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Modulation of a (+)amphetamine discriminative stimulus in rats by 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (8-OH DPAT)

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Abstract

It is well established that the discriminative stimulus (DS) effect of amphetamine involves a dopaminergic and/or noradrenergic mechanism. These catecholamines can be modulated by the 5-HT_{1A} serotonin receptor agonist 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (8-OH DPAT). The present study was conducted to determine whether 8-OH DPAT could influence the DS effects of (+)amphetamine. Administration of 8-OH DPAT doses to Sprague–Dawley rats trained to discriminate 1 mg/kg of (+)amphetamine (ED_{50}=0.33 mg/kg) using a two-lever operant paradigm (VI-15 s schedule of reinforcement for appetitive reward) failed to result in stimulus generalization when administered alone, and failed to antagonize the stimulus effect when administered in combination with the training dose of (+)amphetamine. However, administration of 8-OH DPAT doses that produced saline-like responding (i.e., 0.01–0.1 mg/kg; <20% amphetamine-appropriate responding) in combination with the ED_{50} dose of (+) amphetamine resulted in the animals' making a progressively greater number of responses on the drug-appropriate lever such that a combination of 0.1 mg/kg of 8-OH DPAT plus (+)amphetamine (0.33 mg/kg) elicited 91% (+)amphetamine-appropriate responding. In a separate study, administration of (+)amphetamine doses in combination with fixed doses of 8-OH DPAT (either 0.01 or 0.1 mg/kg) resulted in an apparent leftward shift of the dose–response curve. The results indicate that (+)amphetamine can be more effective as a discriminative stimulus in the presence of 8-OH DPAT than in its absence.

Keywords: Drug discrimination; (+)Amphetamine; 8-OH DPAT; Serotonin receptors

MDMA (i.e., *N*-methyl-1(3,4-methylenedioxyphenyl)-2-aminopropane or methylenedioxymethamphetamine) is an empathogenic agent that possesses some degree of amphetamine-like central stimulant character. It also serves as an effective discriminative stimulus in animals (e.g. Glennon, 1989). Although the exact mechanism underlying the MDMA stimulus remains to be fully elucidated, evidence suggests it is probably complex and involves serotonergic, dopaminergic, and noradrenergic components (see Bondareva et al., 2005 for discussion). Recently, we demonstrated that MDMA-stimulus generalization occurs to the 5-HT_{1A} agonist 8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (8-OH DPAT) and its R(+)- and S(−)-optical isomers (Glennon and Young, 2000). The latter results could be explained on the basis that activation of 5-HT_{1A} receptors modulates dopamine and norepinephrine levels in discrete brain areas; this might account for the observed similarity of stimulus effects. In general, administration of 8-OH DPAT can alter dopamine release and synthesis. Some of the particular results are, however, in apparent conflict. For example, 8-OH DPAT has been demonstrated to decrease rat striatal dopamine synthesis (Johnson et al., 1993) whereas local perfusion increased extracellular dopamine levels (Benloucif and Galloway, 1991). 8-OH DPAT and/or its R(+)-isomer decreased (Yoshimoto and McBride, 1992), or had no effect on (Arborelius et al., 1993b; Tanda et al., 1994), extracellular dopamine levels in rat nucleus accumbens or striatum, whereas both agents increased extracellular dopamine levels in prefrontal cortex (Arborelius et al., 1993b; Tanda et al., 1994). 5-HT_{1A} receptor stimulation by 8-OH DPAT has been shown to increase basal dopamine release in rat medial prefrontal cortex

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(Arborelius et al., 1993a; Kuroki et al., 1996; Rasmussen et al., 1994; Smith and Cutts, 1990) and mouse prefrontal cortex (Ago et al., 2003), whereas R(+)8-OH DPAT, at the single time point examined, decreased dopamine synthesis in rat (Kuroki et al., 2000). Furthermore, it has been reported that 8-OH DPAT produces an increase in dopamine and norepinephrine turnover in the ventral tegmentum (Chen and Reith, 1995). Arborelius et al. (1993a), however, found that the effect of R(+)8-OH DPAT on firing of dopaminergic neurons (ventral tegmental area) was biphasic, producing an increase at low doses and a decrease at high doses. A general conclusion is that dopaminergic and adrenergic mechanisms can be modulated by 8-OH DPAT, but the results suggest that drug concentrations, brain regions, and temporal parameters play a substantial role in the outcome of these studies.

