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Short communication

R(+)-8-OH-DPAT, a 5-HT$_{1A}$ receptor agonist, inhibits amphetamine-induced dopamine release in rat striatum and nucleus accumbens

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Abstract

Systemic administration of *R*(+)-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin), a selective serotonin (5-hydroxytryptamine, 5-HT)$_{1A}$ receptor agonist (25, 50, and 100 μg/kg s.c.), administered 30 min prior to *d*-amphetamine, significantly inhibited the *d*-amphetamine sulfate (1.0 mg/kg s.c.)-induced increase in extracellular dopamine levels in the striatum and nucleus accumbens of freely moving rats, as determined by in vivo microdialysis. The ability of *R*(+)-8-OH-DPAT (50 μg/kg s.c.) to inhibit *d*-amphetamine sulfate (1.0 mg/kg s.c.)-induced increase in extracellular dopamine levels was abolished by WAY 100,635 (*n*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*n*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride), a selective 5-HT$_{1A}$ receptor antagonist (100 μg/kg s.c.), administered 5 min prior to *R*(+)-8-OH-DPAT in both regions. These results indicate that the 5-HT$_{1A}$ receptor may exert an inhibitory effect on amphetamine-induced dopamine release.

Keywords: *R*(+)-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); WAY 100,635 (*n*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*n*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride); *d*-Amphetamine; Dopamine; 5-HT$_{1A}$ receptor; Microdialysis, in vivo; Nucleus accumbens; Striatum; (Rat)

1. Introduction

Modulation of dopaminergic activity by serotonin (5-hydroxytryptamine, 5-HT)$_{1A}$ receptors has been investigated. The 5-HT$_{1A}$ receptor agonist (±)-8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT, 0.3 mg/kg s.c.) has been reported to decrease rat striatal dopamine synthesis, as indicated by accumulation of the dopamine precursor L-3,4-dihydroxyphenylalanine (DOPA), following the centrally active l-aromatic amino acid decarboxylase inhibitor, NSD-1015 (*m*-hydroxybenzylhydrazine dihydrochloride) while the 5-HT$_{1A}$ receptor antagonist NAN 190 (1 and 3 mg/kg s.c.) increased striatal dopamine synthesis (Johnson et al., 1993). On the other hand, local perfusion of 8-OH-DPAT (2 nmol) via the dialysis probe has been reported to increase striatal extracellular dopamine levels while leaving striatal extracellular dopamine levels unaffected by systemic administration of 8-OH-DPAT (100 μg/kg) (Benloucif and Galloway, 1991). Similarly, *R*(+)-8-OH-DPAT (25 μg/kg s.c.) and 8-OH-DPAT (30 μg/kg s.c.) have been reported to have no effect on extracellular dopamine levels in the nucleus accumbens and the striatum, while both increase extracellular dopamine levels in the prefrontal cortex (Arborelius et al., 1993; Tanda et al., 1994). Higher dose of 8-OH-DPAT (225 μg/kg) decreases striatal extracellular dopamine levels but still increases prefrontal extracellular dopamine levels (Rasmusson et al., 1994). These results suggest that basal dopamine release and/or synthesis is influenced by 5-HT$_{1A}$ receptor stimulation, in a region-specific manner. However, the effect of 5-HT$_{1A}$ receptor stimulation on stimulated dopamine release by amphetamine has not been reported. Amphetamine is believed to preferentially facilitate

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dopamine release from the releasable dopamine pool, which is dependent upon the newly synthesized dopamine at the neuron terminal (Butcher et al., 1988; Schmidt et al., 1994). Inhibition of dopamine synthesis via 5-HT_{1A} receptors would be expected to inhibit amphetamine-induced dopamine release, as has been shown with 5-HT_{2A} receptor antagonists amperozide and MDL 100,907 (Ichikawa and Meltzer, 1992; Schmidt et al., 1994). If so, it is possible to speculate that 5-HT_{1A} receptor stimulation may be of value in the treatment of amphetamine-induced psychosis and possibly endogenous psychoses since 5-HT_{2A} receptor antagonists are reported to have antipsychotic action and 5-HT_{1A} receptor agonists and 5-HT_{2A} receptor antagonists share the property of encouraging neuronal hyperpolarization via the opening of K^+ channels, as reviewed by Millan et al. (1992).

