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Role of 5-HT_{1B} receptors in the sensitization to amphetamine in mice

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Abstract

The present study was designed to determine how 5-HT_{1B} receptor ligands affected the development or the expression phase of sensitization to the amphetamine-induced locomotor response in mice. Mice were treated repeatedly (for 5 days) with amphetamine (2.5 mg/kg) in combination with either vehicle, *N*-[3-[3-(dimethylamino)ethoxy]-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1′-biphenyl]-4-carboxamide hydrochloride (SB 216641; an antagonist of 5-HT_{1B} receptors), 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-*b*]pyridine (CP 94,253; an agonist of 5-HT_{1B} receptors), or SB 216641 + CP 94,253; afterwards, on day 10, they received a challenge dose of amphetamine (2.5 mg/kg). In another experiment, mice were given either vehicle or amphetamine (2.5 mg/kg) for 5 days, and were then challenged with amphetamine (2.5 mg/kg) in combination with vehicle, SB 216641, or CP 94,253 on day 10. Locomotor hyperactivity induced by acute administration of amphetamine (day 1) was dose-dependently inhibited by SB 216641 and enhanced by CP 94,253, but not affected by a combination of SB 216641 + CP 94,253. The 5-HT_{1B} receptor ligands affected similarly the behavioral response to the challenge dose of amphetamine on day 10 (ca. 55–110% more potent than the response to its first administration) when they were combined with the psychostimulant during the development phase (days 1–5) of sensitization. On the other hand, neither SB 216641 nor CP 94,253 administered together with the challenge dose of amphetamine (day 10) affected its behavioral hyperactivity effect in mice treated repeatedly (days 1–5) with the psychostimulant alone. Our results suggest that 5-HT_{1B} receptors may play a permissive role in the development, but not expression, of behavioral sensitization, as well as in the acute locomotor response to amphetamine in mice.

Keywords: Amphetamine; CP 94,253; SB 216641; 5-HT_{1B} receptor; Locomotor activity; Sensitization; (Mouse)

1. Introduction

Repeated, intermittent administration of amphetamine and other psychostimulants (e.g. cocaine) results in sensitization (reverse tolerance), a phenomenon characterized by an increase in—among others—behavioral responses (locomotor hyperactivity, stereotypy, positive reinforcing effects) to the subsequent drug challenge after the repeated administration regimen is discontinued (Kalivas et al., 1988; Robinson and Berridge, 1993).

It seems of interest to understand the neural basis of sensitization, since chronic use of psychostimulants in humans may result in psychoses or craving for the drugs of abuse (Segal et al., 1981; Robinson and Berridge, 1993). It has been well established that the mesolimbic dopamine system plays a crucial role in psychostimulant sensitization to a locomotor hyperactivity effect, the ventral tegmental area containing dopamine cell bodies, and the nucleus accumbens where dopamine terminals are located being involved in the development and expression, respectively, of this phenomenon (Kalivas et al., 1988; King et al., 1993; Cador et al., 1995; Heidbreder et al., 1996). It has also been reported that the behavioral effects induced by repeated treatment with psychostimulants can be modulated by other neurotransmitter systems, e.g. excitatory amino acids or 5-hydroxytryptamine (serotonin; 5-HT) (Pierce and Kalivas, 1997). Regarding the latter system, it has been found that activation of 5-HT_{1A} receptors inhibits amphetamine sensitization to its locomotor effect in mice (Przegalinski et al., 2000). Furthermore, 5-HT_3 receptors have been reported to be involved in the development and expression of cocaine sensitization in rats (King et al., 1997, 2000).

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Numerous data indicate that also 5-HT_{1B} receptors may be engaged in sensitization to psychostimulants: (1) 5-HT_{1B} receptors and their mRNA are located in different brain structures including the ventral tegmental area and nucleus accumbens (Pazos and Palacios, 1985; Bruinvels et al., 1993); (2) 5-HT_{1B} receptors act not only as autoreceptors in terminal areas of the 5-HT system where they inhibit 5-HT release from 5-HT axons (Sharp et al., 1989; Hjorth and Tao, 1991), but also as heteroreceptors on other neurotransmitter nerve terminals, including dopamine ones (Sarhan et al., 1999); some in vitro studies have shown that pharmacological stimulation of these receptors inhibits dopamine release in rat striatal synaptosomes (Sarhan et al., 1999, 2000); (3) activation of 5-HT_{1B} receptors under in vivo conditions indirectly increases basal and cocaine-stimulated extracellular dopamine concentrations in rat nucleus accumbens (Guan and McBride, 1989; Boulenguez et al., 1996; Parsons et al., 1999); (4) ligands of 5-HT_{1B} receptors modify several behavioral effects of amphetamine (Fletcher and Korth, 1999a,b) and cocaine (Callahan and Cunningham, 1995, 1997; Parsons et al., 1998; Filip et al., 2001) including sensitization to the locomotor hyperactivity response induced by the latter drug in rats (Przegalinski et al., 2001). Actually, in the latter paper we reported that the development and expression of cocaine sensitization were enhanced by an agonist of 5-HT_{1B} receptors, but were unaffected by their antagonist.