Because i) MDMA possesses at least some amphetamine-like central stimulant character (see Bondareva et al., 2005), ii) MDMA-stimulus generalization occurs to (+)amphetamine, (Glennon et al., 1986; Glennon, 1989; Oberlender and Nichols, 1988), and iii) the stimulus actions of amphetamine involve a dopaminergic and/or adrenergic mechanism (Young and Glennon, 1986), it could be reasonably expected that 8-OH DPAT might also impact the behavioral effects of amphetamine. However, relatively few studies have examined the effect of 8-OH DPAT on amphetamine's behavioral actions. In an early study, 8-OH DPAT failed to inhibit (+)amphetamine-induced locomotor activity when administered directly into the nucleus accumbens (Layer et al., 1992). Subsequently, it was shown that systemically-administered 8-OH DPAT potentiates (+)amphetamine-induced hyperlocomotion in rats (Jackson et al., 1994). However, in another study 8-OH DPAT antagonized the hyperlocomotor effects of (+)amphetamine (Przegalinski and Filip, 1997); the disparate findings were explained, at least in part, on the different rat strains used (Sprague–Dawley in the former and Wistar in the latter). The results could be further confounded by the action of 8-OH DPAT on locomotor activity when administered by itself. 8-OH DPAT and/or its more efficacious R(+)-isomer can increase rat motor activity (e.g. Ahlenius et al., 1993; Chen and Reith, 1995; Jackson et al., 1998; Mignon and Wolf, 2002). But, various aspects of motor activity are influenced differently. For example, although 8-OH DPAT has been shown to suppress horizontal and vertical ("rearing") locomotor action, activity along the walls of an open area ("peripheral activity") was increased (Hillegaart et al., 1989); in comparison, Jackson et al. (1998) also found a decrease in vertical activity, but an increase both in horizontal and peripheral activity. Curiously, the local application of 8-OH DPAT to rat dorsal raphe produced a decrease in locomotor activity whereas application to median raphe nuclei produced a marked increase in locomotor activity (Hillegaart, 1990). These varying actions of 8-OH DPAT on motor activity are not inconsistent with the varying effects that 8-OH DPAT has on the dopaminergic system (see above). In addition, Chen and Reith (1995) also have argued for an adrenergic role in the hyperlocomotor actions of 8-OH DPAT.

8-OH DPAT has been examined for its effect on the discriminative stimulus actions of amphetamine. Pretreatment by 8-OH DPAT of Wistar rats trained to discriminate (+)amphetamine from saline vehicle had no effect on drug-appropriate responding (Przegalinski and Filip, 1997), whereas 8-OH DPAT was shown to antagonize the stimulus effect of (+)amphetamine in monkeys (Nader and Woolverton, 1994). This could be a species-related effect (Przegalinski and Filip, 1997). Furthermore, in pigeons trained to discriminate methamphetamine from vehicle, 8-OH DPAT produced drug-appropriate responding at high doses, and antagonism of the methamphetamine stimulus at lower doses (Sasaki et al., 1995) whereas in methamphetamine-trained rats 8-OH DPAT neither substituted for (i.e., produced <30% drug-appropriate responding), nor antagonized the methamphetamine stimulus (Munzar et al., 1999).

At this time, the effect of 8-OH DAPT on the discriminative stimulus produced by (+)amphetamine in Sprague–Dawley rats has not been examined. In the present investigation, we examined the effect of 8-OH DPAT alone, or in combination with (+)amphetamine, in this strain of rats trained to discriminate 1 mg/kg of (+)amphetamine from vehicle in order to determine if the combination would result in increased, decreased, or no alteration of (+)amphetamine-appropriate responding.

