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N-Methyl-D-aspartate Receptor Antagonists Enhance the Head-twitch Response, a 5-Hydroxytryptamine$_2$ Receptor-mediated Behaviour, in Reserpine-treated Mice

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Abstract

In this study, *N*-methyl-D-aspartate (NMDA)-receptor antagonists enhanced the head-twitch response induced by 5-hydroxytryptamine (5-HT) in reserpine-treated mice.

To minimize the risk of any indirect involvement of NMDA-receptor antagonists (D(−)-2-amino-5-phosphonopentanoic acid (AP-5), D(−)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP), (+)-5-methyl-10,11-dihydroxy-5H-dibenzo-[a,d]-cyclohepten-5,10-imine (MK-801), ketamine, dextrorphan and dextromethorphan) with 5-HT neurones, vesicle stores of monoamines, especially 5-HT, were depleted with reserpine. In addition, the enhancement of 5-HT-induced head-twitch response was inhibited by apomorphine and NMDA as well as ritanserin in reserpine-treated mice.

These results support our previous conclusion that NMDA receptors play important roles in the glutamatergic modulation of 5-HTergic function at the postsynaptic 5-HT$_2$ receptors in mice.

The *N*-methyl-D-aspartate (NMDA)-receptor antagonists, D(−)-2-amino-5-phosphonopentanoic acid (AP-5), D(−)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP), (+)-5-methyl-10,11-dihydroxy-5H-dibenzo-[a,d]-cyclohepten-5,10-imine (MK-801) and phencyclidine, induce a characteristic behavioural syndrome in rats and mice. This includes hyperlocomotion, lateral head weaving, circling and ataxia (Tricklebank et al 1985; Yamaguchi et al 1987; Kelly & Throne 1992; Löscher & Hönack 1992, 1993; Löscher et al 1992, 1993). There is evidence that excitatory amino acids participate in the release of dopamine and in regulation of dopamine metabolism in several brain regions, including the striatum (Bouyer et al 1984; Cheramy et al 1986; Krebs et al 1991). The potential interaction between the glutamatergic and the dopaminergic system has attracted much interest because of its possible implications in pathological processes such as schizophrenia and Parkinson's disease (Lodge & Johnson 1990; Kulkarni & Verma 1991).

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There are several studies that suggest MK-801, in addition to its effects on dopaminergic pathways, might affect other monoamine transmitter systems in the brain. Several of the MK-801-induced motor syndromes, e.g. head weaving, flat body posture, forepaw treading and hyperlocomotion, resemble the characteristic patterns induced by 5-hydroxytryptamine (5-HT) in rodents, yet few studies have investigated the possibility that MK-801 might also interact with the 5-HTergic system (Tricklebank et al 1989; Löscher & Hönack 1992, 1993).

The 5-HTergic-like behavioural syndromes induced by MK-801 in rats have been reported to be blocked by a 5-HT$_{1A}$ receptor antagonist, ipsapirone, but not by a 5-HT$_2$ receptor antagonist, ritanserin (Löscher & Hönack 1992). Thus, it is likely that these behavioural interactions are closely related to 5-HTergic 5-HT$_{1A}$-receptor activation secondary to alteration of glutamatergic receptor function. However, the behavioural responses that result from interaction between glutamatergic and 5-HTergic 5-HT$_2$ receptors have not been well characterized.

One of the distinctive behavioural responses induced by 5-HT in mice, the head-twitch response, has been shown to be mediated via 5-HT$_2$ rather than 5-HT$_{1A}$ receptors (Lucki et al 1984; Goodwin

& Green 1985). Accordingly, the head-twitch response has been used as a common means of assessing striatal 5-HT_2-receptor activity. The head-twitch response cannot easily be mistaken for other behavioural syndromes induced by 5-HT, such as head weaving, hyperlocomotion, flat body posture, reciprocal forepaw treading and hindlimb abduction, which are related to stimulation of 5-HT_1 receptors. Our previous study, in intact mice, reported that the NMDA-receptor antagonists (AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan) could markedly enhance 5-HT-induced head-twitch response in intact mice whereas cyproheptadine, apomorphine and NMDA inhibited 5-HT-induced head-twitch response (Kim et al 1998).

