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EMD 68843, a serotonin reuptake inhibitor with selective presynaptic 5-HT_{1A} receptor agonistic properties

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Abstract

The 5-HT_{1A} receptor agonist 8-hydroxy-(di-*n*-propylamino)tetralin (8-OH-DPAT; 0.55 mg/kg s.c.) and the 5-HT (5-hydroxytryptamine, serotonin) reuptake inhibitor/5-HT_{1A} receptor ligand 5-{4-[4-(5-cyano-3-indolyl)-butyl]-1-piperazinyl}-benzofuran-2-carboxamide (EMD 68843; 55 mg/kg p.o.) inhibited ultrasonic vocalization in rats, an effect which was antagonized by the 5-HT_{1A} receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamide (WAY 100635; 1.0 mg/kg s.c.). 8-OH-DPAT decreased body temperature in rats, an effect which was also antagonized by WAY 100635, whereas EMD 68843 neither affected body temperature by itself nor interacted with 8-OH-DPAT or WAY 100635. The selective 5-HT reuptake inhibitor fluoxetine (100 mg/kg p.o.) had no effect on ultrasonic vocalization or body temperature. Therefore EMD 68843 is suggested to be a 5-HT_{1A} receptor agonist selective for presynaptic 5-HT_{1A} receptors.

Keywords: 5-HT_{1A} autoreceptor; EMD 68843; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); Fluoxetine; WAY 100635; Hypothermia; Ultrasonic vocalization; (Rat)

1. Introduction

Ultrasonic vocalization in rats is an animal model to test for the anxiolytic (De Vry et al., 1993) and antipanic activity (Molewijk et al., 1995) of drugs. Amongst various classes of anxiolytic drugs, serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{1A} receptor full agonists such as 8-hydroxy-(di-*n*-propylamino)tetralin (8-OH-DPAT) and partial agonists such as ipsapirone have been reported to inhibit ultrasonic vocalization (De Vry et al., 1993; Griebel, 1995; Sánchez, 1993), and the anxiolytic effects of 5-HT_{1A} receptor agonists are mediated presynaptically (Schreiber and De Vry, 1993; Jolas et al., 1995). Moreover, 5-HT_{1A} receptor agonists decrease body temperature, and, at least in rats, this effect is mediated postsynaptically (O'Connell et al., 1992; Peglion et al., 1995; Thielen and Frazer, 1995). Both the temperature-lowering effects and the anxiolytic activity of 5-HT_{1A} receptor agonists are counteracted by selective 5-HT_{1A} receptor antagonists (Peglion et al., 1995; De Vry, 1995).

EMD 68843 (Fig. 1) is a serotonin reuptake inhibitor (IC_{50} 0.2 nM in vitro, 3.8 mg/kg p.o. in vivo) which additionally exhibits high affinity for 5-HT_{1A} receptors (IC_{50} 0.5 nM). With a delayed onset of action because of its slow absorption after oral administration, EMD 68843 exhibits antidepressant-like activity and shows anxiolytic activity in the ultrasonic vocalization test in rats (ED_{50} 12.8 mg/kg p.o. when measured 2 h after administration; Bartoszyk et al., 1996). The studies reported investigated the behavioural effects related to the 5-HT_{1A} properties of EMD 68843 at presynaptic versus postsynaptic 5-HT_{1A} receptors.

2. Material and methods

2.1. Core temperature

Core body temperature in rats was measured rectally by a thermograph (Bosch Thermotest) every 15 min, twice before and then for 2 h after administration of single drugs or after administration of the first drug in the combination experiments. Drugs were administered immediately after the preceding temperature measurement at the time indicated in the figures.

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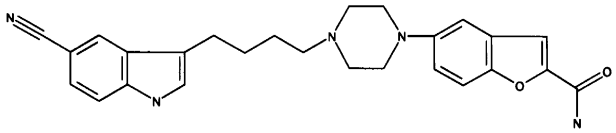

Fig. 1. EMD 68843.

