Full Paper

Modulation of 8-OH-DPAT-Induced Hypothermia by Imipramine in Rats

Yoshihisa Kitamura^{1,*}, Hiroaki Araki², Kazuhiko Shibata³, Yutaka Gomita³, and Yoshiro Tanizaki⁴

¹Division of Pharmacy, and ⁴Division of Meidicine, Misasa Medical Center, Okayama University Medical School, 827 Yamada, Misasa-cho, Tohaku-gun, Tottori 682-0192, Japan

²Division of Hospital Pharmacy, Ehime University Hospital, Shitsukawa, Shigenobu-cho, Onsen-gun, Ehime 791-0295, Japan

³Department of Hospital Pharmacy, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

Received May 6, 2003; Accepted August 4, 2003

Abstract. The effects of imipramine on 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), the 5-hydroxytryptamine (5-HT)_{1A}-receptor full agonist, -induced hypothermia was examined in rats. Single administration of imipramine (30 mg/kg, i.p.) attenuated 8-OH-DPAT-induced hypothermia. This effect of imipramine was blocked by the 5-HT_{2A}-receptor antagonist ketanserin. 8-OH-DPAT-induced hypothermia was not altered 24 h after repeated administration of imipramine (1–10 mg/kg per day) for 14 days. However, 8-OH-DPAT-induced hypothermia was significantly enhanced in repeated imipramine (10 mg/kg per day)-treated rats that received 8-OH-DPAT plus imipramine 24 h after the final imipramine administration for 14 days. The 5-HT_{2A}-receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane ((±)-DOI) attenuated the 8-OH-DPAT-induced hypothermia in drug naive rats. The inhibitory effect of (±)-DOI (0.3 mg/kg, s.c.) on 8-OH-DPAT-induced hypothermia was attenuated by repeated administration of imipramine (10 mg/kg per day) for 14 days. These findings suggest that enhancement of the 5-HT_{1A} receptors by repeated administration of imipramine may be due to reduction of the inhibitory effects from the 5-HT_{2A} receptors to the 5-HT_{1A} receptors.

Keywords: imipramine, 8-OH-DPAT, hypothermia, 5-HT_{1A} receptor, 5-HT_{2A} receptor

Introduction

Imipramine is an antidepressant drug that preferentially inhibits 5-hydroxytryptamine (5-HT) uptake. It was previously suggested that the antidepressive effects of imipramine are mediated by some of 5-HT-receptor subtypes. However, the detailed mechanism of imipramine action still remains unknown. The recent discovery of multiple biochemical and functional subtypes of 5-HT receptors has given new impetus to studies investigating the function of 5-HT in affective disorders (1, 2). The 5-HT receptor subtypes, particularly 5-HT_{1A} receptors and 5-HT_{2A} receptors, have been postulated to play an important role in the pathogenesis of depression (3–7). Pericic and Manev (8) reported that the 5-HT syndrome including tremor, hindlimb abduction, fore-

paw padding, and raised or rigid Staub tail elicited by pargyline with 5-hydroxy-L-tryptophan in rats was potentiated by a single administration of imipramine (15–30 mg/kg, i.p.). The enhancing effect of imipramine (30 mg/kg, i.p.) on the 5-HT syndrome was inhibited by the 5-HT_{1A}-receptor antagonist, (–)-propranolol (9). These findings suggest that single administration of imipramine was associated with the activation of 5-HT_{1A} receptors. On the other hand, Maj et al. (10) suggested that 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT)-induced flat body posture was slightly inhibited by a single administration of imipramine (10 mg/kg, p.o.). Repeated administration of imipramine (10 mg/kg, p.o.), twice daily for 14 days, did not affect the 8-OH-DPAT-induced flat body posture in rats. Wozniak et al. (11) suggested that 8-OH-DPAT-induced hypothermia did not change by repeated administration of imipramine (5 mg/kg, i.p.). Although these findings suggest that the effect of imipramine is medi-

*Corresponding author. FAX: +81-858-43-1305
E-mail: ykita@cc.okayama-u.ac.jp

ated by 5-HT_{1A} receptors, there are some discrepancies in the literature regarding the effects of 5-HT_{1A} receptors.