In the light of the above-cited data it seemed of interest to study the role of 5-HT_{1B} receptors in the sensitization to amphetamine, since this psychostimulant acts through a slightly different than cocaine mechanism to augment the extracellular content of dopamine, an effect connected with sensitization to either psychostimulant (Kalivas and Stewart, 1991; Pierce and Kalivas, 1997). In fact, several biochemical and electrophysiological results indicate that amphetamine preferentially releases dopamine by promoting its reverse transport, whereas cocaine blocks the dopamine transporter (Ritz et al., 1990; Sulzer et al., 1995; Scarponi et al., 1999).

In the present paper, we examined the effect of 5-HT_{1B} receptor ligands on the development and expression of sensitization to the hyperlocomotion induced by amphetamine in mice. To this end we used *N*-[3-[3-(dimethylamino)ethoxy]-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1′-biphenyl]-4-carboxamide hydrochloride (SB 216641) and 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-*b*]pyridine (CP 94,253), an antagonist (Hagan et al., 1997) and an agonist (Koe et al., 1992) of 5-HT_{1B} receptors, respectively.

2. Materials and methods

2.1. Animals

The experiment was performed on male Albino–Swiss mice (28–31 g). The animals were housed in groups of 10 per cage at a room temperature of 20 ± 1 °C on a 12-h light/dark cycle (the light on between 6:00 and 18:00 h). The mice had free access to food (Bacutil pellets) and water before assays. All the experiments were carried out in compliance with the Polish Animal Protection Bill of April 21, 1997, and with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

The following drugs were used (in parentheses are pre-session injection times and suppliers): D-amphetamine sulfate (−5 min; Sigma, USA), 3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-*b*]pyridine (CP 94,253; −30 min; Pfizer, USA) and *N*-[3-[3-(dimethylamino)ethoxy]-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-[1,1′-biphenyl]-4-carboxamide hydrochloride (SB 216641; −40 min; Tocris, UK). All the drugs were dissolved in distilled water and injected i.p. at a volume of 0.1 ml/10 g.

2.3. Locomotor activity measurements

The locomotor activity of mice was recorded individually on days 1, 8 and 10 for each animal in photoresistor actometers described previously (Chojnacka-Wojcik, 1992). Measurements of the animals' activity started 5 min after the last injection of a drug (see below). Additionally, on day 5, the animals spent 1 h in the actometers following the last injection of a drug (see below). Seven to ten animals per group were used.

2.4. Experimental regimen (Table 1)

2.4.1. Development of amphetamine sensitization

During the first 5 days of the experiment, the animals received the following injections: vehicle + vehicle, vehicle + amphetamine (2.5 mg/kg), SB 216641 (5–20 mg/kg) + amphetamine (2.5 mg/kg), or CP 94,253 (1.25–5 mg/kg) + amphetamine (2.5 mg/kg). On day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for development of sensitization), they received a challenge dose of amphetamine (2.5 mg/kg). On days 6, 7 and 9, the animals remained drug-free in their home cages.

In another experiment, during the first 5 days, the animals received the following injections: vehicle + vehicle + vehicle, vehicle + vehicle + amphetamine (2.5 mg/kg), vehicle + CP 94,253 (5 mg/kg) + amphetamine (2.5 mg/kg), or SB 216641 (10 mg/kg) + CP 94,253 (5 mg/kg) + amphetamine (2.5 mg/kg). On day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for development of sensitization), they received a challenge dose of amphetamine (2.5 mg/kg). On days 6, 7 and 9, the animals remained drug-free in their home cages.