2.2. Ultrasonic vocalization

Ultrasonic vocalization was measured in a sound-attenuated test chamber (W 24 cm, L 22 cm, H 22 cm) with a grid floor for delivery of footshocks (scrambled shock of 1.8 mA for 0.3 s, shocker Getra BN 2002). Ultrasonic vocalization was recorded (microphone 4004, Bruel and Kjær) and processed by an interface (developed at Merck KGaA) to select 22 ± 4 kHz signals and to digitize the resulting signals for automatic processing in a personal computer.

In a priming phase, each rat was placed in the test chamber. After 2 min, a series of at most ten shocks (trials), 1.8 mA for 0.3 s, separated by 20 s shock-free intervals, was delivered via the grid floor of the test chamber. In the shock-free intervals the occurrence of ultrasonic vocalization was automatically recorded, and the duration of ultrasonic vocalization was calculated immediately. The priming session was terminated either when the rat constantly vocalized at least for 10 s on three consecutive trials or after the tenth trial. Rats that did not respond with ultrasonic vocalization on three consecutive trials were excluded from the test. In the actual test performed the next day, each rat received five initial shocks (1.8 mA for 0.3 s, separated by 20-s shock-free intervals) in the test chamber, and the duration of ultrasonic vocalization was recorded after the last shock for 3 min. Ultrasonic vocalization was measured 30 min, 120 min and 210 min after administration of single drugs. In the interaction experiments, WAY 100635 or placebo was administered 10 min before EMD 68843, 8-OH-DPAT, fluoxetine or placebo, i.e., 40 min before the first test; fluoxetine was given 10 min before 8-OH-DPAT.

2.3. Animals

Male rats were obtained from Charles River (Sulzfeld, Germany). For measurement of core temperature, Wistar rats (173–287 g) were used and in the ultrasonic vocalization test Sprague-Dawley rats (290–390 g) were used. Animals were housed in groups (two rats per cage) in a temperature- (20 ± 2°C) and humidity- (50–60%) controlled colony room under a non-reversed 12 (6–18 on)/12 h light-dark cycle with food and water ad libitum except during the actual experiments. Testing was done between 8 h and 14 h during the light phase of the day-night cycle.

2.4. Drugs

EMD 68843 (5-{4-[4-(5-cyano-3-indolyl)-butyl]-1-piperazinyl} -benzofuran-2-carboxamide, HCl salt; Merck, Darmstadt, Germany, lots 4 and 6) and fluoxetine (*N*-methyl-3-(4-trifluormethylphenoxy)-3-phenylpropylamine, oxalate salt; Merck) were suspended in 5% gum Arabic for oral administration. WAY 100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl]-N-(2-pyridyl)-cyclohexancarboxamide, 3HCl salt; Merck) and 8-OH-DPAT ((±)-8-hydroxy-(di-*n*-propylamino)tetralin, HBr salt; Research Biochemicals International, Cologne, Germany) were dissolved in physiological saline for subcutaneous administration. The volumes were 1 ml/kg for s.c. and 2 ml/kg for p.o. administration. Single doses used were EMD 68843 (55 mg/kg p.o.), fluoxetine (100 mg/kg p.o.), 8-OH-DPAT (0.55 mg/kg s.c.) and WAY 100635 (1.0 mg/kg s.c.) or respective placebo. For each drug or combination thereof, six rats were used in the ultrasonic vocalization test and four rats in the core temperature test.

2.5. Statistics

Means and S.E.M. were calculated for each group for any time measured and compared to the data for the