In order to establish definitively the involvement of the NMDA receptor in 5-HT-induced head-twitch response at the postsynaptic 5-HT_2 receptor, we have investigated whether the NMDA-receptor antagonists would enhance these phenomena in reserpine-treated mice, that is mice that are devoid of any involvement of indirect monoamines. The reserpine treatment depleted vesicle stores of monoamines, especially 5-HT, and so the risk of any indirect involvement of NMDA-receptor antagonists was minimized.

Materials and Methods

Animals and drugs

ICR male mice (20–25 g; Samyuk Laboratory Animal Inc., Osan, Korea) were housed in acryl-fiber cages in groups of 12–15 in a controlled room (temperature $22 \pm 3^{\circ}$C) maintained on a 12-h light–dark cycle. They were given a solid diet and tap water was freely available.

(+)MK-801 hydrogen maleate ((+)-5-methyl-10,11-dihydroxy-5H-dibenzo-[a,d]-cyclohepten-5,10-imine hydrogen maleate), ketamine hydrochloride, dextrorphan tartrate, dextromethorphan hydrobromide, AP-5 (D(−)-2-amino-5-phosphonopentanoic acid), CPP (D(−)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid) and ritanserin were obtained from Research Biochemical International (Boston, MA). Apomorphine hydrochloride, NMDA, 5-HT creatinine sulphate and reserpine were obtained from Sigma Chemical (St Louis, MO). Reserpine was dissolved in a few drops of glacial acetic acid and diluted with 5·5% glucose solution. Ritanserin was dissolved in a small amount of ethanol and then diluted with saline. Except for apomorphine, which was dissolved in saline containing 0·1% ascorbic acid, all drugs were dissolved in physiological saline just before the experiments.

Measurement of 5-HT-induced head-twitch response in mice

This study was conducted with minor modifications to the methods of Kim et al (1998, 1999). Kim et al (1998, 1999) administered a single dose of 5-HT (20, 50 or 80 μg/10 μL/mouse, i.c.v.) to intact mice. This dose-dependently increased the incidence of the head-twitch response at 10 min for 2 min, by 20, 40 or 100%, respectively. However, in this study, a single administration of 12·5, 25 or 50 μg/10 μL/mouse 5-HT produced a dose-dependent increase in head-twitch response by 20, 40 or 100%, respectively, compared with the saline group in reserpine-treated mice. The increased incidence was the result of postsynaptic 5-HT_2 receptor supersensitivity that was developed in reserpine-treated mice. Therefore, 25 μg/mouse 5-HT, showing an approximately 40% increase in the incidence of the head-twitch response, was selected for use in reserpine-treated mice. Kim et al (1998, 1999) used 50 μg/intact mouse 5-HT, which showed an increase of approximately 40% in head-twitch response.

To deplete monoaminergic stores, all mice were pretreated with reserpine (5 mg kg^{-1}, i.p.) 24 h before evaluation of the head-twitch response test (Goodwin et al 1992; Ferre et al 1994; Kaur & Starr 1996). The reserpine-treated mice were kept at an elevated temperature ($28 \pm 1^{\circ}$C) to prevent them from becoming hypothermic (Goodwin et al 1992). After 24 h, the mice were injected intracerebroventricularly with 5-HT to induce the head-twitch response. Each mouse was anaesthetized by ether and its head was oriented in a stereotaxic instrument (David Kopf Instruments, Tujunga, CA) so that the plane formed by the frontal and parietal bones was parallel to the instrument table top. A 26-gauge stainless-steel cannula was positioned above the lateral cerebral ventricle (AP, −0·6 mm; LAT, 1·6 mm to the bregma; HOR, −2·0 mm to the dura mater) and secured with two stainless-steel screws and cranioplastic cement. Drugs were injected intracerebroventricularly in a volume of 10 μmL/mouse over a period of 30 s using a 28-gauge injection needle connected by polyethylene tubing to a Hamilton 50-μL syringe. Cannula position was verified after each experiment by gross examination of the brain following injection of dye. For evaluation of the effects of AP-5, CPP and NMDA, intracerebroventricular injections of 5-HT were made immediately following injections of AP-5, CPP or NMDA. Apomorphine was

administered subcutaneously to mice 5 min before, while ketamine (i.p.), dextromethorphan (i.p.) and ritanserin (s.c.) were given 30 min before, and dextrorphan (i.p.) 1 h before the intracerebroventricular injection of 5-HT. Each animal was placed into a transparent plexiglas cylinder (20 cm diameter; 25 cm height) (Hamilton et al 1986). The head-twitch response frequency was scored for a period of 2 min, beginning 10 min after the injection of 5-HT, by an observer who had no knowledge of the drug treatment. The various NMDA antagonists alone did not induce any head-twitch response in reserpinized and non-reserpinized mice. Therefore, these data are not presented.