1. Materials and methods

Five male Sprague–Dawley rats (Charles River Laboratories), weighing 250–300 g at the beginning of the study, were trained to discriminate (15-min pre-session injection interval) 1.0 mg/kg of *S*(+)amphetamine from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reinforcement for sweetened condensed milk reward using standard two-lever Coulbourn Instruments operant equipment. Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

In brief, animals were food-restricted to maintain body weights of approximately 80% that of their free-feeding weight, but were allowed access to water ad lib in their individual home cages. Daily training sessions were conducted with the training dose of (+)amphetamine or saline. For approximately half the animals, the right lever was designated as the drug-appropriate lever, whereas the situation was reversed for the remainder of the animals. Learning was assessed every fifth day during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. Data collected during the extinction session included response rate (i.e., responses per minute) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the subsequent stimulus generalization studies until they consistently made ≥80% of their responses on the drug-appropriate lever after administration of training drug and ≤20% of their responses on the same drug-appropriate lever after administration of saline. During the testing (i.e., stimulus generalization or antagonism) phase of the study, maintenance of the training-drug/saline discrimination was insured by continuation of the training sessions on a daily basis (except on a test day). On one of the two days before an antagonism or generalization test, approximately half the animals would receive the training dose

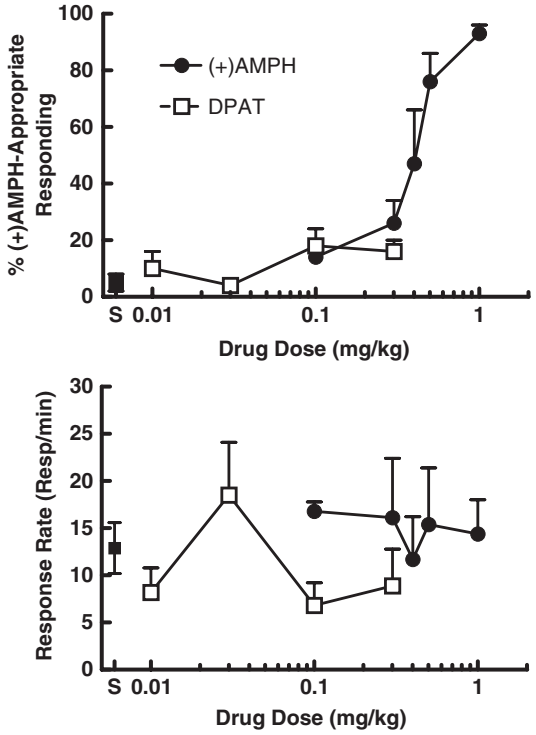

Fig. 1. Results of stimulus generalization studies in rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (upper panel). Shown is the mean (± S.E.M.) percent drug-appropriate responding following administration of (+)amphetamine and 8-OH DPAT (DPAT) doses; S = effect of saline (1 ml/kg). The animals' response rates (± S.E.M.) are shown in the lower panel.

of (+)amphetamine and the remainder would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original training criteria during the extinction session were excluded from the subsequent antagonism or generalization test session. During the investigations of stimulus antagonism or generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under non-reinforcement conditions. An odd number of training sessions (usually 5) separated any two test sessions. Doses of test drugs were administered to the groups of rats in a random order using a 15-min pre-session injection interval. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made ≥80% of their responses (group mean) on the training drug-appropriate lever, whereas antagonism was defined as ≤20% drug-appropriate responding following a drug combination. Animals making fewer than 5 total responses during the 2.5-min extinction session were considered as being behaviorally disrupted. Percent drug-appropriate responding and response rate data refer only to animals making ≥5 responses during the extinction session (Young and Glennon, 1986). If >50% of the animals were disrupted following administration of a given drug dose, data were not plotted. Where applicable, an ED_{50} dose was calculated by the method of Finney (1952). These doses represent the drug dose where animals would be expected to make 50% of their responses on the drug-appropriate lever.

1.1. Drugs

(+)Amphetamine sulfate was available from previous studies conducted in our laboratories and (±)8-OH DPAT hydrobromide was purchased from Sigma-Aldrich (St. Louis, MO). Doses refer to the weight of the salts. Solutions in sterile 0.9% saline were freshly prepared each day and administered by intraperitoneal injection.

2. Results

Animals were trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle; administration of lower (+)amphetamine doses resulted in decreased percent drug-appropriate responding (Fig. 1) (ED_{50} = 0.33 mg/kg; 95% CL = 0.22–0.61 mg/kg). Administration of 8-OH DPAT doses (0.01, 0.03, 0.1, and 0.3 mg/kg) to the (+)amphetamine-trained animals resulted in the animals making < 20% of their responses on the (+)amphetamine-appropriate lever (Fig. 1). The animals' response rates were fairly consistent under the two conditions except that they were generally lower following administration of 8-OH DPAT compared to that observed following administration of (+)amphetamine (Fig. 1). Administered in combination with 1 mg/kg of (+)amphetamine, 8-OH DPAT doses (0.01–0.5 mg/kg) failed to alter percent drug-appropriate responding (Fig. 2). The animals' response rates did not vary substantially under these conditions.