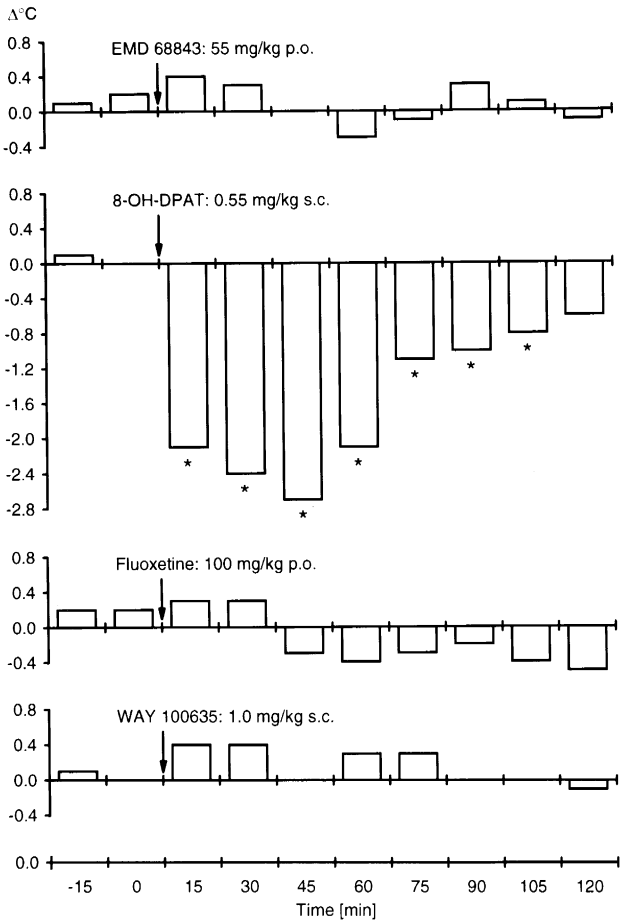

Fig. 2. Effects of EMD 68843, 8-OH-DPAT, fluoxetine and WAY 100635 on core temperature. Given are the mean deviations (Δ) in °C from the respective placebo group; for clearness, S.E.M.s (≤ 0.4°C) are not included. Time points −15 min and 0 min refer to the values before drug administration; all other time points represent time after administration of drug immediately after the preceding measurement. * P at least < 0.05 from control.

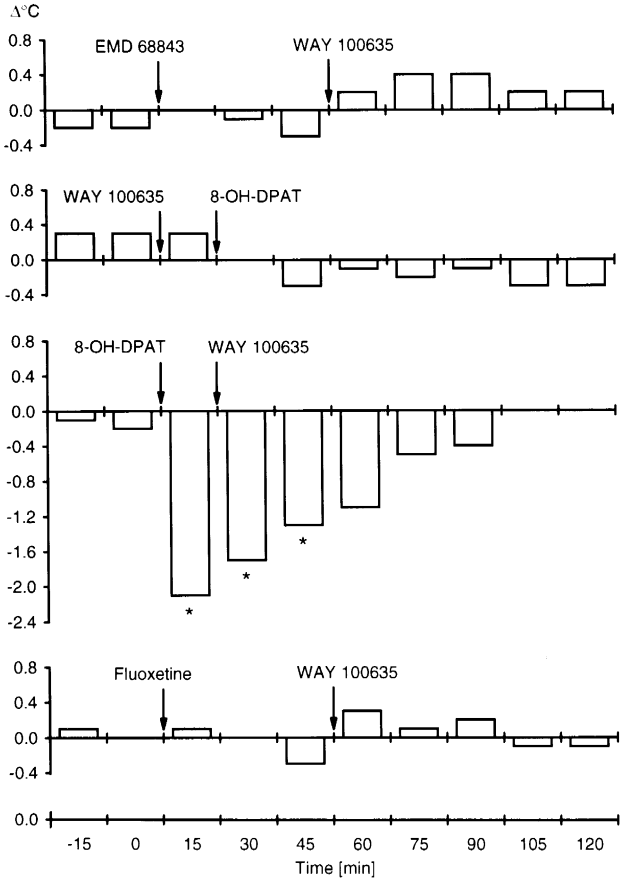

Fig. 3. Effect of combinations of EMD 68843 (55 mg/kg p.o.), 8-OH-DPAT (0.55 mg/kg s.c.), and fluoxetine (100 mg/kg p.o.) with WAY 100635 (1.0 mg/kg s.c.) on core temperature. Time points −15 and 0 min refer to the pre-administration values; all other time points represent time after administration of the first drug. For further details, see legend to Fig. 2.

respective placebo group by analysis of variance followed by Dunnett's test. For clearness, the deviations of core temperature from those of the respective placebo-treated control groups are presented instead of the original temperature curves.