Statistical analysis

The data are expressed as mean ± s.e.m. The statistical significance of drug effects was analysed by the non-parametric Mann–Whitney U-test. When comparisons between groups yielded a value for $P < 0.05$ the difference between those groups was considered statistically significant.

Results

Enhanced effects of competitive NMDA-receptor antagonists on 5-HT-induced head-twitch response in reserpine-treated mice

AP-5 (0·25, 0·5 and 1·0 μg/10 μL/mouse, i.c.v.) administered to reserpine-treated mice just before the injection of 5-HT increased the head-twitch response induced by intracerebroventricular injection of 5-HT (25 μg/10 μL/mouse) by approximately 32·3% (7·5 ± 0·7), 64·6% (9·3 ± 0·9, $P < 0.05$) and 123·5% (12·7 ± 1·2, $P < 0.01$) respectively, compared with the control group (5·67 ± 0·88) (Figure 1a). The 5-HT-induced head-twitch response was also enhanced by intracerebroventricular injection of CPP (0·05, 0·1 and 0·2 μg/10 μL/mouse) in reserpine-treated mice by approximately 28·5% (6·0 ± 0·9), 78·4% (8·3 ± 0·9, $P < 0.05$) and 167·7% (12·5 ± 1·5, $P < 0.01$), respectively, compared with the control group (4·7 ± 0·8) (Figure 1b).

Enhanced effects of noncompetitive NMDA-receptor antagonists on 5-HT-induced head-twitch response in reserpine-treated mice

The noncompetitive NMDA-receptor antagonist, MK-801 (0·05, 0·1 and 0·2 mg kg^{-1}, i.p.) administered 30 min before the injection of 5-HT (25 μg/10 μL/mouse) increased the 5-HT-induced head-twitch response in reserpine-treated mice by 62·1% (10·0 ± 0·7, $P < 0.01$), 102·6% (12·5 ± 1·8, $P < 0.01$) and 281·0% (24·0 ± 2·6, $P < 0.01$), respectively, compared with the control group (6·2 ± 0·3) (Figure 1c). In addition, it appeared that 5-HT-induced head-twitch response was also markedly enhanced in reserpine-treated mice by low doses of three other noncompetitive NMDA-receptor antagonists, ketamine, dextrorphan and dextromethorphan (Figures 1d, e and f).

Decreased effects of 5-HT$_2$-receptor antagonist and dopaminergic-receptor agonist on 5-HT-induced head-twitch response in reserpine-treated mice

The 5-HT$_2$-receptor antagonist ritanserin (0·025, 0·05 and 0·1 mg kg^{-1}, s.c.) administered to reserpine-treated mice 30 min before the injection of 5-HT (50 μg/10 μL/mouse) inhibited the 5-HT-induced head-twitch response by 42·7% (9·0 ± 1·5, $P < 0.05$), 72·9% (4·3 ± 1·7, $P < 0.01$) and 83·4% (2·6 ± 0·4, $P < 0.01$), respectively, compared with the control group (15·7 ± 2·3) (Figure 2a). The dopaminergic-receptor agonist, apomorphine (0·5, 1 and 2 mg kg^{-1}, s.c.) administered to reserpine-treated mice 5 min before the injection of 5-HT (50 μg/10 μL/mouse) also attenuated the 5-HT-induced head-twitch response by 22·2% (11·0 ± 4·2), 44·7% (7·8 ± 1·0, $P < 0.01$) and 55·3% (6·3 ± 1·2, $P < 0.01$), respectively, compared with the control group (14·2 ± 4·0) (Figure 2b).