It is well documented that imipramine affects the 5-HT_{2A} receptors in neurochemical and behavioral studies. It was reported that the density of 5-HT_{2A} receptors decreases by the repeated administration of imipramine (12). Furthermore, several studies have suggested that there are functional interactions between 5-HT_{1A} receptors and 5-HT_{2A} receptors (review: 13). Such interactions may play an important role in the mechanism of action of antidepressant drugs (3, 12, 14, 15). As previous studies have been used for normal or single administration of imipramine, the model of down-regulation of 5-HT_{2A} receptor for repeated administration of imipramine is interesting from the viewpoint of the mechanism of interaction between 5-HT_{1A} receptors and 5-HT_{2A} receptors.

In addition to hypothermia, it was reported that 8-OH-DPAT induced up to seven behaviors (lateral head-weaving, forepaw treading, flat body posture, hindlimb abduction, tremor, Straub tail, rollover). It is suggested that the 8-OH-DPAT-induced hypothermia response is one of the most marked responses in 8-OH-DPAT-induced behavioral changes. Therefore, it is the most reliable parameter for the evaluation of drug action. We investigated the effect of single and repeated administration of imipramine on 8-OH-DPAT-induced hypothermia in rats to study its mode of action through 5-HT_{1A} receptors. Furthermore, the purpose here was to explore the precise mechanism regarding the effect of imipramine in the behavioral interaction of 5-HT_{1A} receptors and 5-HT_{2A} receptors.

Materials and Methods

Animals

Male Wistar strain rats (Charles River, Yokohama), weighing 180–300 g, were used. They were housed in groups of 2–4 animals under controlled conditions of light (from 7:00 a.m. to 7:00 p.m.), temperature (23 ± 1°C), and relative humidity (approximately 60%). The animals were allowed free access to standard laboratory food and tap water.

Drugs

Imipramine hydrochloride was obtained from Wako Pure Chemical (Tokyo). 8-OH-DPAT hydrobromide, (±)-DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), and ketanserin tartrate were obtained from Research Biochemicals Inc. (South Natick, MA, USA). All drugs were dissolved in saline on the day of testing and injected in a volume of 2 ml/kg body weight.

Experimental procedures

The 8-OH-DPAT-induced hypothermia was observed in the same animal. Two animals were put into clear plastic cages (22 × 38 × 18 cm) at an ambient temperature of 23 ± 1°C. Their body temperature was measured with a thermistor probe (connected to an electronic thermometer) inserted 2 cm into the rectum. Temperature was measured immediately before drug administration. The animals were then treated with 8-OH-DPAT and returned to their cages. Body temperature was measured again 30 min following 8-OH-DPAT administration. The hypothermic response to 8-OH-DPAT was calculated from the decrease in body temperature.

Experiment 1. The effects of single and repeated administration of imipramine for 14 days on the 8-OH-DPAT-induced hypothermia in rats

Single administration of imipramine (3–30 mg/kg, i.p.) was injected 15 min before the administration of 8-OH-DPAT (0.3 mg/kg, s.c.). In experiments for the repeated administration, imipramine (1–10 mg/kg, i.p.) was injected once daily for 14 days. At 24 h after the final administration of imipramine, rats were administered 8-OH-DPAT 15 min after the administration of saline on the 15th day.

Experiment 2. The effects of challenge imipramine administration on corresponding day 15 on the 8-OH-DPAT-induced hypothermia after 14 days of repeated administration of imipramine

Imipramine (10 mg/kg, i.p.) was administered once daily for 14 days. At 24 h after the final administration of imipramine (10 mg/kg, i.p.) for 14 days, rats were administered a low dose of 8-OH-DPAT (0.1 mg/kg, s.c.) 15 min after the administration of imipramine on the 15th day.