3. Results

3.1. Core temperature

EMD 68843, fluoxetine and WAY 100635 did not significantly alter the body temperature of rats when measured for 2 h after drug administration whereas 8-OH-DPAT decreased body temperature significantly for over 1 h after drug administration (Fig. 2).

WAY 100635 completely prevented (when given before 8-OH-DPAT) or rapidly normalized (when given after 8-OH-DPAT) the hypothermia induced by 8-OH-DPAT (Fig. 3), whereas EMD 68843 did not affect the 8-OH-DPAT-induced decrease in body temperature (Fig. 4), even if a delayed onset of action of EMD 68843 is considered (as verified by the different application schedules). Fluoxetine prolonged the duration of the decrease in core temperature induced by 8-OH-DPAT. The combination of EMD 68843 and fluoxetine with WAY 100635 did not result in significant changes in body temperature (Fig. 3).

3.2. Ultrasonic vocalization

EMD 68843, with a delayed action, and 8-OH-DPAT potently inhibited ultrasonic vocalization whereas fluoxe-

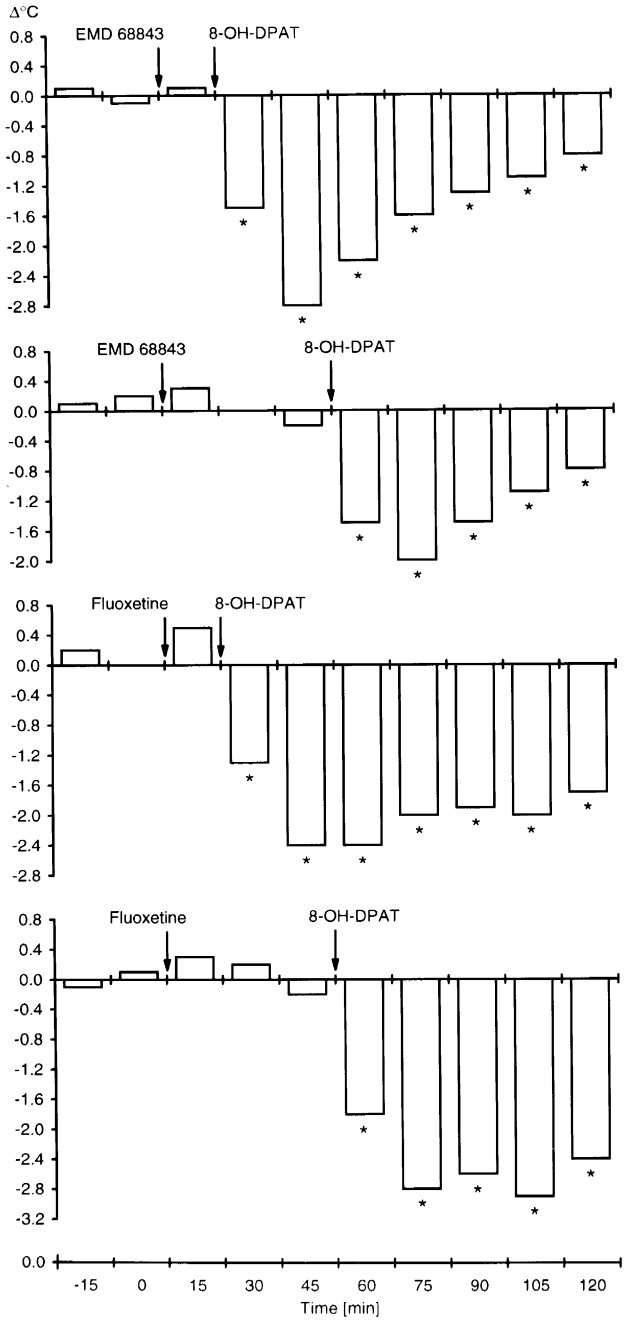

Fig. 4. Effects of combinations of EMD 68843 (55 mg/kg p.o.) and fluoxetine (100 mg/kg p.o.) with 8-OH-DPAT (0.55 mg/kg s.c.) on core temperature. For further details, see legend to Fig. 3.