The purpose of the present study was to test the hypothesis that the 5-HT_{1A} receptor full agonist *R*(+)-8-OH-DPAT would have an effect similar to the 5-HT_{2A} receptor antagonist amperozide to inhibit amphetamine-induced increase in extracellular dopamine in the striatum and the nucleus accumbens, possibly due to stimulation of 5-HT_{1A} receptors, as determined by in vivo microdialysis of awake, freely moving rats.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley albino rats (Zivic-Miller, PA, USA) weighing 200–300 g are used throughout the study. They are housed two per cage and maintained in a controlled 12–12 h light–dark cycle and under constant temperature at 22°C, with free access to food and water.

2.2. Drug challenge

R(+)-OH-DPAT hydrobromide (25, 50, 100 and 1000 μg/kg, RBI, Natick, MA, USA), WAY 100,635 (*n*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*n*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride) (100 μg/kg, gifted by Sandoz, Basel, Switzerland) and *d*-amphetamine sulfate (1.0 mg/kg, Sigma) are dissolved in deionized water and administered subcutaneously (s.c.).

2.3. Microdialysis procedure and dialysate analysis

Rats are anesthetized with a combination (intraperitoneal injection) of xylazine (6 mg/kg) and ketamine hydrochloride (70 mg/kg) and mounted in a stereotaxic frame (David-Kopf). Two stainless guide cannulas (21 gauge) with a dummy probe are fixed onto the cortex dorsal to both striatum and nucleus accumbens. Three to five days following cannulation, the dialysis probes are implanted into both striatum and nucleus accumbens in the same rat under anesthesia with methoxyflurane (Metofane) and then connected to an infusion pump which delivers modified Dulbecco's phosphate buffered saline solution including 1.2 mM Ca^{2+} (pH = 7.4) at 0.8 μl/min for the experiment of *R*(+)-8-OH-DPAT and at 0.5 μl/min for the experiment of WAY 100,635. The striatum co-ordinate is A +0.5, L −4.0, V −5.5 and for the nucleus accumbens, A +2.0, L +1.5, V −7.5 mm, relative to bregma; the incision bar level is −3.0 mm, according to the atlas of König and Klippel (1963). The dialyzing membrane length (AN69 HF, Hospal) is 2 mm for the striatum and the nucleus accumbens. The day after implantation of the two probes, dialysate samples are collected every 30 min and each 20 μl of 24 μl (0.8 μl × 30 min) for the experiment of *R*(+)-OH-DPAT and 15 μl (0.5 × 30 min) for the experiment of WAY 100,635 is directly applied onto a high-performance liquid chromatography (HPLC) system with electrochemical detection. After obtaining stable baseline values in the dialysates, each drug (s.c.) is administered to the rats. The effect of the drug is followed for at least another 180 min. The locations of the dialysis probes are verified at the end of each experiment by dissection of the brain.

Dopamine is separated on reversed phase column (Ultracarb 3 μm C18, 2.0 × 100 mm, Phenomenex) at 35°C maintained by column heater (LC-22C, BAS). The mobile phase (pH 4.2) consists of 32 mM citric acid anhydrous, 54.3 mM sodium acetate, EDTA-2Na (50 mg/l), octyl sodium sulfate (50 mg/l, Kodak), and 5% (v/v) methanol. Dopamine is detected by a dual glassy carbon working electrode (MF-1000, BAS) set at +0.50 V (LC-4C, BAS) vs. Ag/AgCl reference electrode. Reagents used are analytical or HPLC grade.

2.4. Analysis of data

Statistical differences are determined using a repeated measure analysis of variance (ANOVA) followed by the Fisher's PSLD post-hoc pairwise comparison procedure wherever possible (StatView 4.02 for the Macintosh). A probability, *P*, of less than 0.05 is considered significant in this study. All results are given as mean ± S.E.M. and expressed as absolute net increase which is calculated from each absolute level over each pre-drug basal value, or as net-area under the curve (net-AUC) which is calculated from the absolute net increase for a 180-min period after amphetamine or vehicle (six samples) over each pre-drug basal value.

3. Results

3.1. Effect of R(+)-8-OH-DPAT (Fig. 1)

d-Amphetamine sulfate (1.0 mg/kg s.c.) alone with vehicle pretreatment produced a marked increase in extracellular dopamine in the nucleus accumbens (absolute net increase: 307 ± 39 compared to basal value 15.2 ± 7.4 fmol/30 min) and the striatum (457 ± 62 compared to basal value 26.7 ± 8.4 fmol/30 min), respectively, 30 min after amphetamine administration. *R*(+)-8-OH-DPAT (50 μg/kg) alone, which produced the greatest inhibition among the doses studied, had no significant effect on net-area under the curve of extracellular dopamine levels in either region for a 180 min period after its injection (−0.9 ± 3.0 fmol/180 min for the nucleus accumbens, $n = 4$ and −0.4 ± 4.9 fmol/180 min for the striatum, $n = 5$).

