Fig. 2A and B), as did other nonselective 5-HT_{2C} receptor agonists (Berendsen et al., 1990; Millan et al., 1997), in spite of the highly functional selectivity of YM348 for 5-HT_{2C} receptors. While the dose–response curve for hypolocomotion was a sigmoid, that for penile erections was an inverted U-shape; the penile erection frequency declined at 2.03 mg/kg p.o. Several possibilities are considered as causes of the decline in penile erection frequency. One possibility is 5-HT_{2A} receptor activation, since it is reported that 5-HT_{2A} agonistic properties prevented or counteracted penile erections induced by 5-HT_{2C} receptor activation. (±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI), which has a similar affinity for 5-HT_{2A} and 5-HT_{2C} receptors, is reported to induce penile erections in the presence of 5-HT_{2A} receptor antagonist but not alone (Bagdy et al., 1992; Berendsen et al., 1990). Berendsen et al. (1990) also reported that DOI showed an inhibitory effect on mCPP-induced penile erections. We cannot explain the decline of penile erection frequency at 2.03 mg/kg of YM348, however, in the context of the reported effect of DOI on 5-HT_{2A} receptors. Unlike DOI, YM348 showed excellent functional selectivity for 5-HT_{2C} receptors over 5-HT_{2A} receptors in the in vitro assay (Table 2). A selective 5-HT_{2A} receptor antagonist, MDL100907 had no effect on the decline in penile erection frequency at 2.03 mg/kg of YM348 (Fig. 4A). Furthermore, YM348 at 2.03 mg/kg did not induce typical 5-HT_{2A} receptor-mediated behaviors such as hyperactivity (Fig. 3B) and wet-dog shake in the presence of SB242084, in contrast to the observation of Ro60-0175 (Higgins et al., 2001). 5-HT_{2A} receptor activation is, therefore, unlikely to contribute to the decline in penile erection frequency.

Activation of 5-HT_{2B} receptors is another possibility, since YM348 has a relatively high affinity for 5-HT_{2B} receptors. 5-HT_{2B} receptor activation is, however, also unlikely to contribute to the decline in penile erection frequency, since a selective 5-HT_{2B} receptor antagonist, RS-127445, did not affect the decline in penile erection frequency (Fig. 4B).

A cardiovascular effect is also considered as another possible cause, since penile erections are produced by vascular dilatation and relaxation of the penile smooth muscle leading to increased blood flow. This possibility is ruled out, however, since YM348 at 2.03 mg/kg p.o. had little effect on blood pressure (Fig. 5).

Hypolocomotion may be one of the causes inducing an inverted U-shape dose–response curve for penile erections. Further investigation is needed to clarify this possibility.

In conclusion, YM348 is a novel, potent and orally active 5-HT_{2C} receptor agonist, and neither the activation of 5-HT_{2A} or 5-HT_{2B} receptors nor a cardiovascular effect is likely to contribute to an inverted U-shape dose–responsive curve for penile erections.

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