Table 1
Treatment protocol (in parantheses doses; mg/kg)

Repeated treatment (Days 1–5)	Challenge	
	Day 8	Day 10
Development of sensitization		
2 × vehicle	vehicle	amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	amphetamine (2.5)
SB 216641 (5) + amphetamine (2.5)	vehicle	amphetamine (2.5)
SB 216641 (10) + amphetamine (2.5)	vehicle	amphetamine (2.5)
SB 216641 (20) + amphetamine (2.5)	vehicle	amphetamine (2.5)
CP 94,253 (1.25) + amphetamine (2.5)	vehicle	amphetamine (2.5)
CP 94,253 (2.5) + amphetamine (2.5)	vehicle	amphetamine (2.5)
CP 94,253 (5) + amphetamine (2.5)	vehicle	amphetamine (2.5)
3 × vehicle	vehicle	amphetamine (2.5)
2 × vehicle + amphetamine (2.5)	vehicle	amphetamine (2.5)
Vehicle + CP 94,253 (5) + amphetamine (2.5)	vehicle	amphetamine (2.5)
SB 216641 (10) + CP 94,253 (5) + amphetamine (2.5)	vehicle	amphetamine (2.5)
Expression of sensitization		
2 × vehicle	vehicle	vehicle + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	vehicle + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	SB 216641 (5) + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	SB 216641 (10) + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	SB 216641 (20) + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	CP 94,253 (1.25) + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	CP 94,253 (2.5) + amphetamine (2.5)
Vehicle + amphetamine (2.5)	vehicle	CP 94,253 (5) + amphetamine (2.5)

2.4.2. Expression of amphetamine sensitization

During the first 5 days of the experiment, the animals received the following injections: vehicle + vehicle or vehicle + amphetamine (2.5 mg/kg). On day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for expression of sensitization), they received vehicle + amphetamine (2.5 mg/kg), SB 216641 (5–20 mg/kg) + amphetamine (2.5 mg/kg),

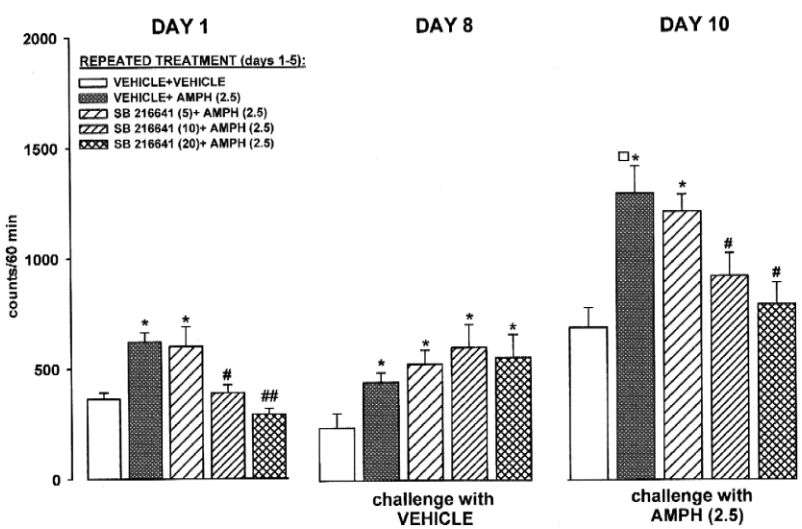

Fig. 1. Effect of SB 216641 on the development of amphetamine sensitization in mice. Amphetamine (AMPH; 2.5 mg/kg) and SB 216641 (5–20 mg/kg) were injected to animals daily for 5 days; on day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for development of sensitization), they were given a challenge dose of amphetamine (2.5 mg/kg). Student's paired *t*-test showed a significant effect between days 1 and 10 ($t_{10} = 5.12$, $^{\square}P < 0.001$); ANOVA showed a significant treatment effect: $F(4,35) = 5.48$, $P < 0.01$ (day 8), $F(4,35) = 3.2$, $P < 0.05$ (day 10). $^{*}P < 0.001$ vs. vehicle + vehicle; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. vehicle + amphetamine (Duncan's test).