Experiment 3. The effect of ketanserin on the inhibitory effect of a single administration of imipramine on 8-OH-DPAT-induced hypothermia in rats

In the experiment with the single administration of ketanserin (0.3 mg/kg, s.c.) and imipramine (30 mg/kg, i.p.), ketanserin and imipramine were injected 20 and 15 min before administration of 8-OH-DPAT, respectively.

Experiment 4. The effects of (±)-DOI on 8-OH-DPAT-induced hypothermia in naive or repeated administration of imipramine for 14 days of rats

(±)-DOI (0.03–0.3 mg/kg, s.c.) was administered 15 min before the administration of 8-OH-DPAT (0.3 mg/kg, s.c.). In the experiment of repeated admin-

istration of imipramine (10 mg/kg, i.p.), imipramine was administered once daily for 14 days. At 24 h after the final administration of imipramine (10 mg/kg, i.p.), rats were injected with ($\pm$)-DOI without administration of imipramine on the 15th day.

Experiment 5. The effect of ($\pm$)-DOI on body temperature in rats

Measurement of body temperature was performed 30 min after administration of ($\pm$)-DOI (0.1–1 mg/kg, s.c.).

Experiment 6. The effects of repeated administration of imipramine for 14 days on ($\pm$)-DOI-induced hyperthermia in rats

Imipramine (10 mg/kg, i.p.) was administered once daily for 14 days. At 24 h after the final administration of imipramine, rats were administered ($\pm$)-DOI (1 mg/kg, s.c.) 15 min after the administration of saline on the 15th day.

Statistics

Values are expressed as group means and S.E.M. of the means. Data were analyzed by one-way analysis of variance (ANOVA), and the group means were compared by Dunnett's test for multiple comparisons.

Results

Experiment 1. The effect of single and repeated administration of imipramine for 14 days on the 8-OH-DPAT-induced hypothermia in rats

The pretreatment with a single administration of imipramine (3–30 mg/kg, i.p.) significantly attenuated the 8-OH-DPAT (0.3 mg/kg, s.c.)-induced hypothermia [$F(3,20) = 3.87$, $P < 0.05$] (Fig. 1A). The repeated administration of imipramine (1–10 mg/kg, i.p.) for 14 days did not alter the 8-OH-DPAT-induced hypothermia at 24 h after the final administration of imipramine [$F(3,20) = 0.007$, $P = 0.994$] (Fig. 1B).

Experiment 2. The effect of challenge imipramine administration on corresponding day 15 on the 8-OH-DPAT-induced hypothermia after 14 days of repeated administration of imipramine

The 8-OH-DPAT (0.1 mg/kg, s.c.)-induced hypothermia was significantly enhanced by challenge co-administration of imipramine (10 mg/kg, i.p.) and 8-OH-DPAT at 24 h after repeated administration of imipramine (10 mg/kg, i.p.) for 14 days [$P = 0.02$] (Fig. 2).

(A) Single administration

(B) Repeated administration

Fig. 1. Effects of single (A) and repeated (B) administration of imipramine for 14 days on 8-OH-DPAT-induced hypothermia in rats. A: Imipramine was administered 15 min before 8-OH-DPAT (0.3 mg/kg, s.c.) administration. B: For the repeated administration, imipramine (10 mg/kg, i.p.) was injected once daily for 14 days. On the 15th day, rats were administered 8-OH-DPAT without imipramine administration. Changes in body temperature were measured before and after administration of 8-OH-DPAT. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. * $P < 0.05$, significantly different from the saline value.

Fig. 2. Effects of challenge imipramine administration on corresponding day 15 on 8-OH-DPAT-induced hypothermia after 14 days of repeated administration of imipramine. For the repeated administration, imipramine (10 mg/kg, i.p.) was injected once daily for 14 days. On the 15th day, rats were administered imipramine 15 min before 8-OH-DPAT (0.1 mg/kg, s.c.) administration. Changes in body temperature were measured before and after administration of 8-OH-DPAT. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. ** $P < 0.01$, significantly different from the saline value.