R(+)-8-OH-DPAT (25, 50 and 100 μg/kg) significantly inhibited amphetamine-induced increase in extracellular dopamine levels in both striatum and nucleus accumbens during a 180-min period following amphetamine, while the effect of 1000 μg/kg of *R*(+)-8-OH-DPAT was not significant in either region. (*F*, *P*)[doses] = (11.25, 0.001)[25], (13.56, 0.004)[50], (6.96, 0.01)[100], (3.19, 0.08)[1000] for the striatum and (7.75, 0.007)[25], (15.01, 0.0002)[50], (4.50, 0.04)[100], (0.49, 0.49)[1000] for the nucleus accumbens, respectively. However, during the first 90-min period, 1000 μg/kg of *R*(+)-8-OH-DPAT significantly attenuated

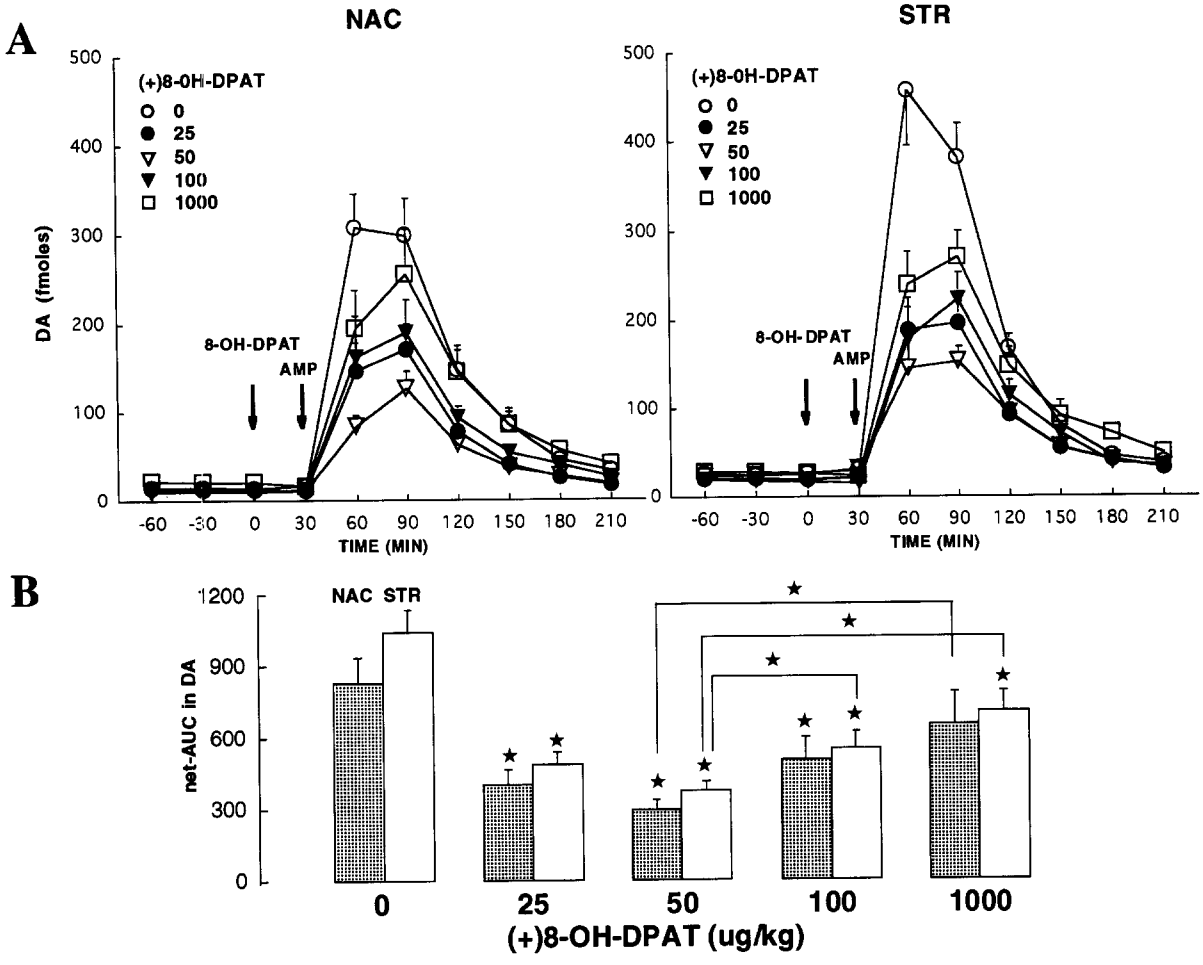

Fig. 1. The time course of the pretreatment effect of single doses of *R*(+)-8-OH-DPAT (0, 25, 50, 100 and 1000 μg/kg s.c.) on the ability of *d*-amphetamine (AMP, 1.0 mg/kg s.c.), 30 min later *R*(+)-8-OH-DPAT, to increase in vivo extracellular dopamine levels in rat nucleus accumbens (NAC) and striatum (STR). Repeated measure analysis of variance (ANOVA) revealed that *R*(+)-8-OH-DPAT significantly prevented amphetamine-induced increase in extracellular dopamine levels in both the striatum and the nucleus accumbens, except that 1000 μg/kg *R*(+)-8-OH-DPAT had no significant effect in either region during the 180-min period. Note 1000 μg/kg *R*(+)-8-OH-DPAT had significant effect on amphetamine-induced increase in extracellular dopamine levels during the first 90-min period in the striatum, but not the nucleus accumbens. *R*(+)-8-OH-DPAT (1000 μg/kg) produced a significantly smaller inhibition of amphetamine-induced dopamine release compared to that by *R*(+)-8-OH-DPAT (25 and 50 μg/kg) in both regions. Data are means ± S.E.M. (bars) of corresponding time points, expressed as absolute dopamine values ($n = 6$–10).