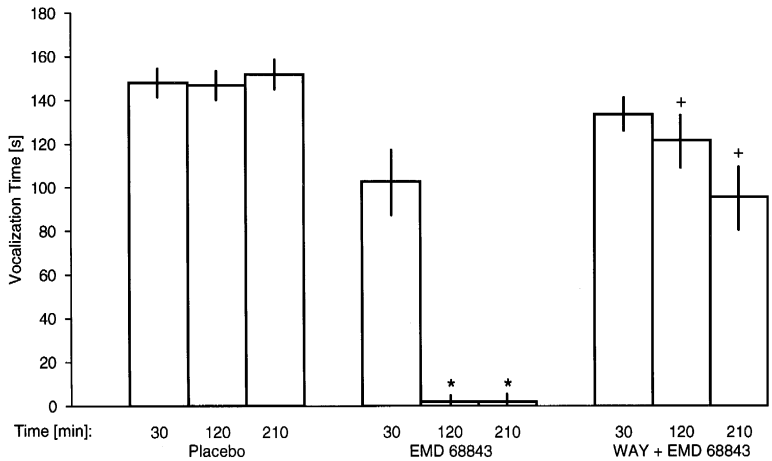

Fig. 5. Inhibition of ultrasonic vocalization at various times after administration of EMD 68843 (55 mg/kg p.o.), alone or in combination with WAY 100635 (1.0 mg/kg s.c., 10 min before EMD 68843). Given are the mean vocalization times ±S.E.M. (maximal time: 180 s). * P at least < 0.05 vs. placebo control; + P at least < 0.05 vs. drug alone.

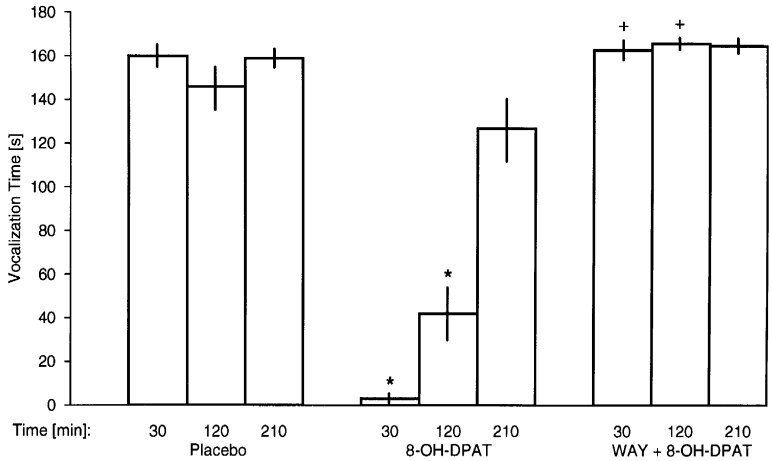

Fig. 6. Inhibition of ultrasonic vocalization at various times after administration of 8-OH-DPAT (0.55 mg/kg s.c.), alone or in combination with WAY 100635 (1.0 mg/kg s.c., 10 min before 8-OH-DPAT). Given are the mean vocalization times ±S.E.M. (maximal time: 180 s). * P at least < 0.05 vs. placebo control; + P at least < 0.05 vs. drug alone.