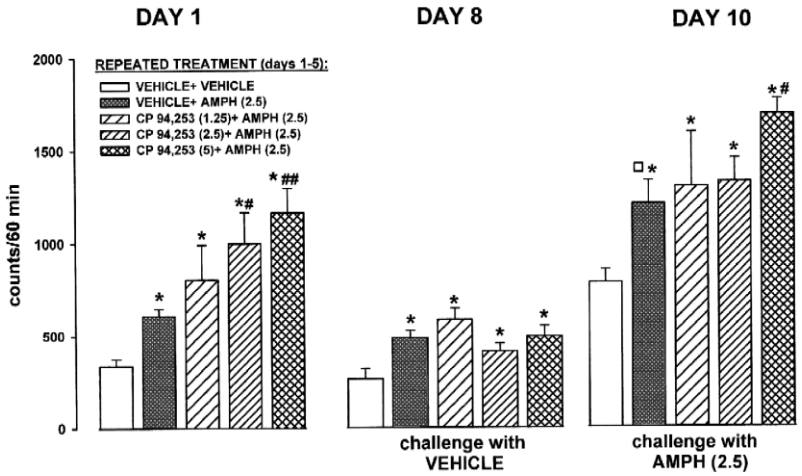

Fig. 2. Effect of CP 94,253 on the development of amphetamine sensitization in mice. Amphetamine (AMPH; 2.5 mg/kg) and CP 94,253 (1.25–5 mg/kg) were injected to animals daily for 5 days; on day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for development of sensitization), they were given a challenge dose of amphetamine (2.5 mg/kg). Student's paired *t*-test showed a significant effect between days 1 and 10 ($t_{11} = 5.57$, $^{\square}P < 0.001$); ANOVA showed a significant treatment effect: $F(4,44) = 2.67$, $P < 0.05$ (day 8), $F(4,44) = 2.97$, $P < 0.05$ (day 10). $^{*}P < 0.001$ vs. vehicle + vehicle; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. vehicle + amphetamine (Duncan's test).

or CP 94,253 (1.25–5 mg/kg) + amphetamine (2.5 mg/kg). On days 6, 7 and 9, the animals remained drug-free in their home cages.

2.5. Data analysis

To evaluate behavioral sensitization, the response to amphetamine on day 10 was compared with the response to its first injection (day 1) in the same animal, or with the response to test drug injection (day 10) in animals treated with repeated vehicle, using a paired Student *t*-test or a one-way analysis of variance (ANOVA), respectively. ANOVA, followed by the post hoc Duncan test, were applied to evaluate the treatment group effect separately on days 1, 8 and 10. The significance was set at $P < 0.05$.

3. Results

3.1. Effects of 5-HT_{1B} receptor ligands on the development of amphetamine sensitization

Administration of a single dose of amphetamine (2.5 mg/kg) to mice induced approximately a two-fold in-

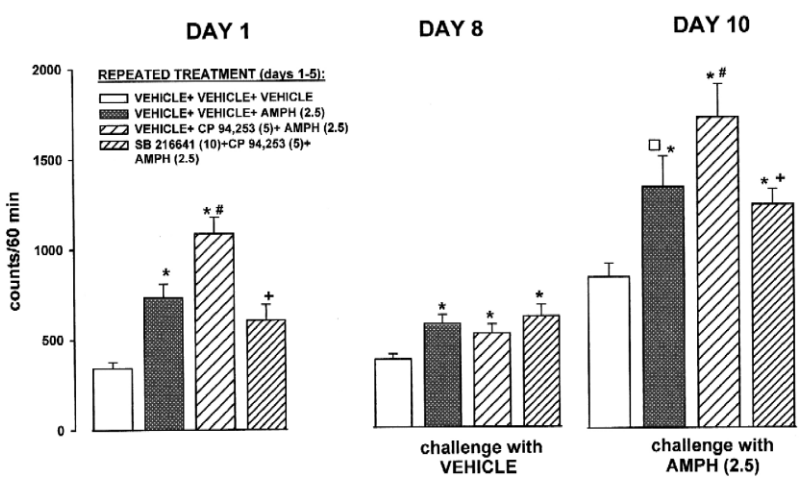

Fig. 3. Effect of SB 216641 on the CP 94,253-induced enhancement of development of amphetamine sensitization in mice. Amphetamine (AMPH; 2.5 mg/kg), CP 94,253 (5 mg/kg) and SB 216641 (10 mg/kg) were injected to animals daily for 5 days; on day 8 (a test for conditioned locomotion), the mice were challenged with vehicle, and on day 10 (a test for development of sensitization), they were given a challenge dose of amphetamine (2.5 mg/kg). Student's paired *t*-test showed a significant effect between days 1 and 10 ($t_9 = 2.99$, $^{\square}P < 0.05$); ANOVA showed a significant treatment effect; $F(4,31) = 5.84$, $P < 0.01$. $^{*}P < 0.001$ vs. vehicle + vehicle + vehicle; $^{\#}P < 0.05$ vs. vehicle + vehicle + amphetamine; $^{+}P < 0.05$ vs. vehicle + CP 94,253 + amphetamine (Duncan's test).

