Forum Minireview

Neuropsychotoxicity of Abused Drugs: Effects of Serotonin Receptor Ligands on Methamphetamine- and Cocaine-Induced Behavioral Sensitization in Mice

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Abstract. Repeated administration of psychostimulants elicits a progressive enhancement of locomotor activity known as behavioral sensitization. Central dopamine (DA) neurons play key roles as the neural substrates mediating behavioral sensitization, but the role of the serotonin (5-HT) system in the sensitization is not fully elucidated. We have recently demonstrated that osemozotan, a specific 5-HT_{1A}-receptor agonist, and ritanserin, a 5-HT₂-receptor antagonist, inhibited the expression and development of both methamphetamine- and cocaine-induced behavioral sensitization in mice and that these drugs attenuated the maintenance of behavioral sensitization of methamphetamine, but not that of cocaine. We also found that azasetron, a 5-HT₃-receptor antagonist, inhibited the expression and development of the sensitization induced by methamphetamine and cocaine, respectively. Neurochemical studies using a microdialysis technique showed that repeated methamphetamine enhanced the methamphetamine-induced increase in 5-HT release in the prefrontal cortex. The sensitization of 5-HT release in methamphetamine-treated mice was attenuated by osemozotan and ritanserin. These findings suggest that the 5-HT system plays an important role in methamphetamine- and cocaine-induced behavioral sensitization in mice and imply that 5-HT_{1A}-receptor agonists and 5-HT₂-receptor antagonists may have a potential therapeutic value for the treatment of methamphetamine abuse or psychosis.

Keywords: drugs of abuse, behavioral sensitization, methamphetamine, cocaine, serotonin (5-HT)-receptor ligand

Introduction

Amphetamine, methamphetamine, and cocaine are the central nervous system stimulants, and its prolonged use results in addiction and psychosis that is indistinguishable from paranoid type schizophrenia (1). Repeated administration of these psychostimulants can enhance the stimulating effect on locomotor activity, a phenomenon called behavioral sensitization. This

behavioral model has been used to analyze the neural modification associated with repeated psychostimulants exposure and withdrawal (2). The mesocorticolimbic dopamine (DA) system plays a crucial role (3–5), but several lines of evidence have clearly demonstrated that DA is not the sole mediator of the behavioral effects of psychostimulant drugs. The occupation of the DA transporter by selective DA reuptake blockers does not correlate with their locomotor stimulant effects (6, 7). In addition, the expression of psychostimulant-induced locomotor sensitization can be dissociated from the expression of the sensitization of the DA response in the nucleus accumbens (8, 9), striatum (10, 11) and

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prefrontal cortex (12). Since psychostimulants do not only interact with the DA reuptake site, but also with the serotonin (5-HT) reuptake site, it is possible that the increased levels of extracellular 5-HT may participate in psychostimulant-induced behavioral sensitization. This increased 5-HT interacts with 5-HT receptors, so that 5-HT receptors may be important targets for pharmacological interventions. To date, at least 14 different 5-HT receptors have been characterized (13). Particularly, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, and 5-HT₆ receptors are more abundant in mesolimbic regions including the ventral tegmental area and terminates in several forebrain structures that regulate drug craving, emotion, and reward. We have recently examined the effects of the 5-HT_{1A}-receptor agonist osetozotan (14), the 5-HT₂-receptor antagonist ritanserin (15), and the 5-HT₃-receptor antagonist azasetron (16) on methamphetamine- and cocaine-induced behavioral sensitization in mice (17–19). This mini-review summarizes the effects of these 5-HT-receptor ligands on methamphetamine- and cocaine-induced behavioral sensitization in mice and the possible role of the prefrontal 5-HT system in the sensitization.