Decreased effects of NMDA-receptor agonist on 5-HT-induced head-twitch response in reserpine-treated mice

NMDA (0·01, 0·025 and 0·05 μg/10 μL/mouse, i.c.v.) administered to reserpine-treated mice just before the injection of 5-HT (50 μg/10 μL/mouse, i.c.v.) inhibited 5-HT-induced head-twitch response by 31·6% (8·3 ± 1·7), 49·3% (6·2 ± 1·1, $P < 0.05$) and 57·3% (5·2 ± 0·7, $P < 0.01$), respectively, compared with the control group (12·2 ± 1·2) (Figure 2c).

Discussion

The results demonstrate that NMDA-receptor antagonists enhanced the head-twitch response induced by 5-HT in reserpine-treated mice. Ritanserin, apomorphine and NMDA inhibited the head-twitch response induced by 5-HT in reserpine-treated mice, as shown in intact mice by Kim et al (1998). In this study, 25 and 50 μg/10 μL/mouse 5-HT produced an increase in the incidence of head-twitch response by approximately 40 and 100%, respectively, in reserpine-treated mice. Kim et al

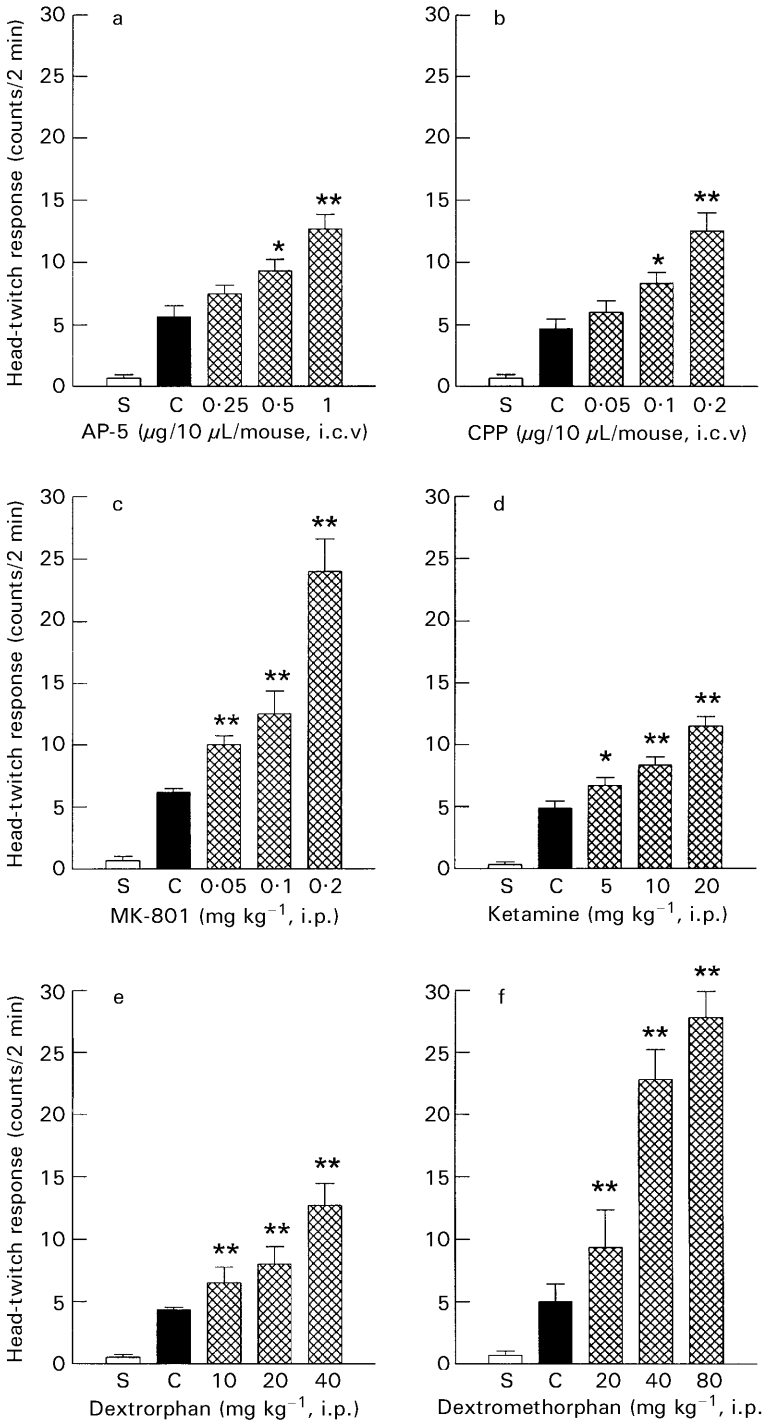

Figure 1. Effects of AP-5, CPP, MK-801, ketamine, dextrorphan and dextromethorphan on the 5-HT-induced head-twitch response in reserpine-treated mice. AP-5 and CPP were administered (i.c.v.) to reserpine-treated mice just before the injection of 5-HT (25 μg/10 μL/mouse, i.c.v.). MK-801, ketamine and dextromethorphan were administered (i.p.) to reserpine-treated mice 30 min before the injection of 5-HT. Dextrorphan was administered 1 h before the 