crease in the locomotor activity (Figs. 1–3, day 1). SB 216641 in doses of 10 and 20 mg/kg, but not 5 mg/kg, significantly attenuated the effects of amphetamine (Fig. 1, day 1). CP 94,253 (1.25–5 mg/kg) enhanced in a dose-dependent manner the amphetamine-evoked hyperactivation (Fig. 2, day 1).

After 5 days of repeated amphetamine (2.5 mg/kg) administration and following its 5-day withdrawal, a challenge dose of amphetamine (2.5 mg/kg) induced marked behavioral sensitization, observed as a ca. 55–110% increase in locomotor activity compared with that after its first injection (day 1) in the same animal, or with the response to acute amphetamine injection (day 10) in animals treated with repeated vehicle (Figs. 1–3). Pretreatment with SB 216641 (10 and 20 mg/kg, but not 5 mg/kg) before each of the 5 daily amphetamine injections reduced the amphetamine-induced sensitization, tested 5 days after its withdrawal (Fig. 1, day 10). CP 94,253 (5 mg/kg, but not 1.25 or 2.5 mg/kg), injected following the same regimen as SB 216641, enhanced the sensitized response of amphetamine 5 days after its withdrawal (Fig. 2, day 10).

SB 216641 (10 mg/kg) abolished the enhancing effect of CP 94,253 (5 mg/kg) on the amphetamine-induced locomotor hyperactivity (on day 1) and the sensitization to amphetamine (on day 10) (Fig. 3).

Neither acute nor repeated (5 days) treatment with SB 216641 (10 or 20 mg/kg; data not shown) or CP 94,253 (5 mg/kg; data not shown) affected basal locomotor activities of the animals.

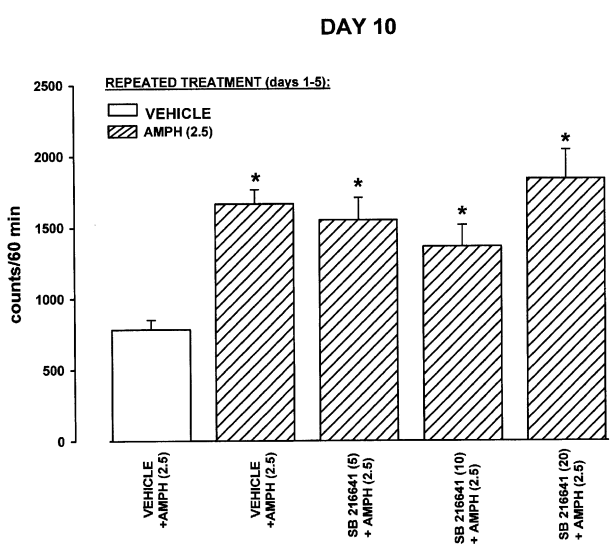

Fig. 4. Effect of SB 216641 on the expression of amphetamine sensitization in mice. Amphetamine (AMPH; 2.5 mg/kg) or vehicle was injected to animals daily for 5 days; on day 8 (a test for conditioned locomotion), the animals were challenged with vehicle, and on day 10 (a test for expression of sensitization), they were given amphetamine (2.5 mg/kg) or SB 216641 (5–20 mg/kg) + amphetamine (2.5 mg/kg). ANOVA showed a significant treatment effect; $F(4,41) = 9.78$, $P < 0.001$ (day 10). $^{*}P < 0.001$ vs. vehicle (Duncan's test).