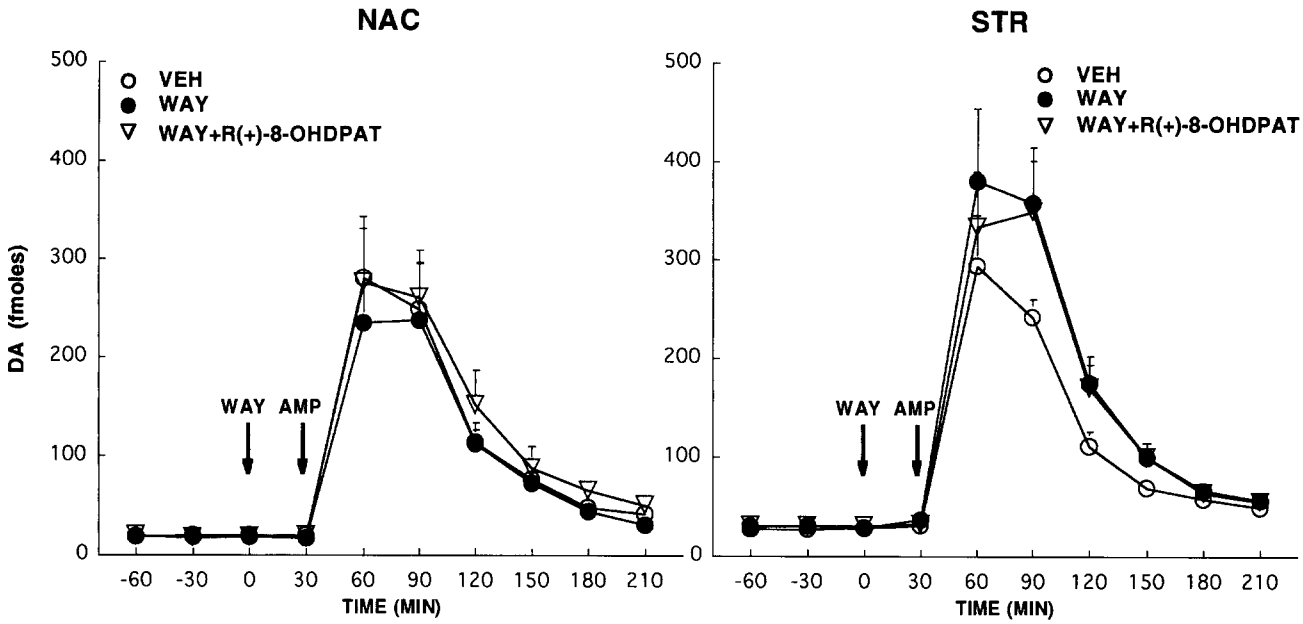

Fig. 2. The time course of the pretreatment effect of $R(+)$-8-OH-DPAT (50 μg/kg) 5 min after WAY 100,635 (100 μg/kg s.c.) on the ability of *d*-amphetamine (AMP, 1.0 mg/kg s.c.) to increase in vivo extracellular dopamine levels in rat nucleus accumbens (NAC) and striatum (STR). Repeated measure analysis of variance (ANOVA) revealed that WAY 100,635 (100 μg/kg s.c.), administered 5 min prior to $R(+)$-8-OH-DPAT (50 μg/kg s.c.) had no significant effect on the ability of amphetamine (1.0 mg/kg s.c.) to increase extracellular dopamine levels in the striatum and the nucleus accumbens. WAY 100,635 (100 μg/kg s.c.) alone did not affect amphetamine-induced increase in extracellular dopamine levels in either regions. Data are means ± S.E.M. (bars) of corresponding time points, expressed as absolute dopamine values (n = 6–9).

amphetamine-induced increase in extracellular dopamine levels in the striatum ($F = 8.64$, $P = 0.0096$), but not in the nucleus accumbens ($F = 0.83$, $P = 0.38$). The effect of $R(+)$-8-OH-DPAT (1000 μg/kg) was significantly diminished compared to the effect of $R(+)$-8-OH-DPAT (25 and 50 μg/kg) in both regions (F, $P = 5.26$, 0.02; 9.51, 0.03, respectively, for the striatum and 5.49, 0.02; 13.78, 0.0004, respectively, for the nucleus accumbens).

3.2. Effect of WAY 100,635 (Fig. 2)

d-Amphetamine sulfate (1.0 mg/kg s.c.) alone with vehicle pretreatment produced a marked increase in extracellular dopamine in the nucleus accumbens (absolute net increase: 280 ± 63 compared to basal value 19.9 ± 2.04 fmol/30 min) and the striatum (293 ± 53 compared to basal value 28.3 ± 2.91 fmol/30 min), respectively, 30 min after amphetamine administration. WAY 100,635 (100 μg/kg s.c.), a selective 5-HT_{1A} receptor antagonist (Fletcher et al., 1994), administered 5 min prior to $R(+)$-8-OH-DPAT (50 μg/kg s.c.) abolished the inhibitory effect of $R(+)$-8-OH-DPAT on amphetamine-induced increase in extracellular dopamine levels in both striatum and nucleus accumbens during a 180-min period following