Experiment 3. The effect of ketanserin on the inhibitory effects of a single administration of imipramine on 8-OH-DPAT-induced hypothermia in rats

The inhibitory effects of pretreatment with imipramine (30 mg/kg, i.p.) singly on the 8-OH-DPAT (0.3 mg/kg, s.c.)-induced hypothermia was blocked by the ketanserin (0.3 mg/kg, s.c.) [$P = 0.03$] (Table 1).

Experiment 4. The effect of ($\pm$)-DOI on 8-OH-DPAT-induced hypothermia in naive or repeated administration of imipramine for 14 days of rats

The ($\pm$)-DOI significantly attenuated the 8-OH-DPAT-induced hypothermia [$F(3,20) = 16.54$, $P < 0.01$] in naive rats (Fig. 3). On the other hand, the inhibitory effect of ($\pm$)-DOI on 8-OH-DPAT-induced hypothermia was significantly attenuated at 24 h after repeated administration of imipramine (10 mg/kg, i.p.) for

Table 1. Ketanserin prevents the inhibitory effect of imipramine on the 8-OH-DPAT-induced hypothermia in rats

Pretreatment	Δt
Imipramine + Saline	-0.02 ± 0.39
Imipramine + Ketanserin	$-1.17 \pm 0.26^*$

Imipramine (30 mg/kg, i.p.) was administered 15 min before 8-OH-DPAT (0.3 mg/kg, s.c.) administration. Ketanserin (0.3 mg/kg, s.c.) was administered 5 min before imipramine administration. Changes in body temperature (Δt) were measured before and after administration of 8-OH-DPAT. Results are expressed as means $\pm$ S.E.M. of 6 rats. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $*P < 0.05$, significantly different from the saline value.

Fig. 3. Effects of ($\pm$)-DOI administration on 8-OH-DPAT-induced hypothermia in rats. ($\pm$)-DOI (0.03–0.3 mg/kg, s.c.) was administered imipramine 15 min before 8-OH-DPAT (0.3 mg/kg, s.c.) administration. Changes in body temperature were measured before and after administration of 8-OH-DPAT. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $**P < 0.01$, significantly different from the saline value.

Fig. 4. Effects of ($\pm$)-DOI administration on 8-OH-DPAT-induced hypothermia in repeatedly imipramine-treated (14 days) rats. For the repeated administration, imipramine (10 mg/kg, i.p.) was injected once daily for 14 days. On the 15th day, rats were administered ($\pm$)-DOI (0.3 mg/kg, s.c.) 15 min before 8-OH-DPAT (0.3 mg/kg, s.c.) administration. Changes in body temperature were measured before and after administration of 8-OH-DPAT. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $**P < 0.01$, significantly different from the saline value.

Table 2. Effect of ($\pm$)-DOI on body temperature in rats

Dose	Δt
Saline	-0.23 ± 0.06
0.1 mg/kg, s.c.	0.25 ± 0.27
0.3	$1.90 \pm 0.34^{**}$
1	$2.17 \pm 0.44^{**}$

Measurement of body temperature was performed 30 min after administration. Changes in body temperature (Δt) were measured before and after administration of ($\pm$)-DOI. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $**P < 0.01$, significantly different from the saline value.

Table 3. Effect of repeated administration of imipramine for 14 days on ($\pm$)-DOI-induced hyperthermia in rats

Dose	Δt
Saline	1.48 ± 0.28
1 mg/kg, i.p.	0.98 ± 0.49
3	0.87 ± 0.26
10	$0.52 \pm 0.14^{**}$

Repeated administration of imipramine (1–10 mg/kg, i.p.) was injected once daily for 14 days. On the 15th day, rats were administered ($\pm$)-DOI (1 mg/kg, s.c.). Changes in body temperature (Δt) were measured before and after administration of ($\pm$)-DOI. Results are expressed as means $\pm$ S.E.M. of 6 animals. Data were analyzed by one-way ANOVA, followed by Dunnett's test. $**P < 0.01$, significantly different from the saline value.

14 days [$P = 0.005$] (Fig. 4).