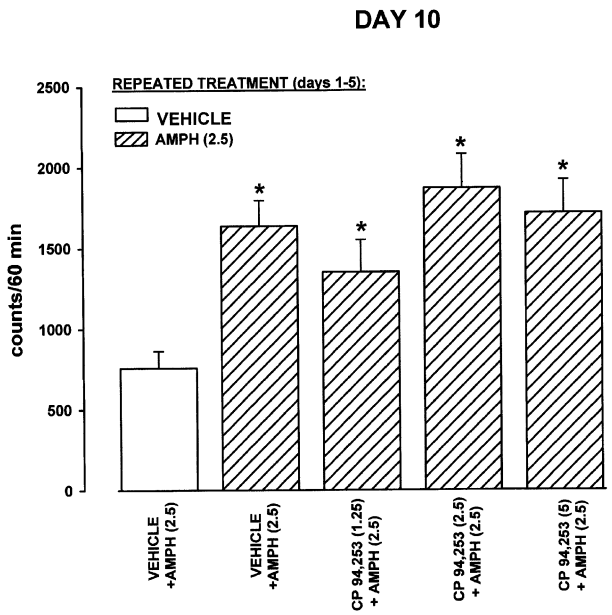

Fig. 5. Effect of CP 94,253 on the expression of amphetamine sensitization in mice. Amphetamine (AMPH; 2.5 mg/kg) or vehicle was injected to animals daily for 5 days; on day 8 (a test for conditioned locomotion), the animals were challenged with vehicle, and on day 10 (a test for expression of sensitization), they were given amphetamine (2.5 mg/kg) or CP 94,253 (1.25–5 mg/kg) + amphetamine (2.5 mg/kg). ANOVA showed a significant treatment effect; $F(4,34) = 4.38$, $P < 0.01$ (day 10). $^{*}P < 0.001$ vs. vehicle (Duncan's test).

Mice treated with amphetamine (days 1–5) showed an increased locomotor activity to a challenge with vehicle (day 8) as compared to animals treated and challenged with vehicle (Figs. 1–3). No change in the conditioned locomotion was observed in animals treated repeatedly with either amphetamine alone or SB 216641 + amphetamine (Fig. 1), CP 94,253 + amphetamine (Fig. 2), or SB 216641 + CP 94,253 + amphetamine (Fig. 3).

3.2. Effects of 5-HT$_{1B}$ receptor ligands on the expression of amphetamine sensitization

In mice treated repeatedly with amphetamine (days 1–5), no difference was observed in their locomotor hyperactivity response on day 10 to challenge with amphetamine alone, or with the psychostimulant combined with SB 216641 (5–20 mg/kg) (Fig. 4), or CP 94,253 (1.25–5 mg/kg) (Fig. 5).

4. Discussion

The results of the present study show that in mice treated for 5 days with a dose of 2.5 mg/kg of amphetamine, the locomotor hyperactivity induced by the same challenge dose of the psychostimulant—tested on day 5 after its withdrawal—was about 55–110% more potent than that after its first administration (on day 1 in

amphetamine-treated animals, or on day 10 in saline-treated ones; Figs. 1–3). The above observation may be regarded as a piece of evidence for behavioral sensitization to the locomotor stimulant effect of amphetamine, since it has been proposed that such a phenomenon consists in increased responsiveness to the same or lower doses of a psychostimulant, which follows its repeated administration (Stewart and Badiani, 1993). At the same time, we also observed that challenge with saline (on day 8) produced a significant increase in the locomotor activity of mice treated repeatedly with amphetamine (days 1–5) compared to those treated likewise with saline (Figs. 1–3), which can be interpreted in terms of a well-known conditioning phenomenon related to the pairing of psychostimulant administration with a particular set of environmental stimuli (Stewart and Badiani, 1993; Ohmori et al., 2000).

To examine the role of 5-HT_{1B} receptors in sensitization to the hyperlocomotor effect of amphetamine, we used their selective agonist CP 94,253 (Koe et al., 1992) and the antagonist SB 216641 (Hagan et al., 1997). Both those ligands were used in a dose range in which they produced effects related to stimulation and blockade of 5-HT_{1B} receptors, respectively (Koe et al., 1992; Hagan et al., 1997). Using the above ligands of 5-HT_{1B} receptors we found that pharmacological manipulation of those receptors modulated the development of amphetamine sensitization. In fact, the challenge dose of amphetamine (day 10) produced a weaker hyperactivity response in mice treated repeatedly (days 1–5) with SB 216641 (5–20 mg/kg) + amphetamine than in those treated likewise with amphetamine alone. The above effect depended on the dose of SB 216641, significant results being observed in animals receiving higher doses (10–20 mg/kg) of the 5-HT_{1B} receptor antagonist (Fig. 1). On the other hand, the hyperlocomotion response to amphetamine challenge was significantly stronger (ca. 30–35%) in mice treated repeatedly with a combination of CP 94,253 (5 mg/kg, but not lower doses) and amphetamine than in those treated likewise with the psychostimulant alone (Figs. 2 and 3). Importantly, the above effect of CP 94,253 was prevented by SB 216641, since no difference between the hyperactivity induced by a challenge dose of amphetamine was observed in animals treated repeatedly with either amphetamine alone, or with a combination of SB 216641 + CP 94,253 + amphetamine (Fig. 3), which indicates that the effect of CP 94,253 depends on activation of 5-HT_{1B} receptors. To sum up, all the above results apparently indicate that 5-HT_{1B} receptors play a permissive role in the development of amphetamine sensitization to its locomotor stimulant effect in mice.