5-HT injection. Reserpine (5 mg kg^{-1}, i.p.) was administered to mice 24 h before the head-twitch response test. Each value is expressed at the mean ± s.e.m. of at least 15 mice. *$P < 0.05$, **$P < 0.01$, compared with the 5-HT control group. S, saline; C, control, 25 μg/10 μL/mouse 5-HT.

(1998) demonstrated that 50 and 80 μg/10 μL/mouse 5-HT produced similar increases in the incidence of head-twitch response in intact mice. With those exceptions, the data obtained in this study agree with those previous results.

It is thought that the head-twitch response induced by 5-HT is due to stimulation of CNS 5-HT$_2$ receptors (Goodwin & Green 1985). Our results suggest that blockade of the NMDA receptor resulted in an enhancement of the 5-HT-induced

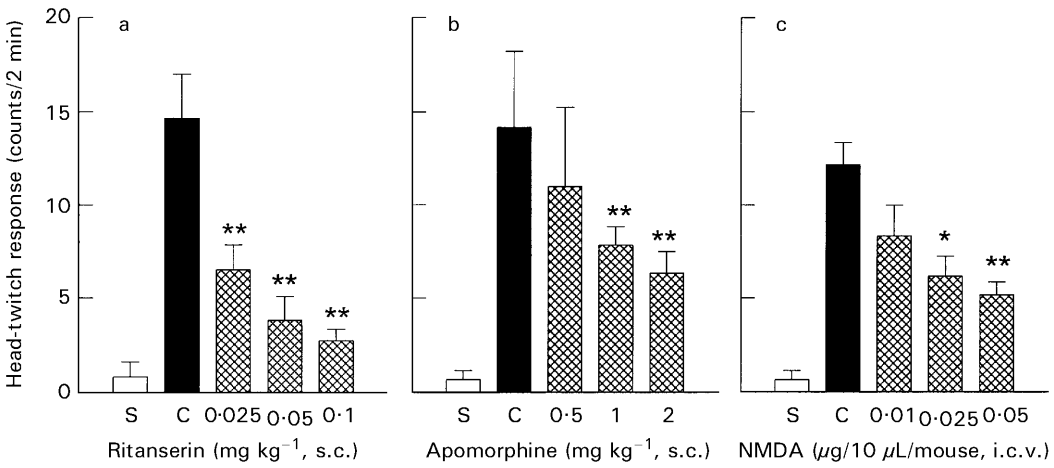

Figure 2. Effects of (a) ritanserin, (b) apomorphine and (c) NMDA on the 5-HT-induced head-twitch response in reserpine-treated mice. Ritanserin (s.c.), apomorphine (s.c.) and NMDA (i.c.v.) were administered to reserpine-treated mice 30 min, 5 min and just before the injection of 5-HT (50 μg/10 μL/mouse, i.c.v.), respectively. Reserpine (5 mg kg^{-1}, i.p.) was administered to mice 24 h before the head-twitch response test. Each value is expressed as the mean $\pm$ s.e.m. of at least 15 mice. $^{*}P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$, compared with the 5-HT control group. S, saline; C, control, 50 μg/10 μL/mouse 5-HT.