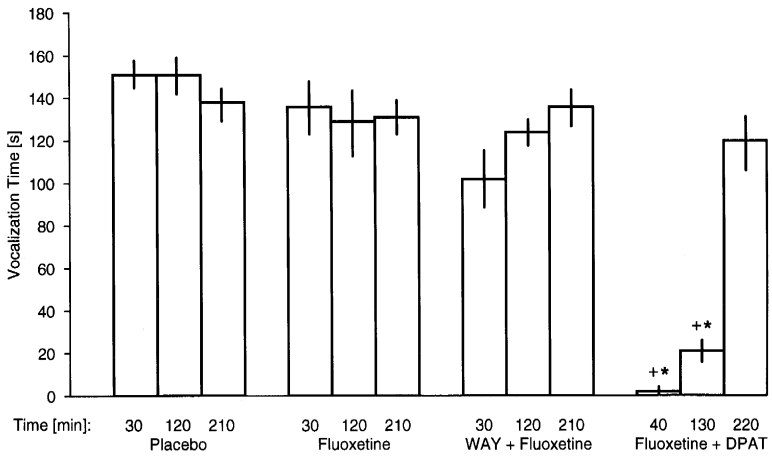

Fig. 7. Inhibition of ultrasonic vocalization at various times after administration of fluoxetine (100 mg/kg p.o.), in combination with placebo or WAY 100635 (1.0 mg/kg s.c., 10 min before fluoxetine) or 8-OH-DPAT (0.55 mg/kg s.c., 10 min after fluoxetine). Given are the mean vocalization times ±S.E.M. (maximal time: 180 s). * P at least < 0.05 vs. placebo control; + P at least < 0.05 vs. drug alone.

tine had no effect on ultrasonic vocalization (Figs. 5–7). WAY 100635 itself also had no effect on ultrasonic vocalization (mean vocalization time ± S.E.M.: 153 ± 17 s vs. placebo 156 ± 20 s).

The inhibition of ultrasonic vocalization by EMD 68843 and 8-OH-DPAT was completely antagonized by WAY 100635 (Figs. 5 and 6), whereas no effect was observed for the combination of fluoxetine with WAY 100635 or 8-OH-DPAT (Fig. 7).

4. Discussion

5-HT_{1A} receptors are located both postsynaptically (e.g., in the hippocampus, lateral septum, hypothalamus) and presynaptically as autoreceptors on soma and dendrites of 5-HT neurons in the raphe nuclei (Pazos and Palacios, 1985; Pazos et al., 1988). In rats, the decrease in body temperature observed with 5-HT_{1A} receptor agonists is postsynaptically mediated because hypothermia is still present following depletion of endogenous 5-HT (Hjorth, 1985; Hutson et al., 1987; Millan et al., 1993). The antianxiety effects of 5-HT_{1A} receptor agonists, at least in the ultrasonic vocalization test, result from activation of presynaptic (somatodendritic) receptors because local (as well as systemic) injections of 5-HT_{1A} receptor agonists inhibit firing of raphe nuclei neurons and reduce ultrasonic vocalization even after hippocampal lesions (Schreiber and De Vry, 1993; Sommermeyer et al., 1993; Jolas et al., 1995).

The potent silent 5-HT_{1A} receptor antagonist WAY 100635 (Craven et al., 1994; Fletcher et al., 1994) antagonized the 5-HT_{1A} receptor agonist-induced, i.e., 8-OH-DPAT-induced, decrease in body temperature (this study; Peglion et al., 1995) and inhibition of ultrasonic vocalization (this study; see also De Vry, 1995). EMD 68843 had no effect on body temperature itself and did not affect hypothermia induced by 8-OH-DPAT. Because hypothermia is a highly sensitive parameter even for weak partial 5-HT_{1A} receptor agonists (Hadrava et al., 1995; Peglion et al., 1995), agonistic or antagonistic properties of EMD 68843 at postsynaptic 5-HT_{1A} receptors can be excluded. But EMD 68843 potently inhibited ultrasonic vocalization, an effect which was counteracted by WAY 100635. Because the selective serotonin reuptake inhibitor fluoxetine had no effect on either core temperature (this study; Yamada et al., 1994) or ultrasonic vocalization (this study; De Vry et al., 1993), a contribution of the potent 5-HT uptake inhibiting properties of EMD 68843 to the observed effects is unlikely. Whereas 8-OH-DPAT is an agonist and WAY 100635, like other antagonists, is an antagonist at both presynaptic and postsynaptic 5-HT_{1A} receptors (Lanfumey et al., 1993; Mundey et al., 1996), EMD 68843 exhibited agonistic properties selectively at presynaptic 5-HT_{1A} receptors and had virtually no effects at postsynaptic 5-HT_{1A} receptors. But it should be mentioned that only further studies using, e.g., electrophysiological (Blier and De Montigny, 1990) or voltammetric (Davidson and Stamford, 1995) methods can finally confirm this interpretation.