Although modulation of the development of amphetamine sensitization by 5-HT_{1B} receptor ligands may result from their similar effects on the locomotor hyperactivity produced by acute administration of the psychostimulant, it seems to be unrelated with their effects on the conditioned locomotion or basal activity in naive animals. Actually, the locomotor hyperactivity response to a single dose of amphetamine was dose-dependently reduced by SB 216641 and enhanced by CP 94,253, the effect of the 5-HT_{1B} receptor agonist being blocked by SB 216641 (day 1; Figs. 1–3). On the other hand, challenge with saline on day 8 induced similar hyperactivity in mice treated repeatedly (day 1–5) with amphetamine alone and in animals treated likewise with a combination of the psychostimulant and either of the 5-HT_{1B} receptor ligands (Figs. 1–3). Moreover, neither SB 216641 nor CP 94,253 (see Results; Koe et al., 1992) administered in doses used in the present study modified the locomotor activity of drug-naive mice after either single or repeated administration. In other words, 5-HT_{1B} receptors do not seem to be tonically active in the latter experimental paradigm.

In contrast to the development of amphetamine sensitization, the 5-HT_{1B} receptor ligands did not affect the expression phase of the phenomenon. In fact, in mice treated repeatedly with amphetamine, no difference was observed in their locomotor hyperactivity response to challenge with amphetamine alone or in combination with SB 216641 or CP 94,253. In other words, the above results seem to indicate that 5-HT_{1B} receptors are not involved in the expression of amphetamine sensitization, and that this phase of the phenomenon is resistant to pharmacological manipulation of these receptors.

The recently published data on the interaction between 5-HT_{1B} receptor ligands and behavioral effects induced by amphetamine or another psychostimulant, cocaine, both differ and are similar to the results of the present study. As far as amphetamine effects are concerned, Chaouloff et al. (1999) reported that blockade of 5-HT_{1B} receptors did not affect the psychostimulant-induced hyperlocomotion in Wistar–Kyoto hyperactive rats, while Fletcher and Korth (1999a,b) found that activation of those receptors reduced the amphetamine-induced enhancement of responding to a conditioned reward and disrupted the drug self-administration in rats. The reason for the discrepancy between the above-cited data and the results of the present study is not clear; all the same the strain difference (rats vs. mice), as well as differences in the 5-HT_{1B} receptor ligands used and the test protocols applied (drug doses, routes of administration) should be taken into account. Furthermore, a possible discrepancy between the roles of 5-HT_{1B} receptors in the locomotor and reinforcing effects of amphetamine cannot be excluded.

On the other hand, our present results resemble the findings with 5-HT_{1B} receptor ligands on cocaine effect in rats. In fact, agonists of those receptors were demonstrated to enhance the acute locomotor and sensitizing effects of the psychostimulant (Przegalinski et al., 2001), its discriminative stimulus effects (Callahan and Cunningham, 1995, 1997; Filip et al., 2001), as well as to augment the reinforcing effect of self-administered cocaine (Parsons et al., 1998). At the same time, blockade of 5-HT_{1B} receptors was shown to antagonize the acute, but not sensitizing,

effect of cocaine on locomotor activity (Przegalinski et al., 2001).