amphetamine. Repeated measure ANOVA revealed that there is no significant difference between the three groups, vehicle-amphetamine, WAY 100,635-amphetamine and WAY 100,635 + $R(+)$-8-OH-DPAT-amphetamine in the striatum ($F = 1.90$, $P = 0.18$) and nucleus accumbens ($F = 0.29$, $P = 0.75$). Note that the effect of WAY 100,635 (100 μg/kg s.c.), administered 30 min prior to amphetamine on amphetamine-induced increase in extracellular dopamine levels in the striatum was close to the significant level ($F = 3.78$, $P = 0.07$).

4. Discussion

Inhibition of amphetamine-induced dopamine release by $R(+)$-8-OH-DPAT could be due to a decrease in dopamine synthesis. Reduction of intraneuronal dopamine synthesis by 8-OH-DPAT, as demonstrated by Johnson et al. (1993, see the Introduction), would decrease the size of the releasable dopamine pool on which amphetamine may act, leading to a decrease in amphetamine-induced dopamine release. Interestingly, the lower dose (0.3 mg/kg) but not the higher dose of 8-OH-DPAT (3.0 mg/kg s.c.) decreased DOPA accumulation (Johnson et al., 1993). This could be analogous to the present finding that a higher dose (1000 μg/kg) of $R(+)$-8-OH-DPAT produced a lesser inhibitory effect on amphetamine-induced dopamine release. Possibly, high doses of $R(+)$-8-OH-DPAT may

lose selectivity for 5-HT_{1A} receptor-mediated regulation of dopamine synthesis or activate other system, e.g. noradrenergic system.

R(+)-8-OH-DPAT might be a dopamine receptor agonist which would reduce dopamine synthesis by stimulation of dopamine autoreceptors. However, it seems unlikely since the selective 5-HT_{1A} receptor antagonist WAY 100,635 abolished the effect of *R*(+)-8-OH-DPAT on amphetamine-induced dopamine release (Fig. 2). It should be noted that pretreatment with WAY 100,635 (100 μg/kg s.c.) showed a trend for potentiation of amphetamine-induced dopamine release in the striatum ($P = 0.07$, Fig. 2). This would support the hypothesis that an increase in dopamine synthesis by 5-HT_{1A} receptor blockade potentiates amphetamine-induced dopamine release.