head-twitch response as a result of the development of 5-HT_2-receptor supersensitivity in reserpine-treated mice. This enhancement, by NMDA-receptor antagonists, of 5-HT-induced head-twitch response in reserpine-treated mice supports the notion that NMDA receptors and glutamatergic neurotransmission play important roles in the glutamatergic modulation of 5-HTergic function at 5-HT_2 receptors in intact mice. These are the first data available regarding glutamatergic modulation of 5-HTergic function at the 5-HT_2 receptors in reserpine-treated mice. However, the precise relationship of the synaptic arrangement between glutamate and 5-HT_2 receptors remains undefined. Furthermore, it appears that other neurotransmitters, in particular dopamine, may modify the interactions between glutamate and 5-HT, since it has been reported that dopamine receptor agonists, such as apomorphine, inhibit 5-HT-induced head-twitch response in mice (Bedard & Pycock 1977). In addition, there is evidence that an enhancement of dopaminergic tone at the striatal level may explain the reduction in the incidence of the head-twitch response following administration of quipazine, a 5-HTergic-receptor agonist (Dall' Olio et al 1988). Such results are consistent with those obtained in this study, which indicate that enhancement of dopaminergic tone at the striatal level by apomorphine inhibits the 5-HT-induced head-twitch response (Figure 2b). In addition to direct glutamatergic–5-HTergic interactions, indirect glutamatergic–5-HTergic interactions, mediated via dopaminergic neurons, might be involved in alterations of 5-HT turnover produced by NMDA-receptor antagonists (Löscher et al 1992, 1993; Löscher & Hönack 1993).

Interneuronal substrates might thus exist for both potentiating effects of NMDA-receptor antagonists on 5-HTergic stimulation and their inhibitory effects on dopaminergic stimulation. Consistent with this hypothesis, 5-HT-induced head-twitch response was inhibited by a dopaminergic-receptor agonist, apomorphine, and an NMDA-receptor agonist, NMDA, as well as by a 5-HTergic 5-HT_2-receptor antagonist, ritanserin, in this study.

The functional interactions between glutamatergic and 5-HTergic pathways are less well characterized than those of dopaminergic pathways, but, in the striatum, 5-HT release seems to be under inhibitory-glutamatergic control (Becquet et al 1990; Whitton et al 1994). Microdialysis experiments have shown that MK-801 increases not only 5-HT metabolism but also its release in brain regions including the striatum (Löscher & Hönack 1992, 1993; Löscher et al 1992, 1993; Whitton et al 1994). These results suggest that attenuation of a glutamatergic–5-HTergic interaction by NMDA-receptor antagonists can enhance 5-HTergic transmission at both 5-HT_{1A} and 5-HT_2 receptors. While postsynaptic 5-HT_{1A} receptors are thought to play a primary role in the behavioural syndromes induced by increased brain levels of 5-HT, 5-HT_2 receptors are also involved to a much lesser extent (Tricklebank et al 1985, 1989). The degree of 5-HTergic stimulation that induces head-weaving through activation of the 5-HT_{1A} receptor is not sufficient to induce head-twitch response activation of the 5-HT_2 receptor. Following treatment with NMDA-receptor antagonists, it is much easier to induce head-twitch response when the 5-HT_2 receptors are stimulated by administration of additional 5-HT. In support of these observations, it has been shown

that the behavioural 5-HTergic syndromes induced by the NMDA-receptor antagonist MK-801 are blocked by pretreatment with the 5-HT_{1A} receptor antagonists, ipsapirone (Löscher & Hönack 1992) and (+)-WAY10035 (Löscher & Hönack 1993), but not by the 5-HT_2 receptor antagonist, ritanserin (Löscher & Hönack 1992). Phencyclidine produces head-weaving at low doses and head twitches at high doses. Phencyclidine-induced head twitches and head-weaving are blocked by pretreatment with ritanserin, a selective 5-HT_2-receptor antagonist, and with pindolol, a 5-HT_{1A}-receptor antagonist, respectively (Yamaguchi et al 1987).

Therefore, the present results strongly support our previous conclusion that NMDA receptors play important roles in the glutamatergic modulation of 5-HTergic function at the postsynaptic 5-HT_2 receptors (Kim et al 1999).

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