Experiment 5. The effect of ($\pm$)-DOI on body temperature in rats

The ($\pm$)-DOI significantly increased body temperature in rats [$F(3,20) = 8.57$, $P < 0.01$] (Table 2).

Experiment 6. The effects of repeated administration of imipramine for 14 days on ($\pm$)-DOI-induced hyperthermia in rats

The ($\pm$)-DOI (1 mg/kg, s.c.)-induced hyperthermia was blocked by repeated administration of imipramine (10 mg/kg, i.p.) for 14 days [$F(3,20) = 16.5$, $P < 0.01$] (Table 3).

Discussion

We investigated the effect of imipramine on the 5-HT_{1A}-receptor agonist 8-OH-DPAT-induced hypothermia in rats. It was previously suggested that imipramine modifies the function of central 5-HT_{1A} receptors. Pericic and Manev (8) reported that imipramine administered in a single dose of 10–30 mg/kg (i.p.) stimulates 5-HTP (5 mg/kg, i.p.)- and pargyline (50 mg/kg, i.p.)-induced 5-HT mediated behavior including tremor, hindlimb abduction, forepaw padding, and Straub tail in rats. However, Maj et al. (10) suggested that a single administration of imipramine (10 mg/kg, p.o.) significantly inhibits the 8-OH-DPAT (5 mg/kg, i.p.)-induced flat body posture in rats, and repeated administration of imipramine (10 mg/kg, p.o.) for 14 days did not change this. Wieland et al. (15) suggested that administration of imipramine (10 mg/kg, s.c., twice daily) for 1 day did not alter the 8-OH-DPAT (4 mg/kg, i.p.)-induced 5-HT syndrome including Straub tail, forepaw treading, head weaving, hindlimb abduction, and low, out-stretched body posture in rats. However, repeated administration of imipramine for 14 days blocked elicitation of the 5-HT syndrome when tested 1 h (drug present) after the final drug administration, but not when tested 24 h (drug absent) after the cessation of imipramine administration. Wozniak et al. (11) suggested that the hypothermic effect of 8-OH-DPAT (0.25 mg/kg, s.c.) in rats was not changed by repeated administration of imipramine (5 mg/kg, i.p.) for 3–22 days. There remains a discrepancy in the literature regarding the effects of imipramine on the 8-OH-DPAT induced behavioral changes. It is difficult to explain the effect of imipramine in the present study. Differences in the number of administration, the route of administrations, the dose of the 8-OH-DPAT or imipramine, or differences in the experimental devices used could be reflected in the results.

Binding studies suggested that repeated administration of various antidepressants facilitate 5-HT neurotransmission. Binding data showed that repeated administration of imipramine and various antidepressants either increased or does not change the density of 5-HT_{1A} receptors in the hippocampus (10, 16–18). Concerning the inhibitory effect of the single administration of imipramine in this study, it was suggested that imipramine directly affects the 5-HT_{1A} receptors. However, it does not have affinity for 5-HT_{1A} receptors ($K_i = 21,000$ nM) (19). Furthermore, the 8-OH-DPAT-induced hypothermia was enhanced by challenge co-administration of imipramine with 8-OH-DPAT at the 15th day after the repeated administration of imipramine for 14 days. It can be assumed that this may be caused by the activation of 5-HT_{1A} receptor function for 5-HT uptake inhibition of imipramine. However, following a 24 h withdrawal after 14 days administration to imipramine exposure, no significant alteration in the 8-OH-DPAT-induced hypothermia was observed. It appears reasonable to assume that the 5-HT_{1A} receptors were not changed by repeated administration of imipramine. These results suggest that the 8-OH-DPAT-induced hypothermia is not controlled by the 5-HT_{1A} receptor function alone.