Given the autoinhibitory nature of 5-HT_{1B} receptors (see Introduction), our results—at least these revealing that the agonist of these receptors, CP 94,253, enhances locomotor hyperactivity and the development of amphetamine sensitization—are supported by the findings that other agents reducing 5-HT input (5-HT neurotoxins, 5-HT synthesis inhibitors, 5-HT_{1A} receptor agonists) enhance the locomotor response and sensitization to psychostimulants (Mabry and Campbell, 1973; Morrow and Roth, 1996; DeLa Garza and Cunningham, 2000). However, it has recently been reported that local administration of the 5-HT neurotoxin 5,7-dihydroxytryptamine into the fimbria–fornix/cingular bundle or raphe nuclei either hampered or did not affect the amphetamine-induced hyperlocomotion, respectively (Lehmann et al., 2000). Moreover, we recently found that 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)—which decreases 5-HT release in target structures via stimulation of presynaptic 5-HT_{1A} receptors—antagonized the development and expression of amphetamine sensitization in mice, though postsynaptic rather than presynaptic 5-HT_{1A} receptors were postulated to be engaged in the above effects of that agonist (Przegalinski et al., 2000).

As regards the effects of the 5-HT_{1B} receptor ligands on the development of sensitization and acute locomotor response to amphetamine, two possible mechanisms may be considered.

(1) It is well documented that amphetamine promotes, besides dopamine, also 5-HT release via a direct effect of the 5-HT transporter (Reith et al., 1986; Ritz et al., 1990); moreover, in doses higher than 2 mg/kg, it increases the extracellular 5-HT concentration—at least in rat striatum (Kuczenski and Segal, 1989). Consequently, behavioral effects of the psychostimulant may result from the released 5-HT acting on 5-HT_{1B} receptors, the more so as its effects are blocked by the 5-HT_{1B} receptor antagonist SB 216641. However, such an explanation seems unsatisfactory, since the 5-HT_{1B} receptor agonist CP 94,253 administered acutely or repeatedly does not affect locomotor activity in drug-naive mice (see above).

(2) 5-HT_{1B} receptors act not only as autoreceptors, but also as heteroreceptors located on several neurotransmitter nerve terminals including dopamine ones (see Introduction); moreover, in vitro studies have shown that stimulation of these receptors inhibits dopamine release in rat striatal synaptosomes (Sarhan et al., 1999, 2000). However, under in vivo conditions, pharmacological activation of 5-HT_{1B} receptors leads to an increase in basal and cocaine-stimulated extracellular dopamine concentration in rat nucleus accumbens, most probably via reduction of γ-aminobutyric acid (GABA) release from GABA-ergic afferents and disinhibition of dopamine neurons in the ventral tegmental area (Guan and McBride, 1989; Boulenguez et al., 1996; Parsons et al., 1999). On the other hand, microdialysis studies have shown that 5-HT_{1B} receptor antagonists do not affect basal extracellular dopamine content (Hallbus et al., 1997; Gobert and Millan, 1999), though there are no data available on their effect on psychostimulant-induced dopamine release. In the light of the above results, it may be speculated that augmentation of the development of sensitization and acute locomotor response to amphetamine, evoked by the 5-HT_{1B} receptor agonist, depends on its indirect enhancing impact on dopamine function, an effect which seems to to be pharmacological rather than physiological. At the same time, the mechanism of the inhibitory action of the 5-HT_{1B} receptor antagonist on the behavioral effects of the psychostimulant remains to be elucidated. In this context, it should only be noted—at least if the development of amphetamine sensitization is considered—that recent electrophysiological in vitro studies show that nonselective antagonists of 5-HT receptors (methysergide, methiothepin), but not antagonists of dopamine receptors, inhibit the psychostimulant-induced depression of excitatory glutamatergic synaptic transmission onto the ventral tegmental area (Jones and Kauer, 1999), a brain structure involved in this phase of sensitization to psychostimulants (see Introduction).

It is also an open question why pharmacological manipulation of 5-HT_{1B} receptors does not modulate—in contrast to the development—the expression of amphetamine sensitization, the more so as at least activation of these receptors indirectly increases dopamine function in the nucleus accumbens (Guan and McBride, 1989; Boulenguez et al., 1996; Parsons et al., 1999) which is involved mainly in the latter phase of the phenomenon (see Introduction). However, it has recently been reported that this brain structure is engaged in the development of the psychostimulant-induced behavioral sensitization (De Vries et al., 1998). Nevertheless, further studies, e.g. using local administration of 5-HT_{1B} receptor ligands, may help to answer this question.

In conclusion, the results of the present study suggest that 5-HT_{1B} receptors may play a permissive role in the development, but not expression, of sensitization, as well as in the acute locomotor response to amphetamine in mice.

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