5-HT_{1A} receptors may be functional in the striatum and nucleus accumbens despite their low density (Pompeiano et al., 1992) since: (1) even after inactivation of somatodendritic 5-HT_{1A} receptors by the application of pertussis toxin in the dorsal raphe nucleus, 8-OH-DPAT can still decrease striatal 5-HT release (Romero et al., 1994), (2) local perfusion of 8-OH-DPAT via dialysis probe in the striatum increased dopamine release (Benloucif and Galloway, 1991), (3) local perfusion of 5-HT via dialysis probe increased dopamine release, an effect which is attenuated by co-perfusion of pindolol, a mixed 5-$HT_{1A/1B}$ receptor antagonist (Parsons and Justice, 1993), and (4) Johnson et al. (1993) reported that the effect of 8-OH-DPAT (10 μM) on in vitro inhibition of tyrosine hydroxylation, the rate limiting step in dopamine synthesis, in synaptosome-rich preparations of rat striatum was antagonized by NAN 190 (10 μM), but the effect of 5-HT (10 μM) was not affected by the 5-$HT_{2A/2C}$ receptor antagonist ketanserin (100 nM).

An indirect effect of 5-HT_{1A} receptor stimulation on dopamine synthesis and amphetamine-induced dopamine release is also possible. Reduction of serotonergic input due to a decrease in 5-HT release via 5-HT_{1A} receptors on 5-HT neurons may affect dopaminergic activity since direct injection of 5-HT (2 μg) into the dorsal raphe nucleus which would be expected to stimulate somatodendritic 5-HT_{1A} receptors, decreased extracellular dopamine levels in the nucleus accumbens (Yoshimoto et al., 1992). However, it seems unlikely since 8-OH-DPAT (30 μg/kg) decreased 5-HT release in the nucleus accumbens while leaving dopamine release unaffected (Tanda et al., 1994). More importantly, decrease in 5-HT release in the nucleus accumbens could not result from stimulation of somatodendritic 5-HT_{1A} receptors in the dorsal raphe nucleus as discussed above (Romero et al., 1994). Invernizzi et al. (1991) also reported that 8-OH-DPAT (1 and 5 μg), injected into either the dorsal raphe or medial raphe nucleus, decreased accumulation of the 5-HT precursor 5-HTP (5-hydroxytryptophan) in the striatum and the nucleus accumbens following NSD-1015, but did not modify DOPA accumulation in either region. These results suggest that the effect on dopamine release and synthesis observed here and by Johnson et al. (1993) may not be mediated by somatodendritic 5-HT_{1A} receptor stimulation. A third possibility is that *R*(+)-8-OH-DPAT exerts an inhibitory effect on dopamine uptake which would also inhibit amphetamine-induced dopamine release (Butcher et al., 1988). However, it seems unlikely since *R*(+)-8-OH-DPAT at 50 μg/kg, which is the most effective dose for inhibition of amphetamine-induced dopamine release, had no effect on basal extracellular dopamine levels in the striatum and the nucleus accumbens in the present study. Finally, it could be argued that *R*(+)-8-OH-DPAT inhibits the availability of amphetamine in rat brain. However, it seems unlikely since higher doses of *R*(+)-8-OH-DPAT showed the smaller inhibition.

Discrepancy in the effect of 8-OH-DPAT on synthesis and release of dopamine is not clearly explained at present. Rasmusson et al. (1994) reported that (±)-8-OH-DPAT (225 μg/kg) decreased striatal dopamine release. Benloucif and Galloway (1991) reported (±)-8-OH-DPAT (100 μg/kg) did not affect basal extracellular dopamine levels, but decreased extracellular levels of DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid), major metabolites of dopamine, in the striatum. Decrease in extracellular DOPAC may indicate reduction of intraneuronal dopamine synthesis since origin of extracellular DOPAC is believed to be newly synthesized dopamine. There seems difference in the threshold dose of 8-OH-DPAT to affect synthesis and release of dopamine.

In summary, the present study demonstrated that *R*(+)-8-OH-DPAT, a selective 5-HT_{1A} receptor full agonist, significantly inhibited amphetamine-induced increase in extracellular dopamine levels in the striatum and the nucleus accumbens, an effect which was abolished by WAY 100,635, a selective 5-HT_{1A} receptor antagonist. These results suggest that 5-HT_{1A} receptors may exert an inhibitory effect on amphetamine-induced dopamine release in the striatum and nucleus accumbens.

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