Numerous investigations have demonstrated that there exists a possible interaction between 5-HT_{1A} receptors and 5-HT_{2A} receptors (review: 13). Berendsen and Broekkamp (20) reported that the 8-OH-DPAT-induced hypothermia could be attenuated by the 5-HT_{2A}-receptor agonist ($\pm$)-DOI (0.1–0.22 mg/kg, s.c.) in mice. It appears reasonable to suggest that the activation of 5-HT_{2A}-receptor function exerts an inhibitory effect on the 5-HT_{1A}-receptor function via 5-HT_{2A}-receptor function. In the present study, ($\pm$)-DOI (0.1–0.3 mg/kg, s.c.) clearly blocked the 8-OH-DPAT-induced hypothermia in drug naive rats. Namely, one explanation for the inhibitory effect of 8-OH-DPAT by the ($\pm$)-DOI is that there may exist an inhibitory effect from 5-HT_{2A} receptors to 5-HT_{1A} receptors. However, with regard to the change in the body temperature, ($\pm$)-DOI elicited hyperthermia. Therefore, we can not exclude the possibility that the hypothermia of 8-OH-DPAT may block the hyperthermia of ($\pm$)-DOI without interaction of 5-HT_{2A} receptors and 5-HT_{1A} receptors. However, ($\pm$)-DOI did not affect hyperthermia at doses of 0.1 mg/kg, s.c. in drug naive rats. Accordingly, it is unlikely that ($\pm$)-DOI (0.1 mg/kg) exerted its effect on body temperature without affecting hyperthermia. However, at doses of 0.3 mg/kg, the possibility exists that the 8-OH-DPAT-induced hypothermia may block the ($\pm$)-DOI induced hyperthermia. On the other hand, with respect to the inhibitory effect of the single administration of imipramine in this study, we assumed that the 5-HT_{1A}-re-

ceptor-mediated behavioral changes may be attenuated by enhancement of the 5-HT_{2A} receptors. We confirmed here that the inhibitory effect of single administration of imipramine on the 8-OH-DPAT-induced hypothermia was blocked by the 5-HT_{2A}-receptor antagonist ketanserin in this study. Thus, it is suggested that the inhibitory effect of imipramine on the 5-HT_{1A} receptors may be due to activation of the 5-HT_{2A} receptors.

Repeated administration of imipramine reduces the density of 5-HT_{2A} receptors in rats (12). We have confirmed that repeated administration of imipramine (10 mg/kg/day) for 14 days significantly attenuates the hyperthermia by (±)-DOI. The inhibitory effect of (±)-DOI on the 8-OH-DPAT-induced hypothermia in drug naive rats was significantly blocked by repeated administration of imipramine for 14 days. That is to say, it is reasonable to assume that the enhancing effect of 5-HT_{1A}-receptor function may be due to attenuation of the inhibitory effects of 5-HT_{1A} receptors via 5-HT_{2A} receptors for down-regulation of 5-HT_{2A} receptors by repeated administration of imipramine. Furthermore, we clarified that a low dose (0.1 mg/kg, s.c.) of 8-OH-DPAT-induced hypothermia was enhanced by challenge co-administration of imipramine and 8-OH-DPAT on the 15th day after repeated administration of imipramine for 14 days. Namely, although the availability of synaptic 5-HT concentrations was increased by the mechanisms of 5-HT uptake inhibition of imipramine, the enhancing effect of 5-HT_{1A}-receptor-mediated behavioral changes may be due to the attenuated inhibitory effect of 5-HT_{2A} receptors on 5-HT_{1A} receptors because of the down-regulated 5-HT_{2A} receptors.

In summary, repeated administration of imipramine enhanced the 5-HT_{1A}-receptor function. It is thought that the reason for this enhancing effect of imipramine is the attenuation of the inhibitory effect of 5-HT_{1A} receptors due to 5-HT_{2A} receptors down-regulation.

Acknowledgments

The authors thank Dr. Kozo Ashida and Dr. Shingo Takada for assistance with clinical assessments.