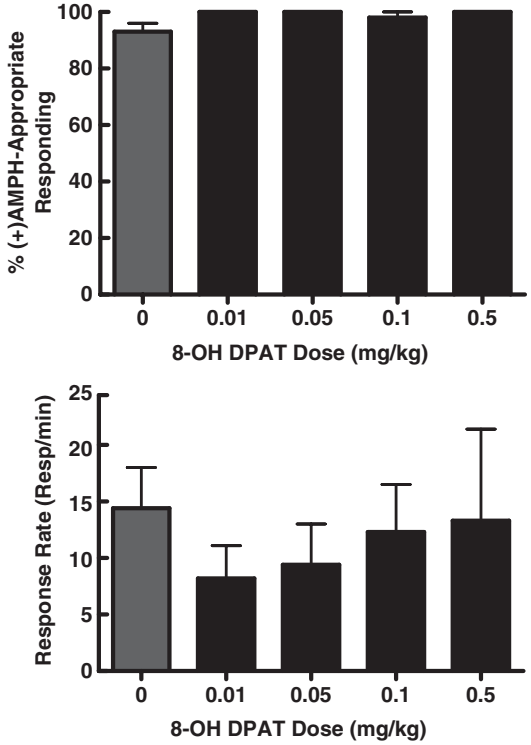

Fig. 2. Results of antagonism studies in rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (upper panel). Shown is the mean (± S.E.M.) percent drug-appropriate responding following administration of 1 mg/kg of (+)amphetamine in the absence or presence of 8-OH DPAT doses. The animals' response rates (± S.E.M.) are shown in the lower panel.

Administration of the ED_{50} dose of (+)amphetamine (i.e., 0.33 mg/kg) elicited 48(± 12)% (+)amphetamine-appropriate responding (response rate = 11.1 ± 1.7 resp/min). Pretreatment of the animals with 0.1 mg/kg of 8-OH DPAT (which by itself produced 18% (+)amphetamine-appropriate responding) resulted in the animals making 91% of their responses on the drug-appropriate lever (Fig. 3); the latter response was statistically different (Students $t = 5.9$, $df = 10$, $p < 0.0001$) from the response produced after administration of the (+)amphetamine ED_{50} dose alone. Response rates were not statistically different ($t = 1.1$, $df = 10$, $p > 0.05$) between the treatment conditions. Results with several other doses of 8-OH DPAT in combination with the ED_{50} dose of (+)amphetamine are also shown in Fig. 3. The animals' response rates did not vary substantially under these conditions.

Various doses of (+)amphetamine were examined in the absence, or in the presence of 8-OH DPAT (0.01 and 0.1 mg/kg) (Fig. 4). There was an apparent leftward shift in the response to (+)amphetamine when (+)amphetamine was administered in combination with 8-OH DPAT (Fig. 4). With the lower 8-OH DPAT dose, all animals responded at each dose combination; however, with the higher 8-OH DPAT dose, only 4/5 animals made >5 total responses during the 2.5-min extinction session under each combination condition ($ED_{50} = 0.19$ mg/kg; 95% CL = 0.13–0.34 mg/kg).