Hypothermia induced by 8-OH-DPAT occurred rapidly within 15 min, and maximal responses lasted for about 1 h after drug administration. Unexpectedly, and to our knowledge not reported before, fluoxetine, administered 15 or 60 min before 8-OH-DPAT, prolonged the duration of the maximal hypothermic response to 8-OH-DPAT. Because we measured body temperature up to 120 min only, the duration of this effect is unknown, and only further investigations can elucidate whether fluoxetine indeed prolongs or even enhances the hypothermia induced by 5-HT_{1A} receptor agonists such as 8-OH-DPAT. In contrast, EMD 68843, although also a potent inhibitor of 5-HT uptake, had no effect on 8-OH-DPAT-induced hypothermia. This discrepant finding cannot be explained so far, but it was previously reported that some (including fluoxetine) but not all serotonin reuptake inhibitors antagonize fenfluramine-induced hyperthermia (Pawlowski et al., 1980; Sugrue, 1980).

The release of 5-HT in the hippocampus and the striatum is regulated by presynaptic 5-HT_{1A} autoreceptors located in the median and dorsal raphe nuclei (Bonvento et al., 1992; Kreiss and Lucki, 1994). Long-term administration of selective serotonin reuptake inhibitors induces desensitization of presynaptic 5-HT_{1A} autoreceptors (Goodwin et al., 1985; Blier et al., 1990; Kreiss and Lucki, 1995), and the latency of the therapeutic effects of the selective serotonin reuptake inhibitor antidepressants is attributed to the necessary development of desensitization of 5-HT_{1A} autoreceptors (Blier et al., 1987; Albert et al., 1996), i.e., desensitization of the normally inhibitory impulses from 5-HT_{1A} autoreceptors (Bonvento et al., 1992; Hjorth and Auerbach, 1994; Auerbach et al., 1995) opposing the required enhancement of 5-HT levels for relieving depression via activation of postsynaptic 5-HT receptors (for review, see Lucki, 1991). If 5-HT_{1A} autoreceptors are blocked acutely, the response to serotonin reuptake inhibitors should be enhanced immediately. Evidence for this approach comes from studies with pindolol which selectively blocks 5-HT_{1A} autoreceptors. Pindolol enhances the increase in extracellular 5-HT levels induced by selective serotonin reuptake inhibitors (Hjorth and Auerbach, 1994; Dreshfield et al., 1996; Hjorth, 1996), and in patients, pindolol has been reported to accelerate the antidepressant effect of selective serotonin reuptake inhibitors (Artigas et al., 1994; Bergeron et al., 1995; Blier and Bergeron, 1995).

Long-term administration of 5-HT_{1A} receptor agonists leads to desensitization of 5-HT_{1A} presynaptic but also postsynaptic receptors (Blier and De Montigny, 1987; Larsson et al., 1990; Godbout et al., 1991; Kreiss and Lucki, 1992; Jackson et al., 1994), and even single administration can induce desensitization of at least some postsynaptic 5-HT_{1A} receptors (Rényi et al., 1992; O'Connell

and Curzon, 1996). Because postsynaptic 5-HT_{1A} receptors are important for the relief of depression by 5-HT uptake inhibition, EMD 68843, which combines 5-HT uptake inhibition with selective presynaptic 5-HT_{1A} receptor agonism, is therefore a candidate for the treatment of depression and is expected to have an improved efficacy and accelerated onset of action, if rapid desensitization of 5-HT_{1A} autoreceptors occurs. Only future clinical studies with EMD 68843 will prove whether the combination of 5-HT reuptake inhibition and agonism at presynaptic 5-HT_{1A} receptors in one molecule has indeed therapeutic advantages.

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