References

- Cowen PJ. Serotonin receptor subtypes: implications for psychopharmacology. *Br J Psychiatry*. 1991;159 Suppl 12:7–14.
- Peroutka SJ. 5-Hydroxytryptamine receptor subtypes. *Annu Rev Neurosci*. 1988;11:45–60.
- Amsterdam JD, Berwisch N, Potter L, Rickels K. Open trial of gepirone in the treatment of major depressive disorder. *Curr Ther Res*. 1987;41:185–193.
- Grof P, Joffe R, Kennedy S, Persad E, Syrotiuk N, Bradford D. An open study of oral flesionxan, a 5-HT_{1A} receptor agonist, in treatment-resistant depression. *Intern Clin Psychopharmacol*. 1993;8:167–172.
- Nemeroff CB. Paroxetine: an overview of the efficacy and safety of a new selective serotonin uptake inhibitor in the treatment of depression. *J Clin Psychopharmacol*. 1993;13:10S–17S.
- Reyntjens A, Gelders YG, Hoppenbrouwers M-L, Vanden Bussche G. Thymosthenic effects of ritanserin (R55667), a central acting serotonin-S2 receptor blocker. *Drug Dev Res*. 1986;8:205–211.
- Robinson DS, Rickels K, Feigher J, et al. Clinical effect of the 5-HT_{1A} partial agonists in depression: a composite analysis of buspirone in the treatment depression. *J Clin Psychopharmacol*. 1990;10:67S–76S.
- Pericic D, Manev H. Behavioral evidence for simultaneous dual changes of 5-HT receptor subtype: mode of antidepressant action? *Life Sci*. 1988;42:2593–2601.
- Pericic D, Muck-Seler D. Do imipramine and hydroergosine possess two components-one stimulating 5-HT₁ and other inhibiting 5-HT₂ receptors? *Life Sci*. 1990;46:1331–1342.
- Maj J, Bijak M, Dziedzicka-Wasylewska M, et al. The effects of paroxetine given repeatedly on the 5-HT receptor subpopulations in the brain. *Psychopharmacology (Berl)*. 1996;127:73–82.
- Wozniak KM, Aulakh CS, Hill L, Murphy DL. The effect of 8-OH-DPAT on temperature in the rat and its modification by chronic antidepressant treatments. *Pharmacol Biochem Behav*. 1988;30:451–456.
- Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. *Science*. 1980;210:88–90.
- Glennon RA, Darmani NA, Martin BR. Multiple populations of serotonin receptors may modulate the behavioral effects of serotonergic agent. *Life Sci*. 1991;48:2493–2498.
- LePoul E, Laaris N, Doucet E, Laporte A-M, Hamon M, Lanfumey L. Early desensitization of somato-dendritic 5-HT_{1A} autoreceptors in rats treated with fluoxetine or paroxetine. *Naunyn Schmiedeberg Arch Pharmacol*. 1995;352:141–148.
- Wieland S, Fischette CT, Lucki I. Effect of chronic treatments with tandospirone and imipramine on serotonin-mediated behavioral responses and monoamine receptors. *Neuropharmacology*. 1993;32:561–573.
- Bijak M, Tokarski K, Czyrak A, Mackowiak M, Wedzony K. Imipramine increases the 5-HT_{1A} receptor-mediated inhibition of hippocampal neurons without changing the 5-HT_{1A} receptor binding. *Eur J Pharmacol*. 1996;305:79–85.
- Klimek V, Zak-Knapik J, Mackowiak M. Effects of repeated treatment with fluoxetine and citalopram, 5-HT uptake inhibitors, on 5-HT_{1A} and 5-HT₂ receptors in the rats brain. *J Psychiatry Neurosci*. 1994;19:63–67.
- Watanabe Y, Sakai RR, McEwen BS, Mendelson S. Stress and antidepressant effects on hippocampal and cortical 5-HT_{1A} and 5-HT₂ receptors and transport sites for serotonin. *Brain Res*. 1993;615:87–94.
- Darmani NA, Ahmad B. Long-term sequential determination of behavioral ontogeny of 5-HT_{1A} and 5-HT₂ receptor functions in the rat. *J Pharmacol Exp Ther*. 1999;288:247–253.
- Berendsen HHG, Broekkamp CLE. Behavioral evidence for functional interactions between 5-HT-receptor subtypes in rats and mice. *Br J Pharmacol*. 1990;101:667–673.