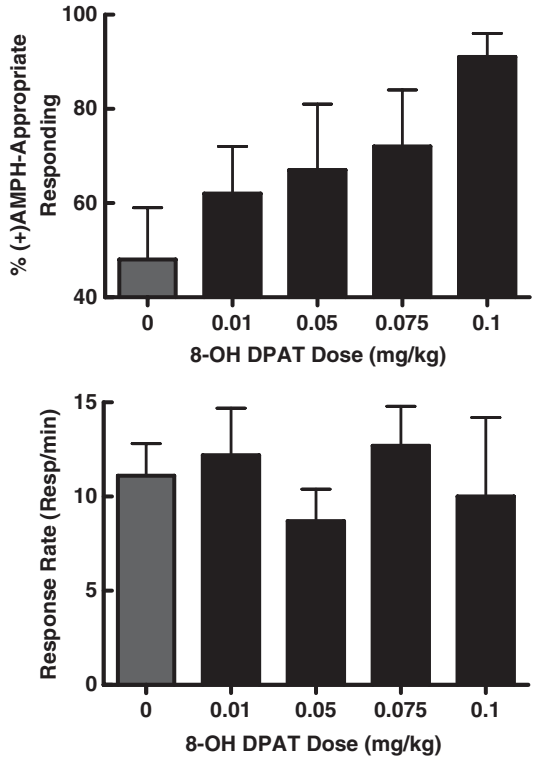

Fig. 3. Results of combination studies in rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (upper panel). Shown is the mean (± S.E.M.) percent drug-appropriate responding following administration of the ED_{50} dose of (+)amphetamine (0.33 mg/kg) in the absence or presence of 8-OH DPAT doses. A statistical difference (i.e., *t*-test; see Results) was noted between the mean percent drug-appropriate response produced by the ED_{50} dose of (+)amphetamine (48%) given alone and the response produced by the administration of 0.10 mg/kg of 8-OH DPAT in combination with the ED_{50} dose of (+)amphetamine (91%). The animals' response rates (± S.E.M.) were not statistically different and are shown in the lower panel.

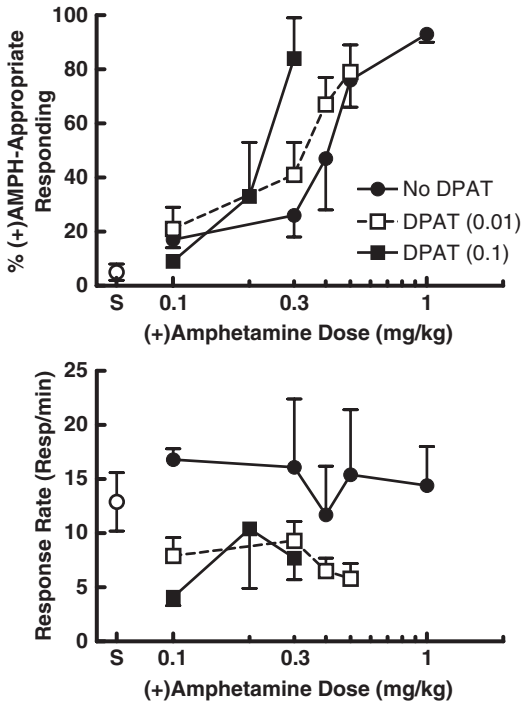

Fig. 4. Results of combination studies in rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (upper panel). Shown is the mean (± S.E.M.) percent drug-appropriate responding following administration of (+)amphetamine doses in the absence (no DPAT) or in the presence of either 0.01 mg/kg (DPAT 0.01) or 0.1 mg/kg (DPAT 0.1) of 8-OH DPAT. The animals' response rates (± S.E.M.) are shown in the lower panel.

3. Discussion

8-OH DPAT is a fairly potent agent and we have previously shown that 8-OH DPAT serves as an effective discriminative stimulus in rats at a training dose of 0.2 mg/kg (Glennon, 1986). Others subsequently employed training doses as low as 0.05 mg/kg (Sanger and Schoemaker, 1992; Tricklebank et al., 1987). Results of these studies indicated that the stimulus actions of 8-OH DPAT are most probably 5-HT_{1A}-mediated. High (micromolar) concentrations of 8-OH DPAT may also function as a direct-acting dopamine (D_2) partial agonist in second messenger studies (Rinken et al., 1999); however, the primary interest of the present investigation was the influence of relatively low doses of 8-OH DPAT.

Although both (+)amphetamine and 8-OH DPAT share a common phenylethylamine skeleton, 8-OH DPAT failed to engender > 20% (+)amphetamine-appropriate responding at doses of up to 0.3 mg/kg (Fig. 1). Administered in combination with the training dose of (+)amphetamine, doses of 8-OH DPAT (0.01–0.5 mg/kg) also failed to antagonize the (+)amphetamine stimulus (Fig. 2). The latter results in Sprague–Dawley rats are consistent with those of Przegalinski and Filip (1997) who showed that 8-OH DPAT doses of from 0.1 to 0.5 mg/kg failed

to antagonize a (+)amphetamine stimulus in Wistar rats trained to discriminate (+)amphetamine from saline vehicle.

8-OH DPAT was administered in combination with the ED_{50} dose (i.e., 0.33 mg/kg) of (+)amphetamine. By itself, this dose of (+)amphetamine produced 48% (+)amphetamine-appropriate responding (Fig. 3). Pretreatment of the animals with 8-OH DPAT doses ranging from 0.01 to 0.1 mg/kg resulted in the animals making a progressively increased number of responses on the drug-appropriate lever such that a combination of the ED_{50} dose of (+)amphetamine plus 0.1 mg/kg of 8-OH DPAT resulted in 91% (+)amphetamine-appropriate responding. That is, at this dose combination, the animals responded to the ED_{50} dose of (+)amphetamine as if they had been administered the (+)amphetamine training dose.

To further assess the ability of 8-OH DPAT to modulate the (+)amphetamine stimulus, dose–response curves were constructed for (+)amphetamine in the absence, and in the presence of a fixed dose (either 0.01 or 0.1 mg/kg) of 8-OH DPAT (Fig. 4). The lower dose of 8-OH DPAT resulted in a slight leftward shift of the (+)amphetamine dose–response curve. Pretreatment with 0.1 mg/kg of 8-OH DPAT resulted in a further leftward shift in the dose–response curve (Fig. 4). The results shown in Figs. 3 and 4 clearly demonstrate that (+)amphetamine appears more effective as a discriminative stimulus in the presence of low doses of 8-OH DPAT than it does in the absence of 8-OH DPAT.

Unlike what was seen with (+)amphetamine trained monkeys (Nader and Woolverton, 1994), 8-OH DPAT failed to antagonize the (+)amphetamine stimulus in rats. As suggested by Przegalinski and Filip (1997), this could be a species-related phenomenon. Unlike with pigeons trained to discriminate methamphetamine from vehicle, 8-OH DPAT failed to substitute for the (+)amphetamine stimulus. Here, the difference could be related either to the animal species and/or to the training drug employed (i.e., methamphetamine versus amphetamine). It might be noted that Munzar et al. (1999) found lack of substitution or antagonism by 8-OH DPAT in methamphetamine-trained rats. One of the present findings is that 8-OH DPAT does not antagonize the stimulus effects of (+) amphetamine at 8-OH DPAT doses equivalent to, and greater than, those that serve as discriminative stimuli in rats. In this regard, the results are consistent with those of Przegalinski and Filip (1997). However, the latter investigators did not investigate the potential stimulus-enhancing effects of 8-OH DPAT on the (+)amphetamine stimulus. In the present study, it was found that co-administration of doses of 8-OH DPAT that produced saline-like responding together with (+)amphetamine doses lower than the training dose, resulted in a high level of drug-appropriate responding. Specifically, this was demonstrated by the administration of the ED_{50} dose of (+)amphetamine in combination with different low doses of 8-OH DPAT, and by co-administration of (+)amphetamine doses in the presence of a fixed dose (either 0.01 or 0.1 mg/kg) of 8-OH DPAT, to (+) amphetamine-trained rats. Taken together, it appears that 8-OH DPAT made (+)amphetamine more amphetamine-like to the (+) amphetamine-trained animals. Although it is tempting to speculate that this is a specific 5-HT_{1A}-mediated effect involving modulation of dopamine and norepinephrine neurotransmission, the mechanistic basis underlying this phenomenon, and possible involvement of dopamine and/or norepinephrine, remains to be determined. In particular, 8-OH DPAT and its *R*-isomer have long been considered prototypical 5-HT_{1A} agonists, but evidence now suggests that they also are 5-HT_7 agonists or, at least, partial agonists (e.g. Krobert et al., 2001; Lovenberg et al., 1993). In fact, some actions previously attributed to a 5-HT_{1A} mechanism, because they were elicited by 8-OH DPAT, are now thought to involve 5-HT_7, or a combination of 5-HT_{1A} and 5-HT_7, mechanisms. For example, the hypothermic effects of 8-OH DPAT in rodents – once attributed solely to a 5-HT_{1A} mechanism – have been recently shown to involve both a 5-HT_{1A} and a 5-HT_7 mechanism; furthermore, low-dose 8-OH DPAT-induced hypothermia was found to be exclusively 5-HT_7-mediated (Hedlund et al., 2004). The specific involvement of 5-HT_{1A} and/or 5-HT_7 serotonin receptors in the (+)amphetamine stimulus-enhancing actions of 8-OH DPAT will require further investigation.

Acknowledgments

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