Methamphetamine-induced behavioral sensitization in mice

There are accumulating evidences that acute amphetamine or methamphetamine-induced hyperlocomotion is modulated by 5-HT_{1A}-, 5-HT_{1B}-, 5-HT_{2A}-, 5-HT_{2C}-, 5-HT₃-, 5-HT₆-, and 5-HT₇-receptor agonists and/or antagonists, while, the roles of 5-HT receptors in the sensitization are not fully elucidated. Przeglasiński et al. (20, 21) reported that a 5-HT_{1A}-receptor agonist, 8-OH-DPAT, inhibited the expression and development of

amphetamine-induced sensitization in mice and that a 5-HT_{1B}-receptor antagonist, SB 216641, inhibited the development, but not the expression, of amphetamine-induced sensitization in mice. Tanaka et al. (22) reported that ritanserin partially inhibited the development of methamphetamine-induced behavioral sensitization in rats, and Auclair et al. (23) reported that a 5-HT_{2A}-receptor antagonist inhibited the development of amphetamine-induced behavioral sensitization in mice. Furthermore, Yoo et al. (24) have shown that ondansetron, a 5-HT₃-receptor antagonist, attenuated the expression and development of methamphetamine-induced behavioral sensitization. However, there are no studies demonstrating whether the 5-HT-receptor ligands improve the behavioral sensitization when administered after establishment of the sensitization. This point appears to be the most important, in view of treatment for drug abuse. Then, we examined the effects of osetozotan, ritanserin, and azasetron on the development, expression, and maintenance of methamphetamine-induced behavioral sensitization in mice (Table 1). Repeated administration of methamphetamine (1 mg/kg) for 7 days enhanced methamphetamine challenge-induced locomotor activity, and this sensitization was observed even after its withdrawal for 7–14 days. Osetozotan and ritanserin, but not azasetron, inhibited the development of methamphetamine-induced locomotor sensitization in mice (17, 19). On the other hand, all these drugs significantly attenuated the expression of the sensitization. Interestingly, osetozotan and ritanserin, but not azasetron, also inhibited the maintenance of the sensitization, that is, these drugs reversed the established behavioral sensitization in mice. Furthermore, the inhibitory effect of osetozotan was antagonized by a low dose of WAY100635, the 5-HT_{1A}-

Table 1. Summary of the effects of 5-HT-receptor ligands on methamphetamine- and cocaine-induced behavioral sensitization in mice

Psychostimulant	Sensitization	Osetozotan	Ritanserin	Azasetron
Methamphetamine	Development	↓	↓	—
	Expression	↓	↓	↓
	Maintenance	↓	↓	—
Cocaine	Development	↓	↓	↓
	Expression	↓	↓	—
	Maintenance	—	—	—

For the development of the sensitization, mice were coadministered drugs and psychostimulants repeatedly for 7 days and then challenged with psychostimulants after a 7-day withdrawal period (on day 15). For the expression of the sensitization, mice were administered psychostimulants repeatedly for 7 days and then challenged with psychostimulants after a 7-day withdrawal period (on day 15). Drugs were injected 30 min before its challenge dose of psychostimulants on day 15. For the maintenance of the sensitization, mice were treated with psychostimulants repeatedly for 7 days, administered drugs twice daily for 7 days, and challenged with psychostimulants after a 7-day withdrawal period (on day 22). ↓: inhibitory effect, —: no effect.

receptor antagonist. Since WAY100635 has a greater affinity for presynaptic 5-HT_{1A} autoreceptors than for postsynaptic 5-HT_{1A} receptors (25), it is possible that the effect of osetozotan may be due to the activation of presynaptic 5-HT_{1A} receptors. Taken together, these findings suggest that 5-HT_{1A}-receptor agonists and 5-HT₂ receptor antagonists may have a therapeutic value for the treatment of methamphetamine abuse or psychosis.

Cocaine-induced behavioral sensitization in mice

Previous studies show that the 5-HT_{1A}- (26, 27), 5-HT_{1B}- (28), 5-HT_{2A}- (29, 30), and 5-HT₃- (31–33) receptor antagonists inhibit cocaine-induced hyperlocomotion and behavioral sensitization, while the 5-HT_{1A}-, 5-HT_{1B}-, and 5-HT_{2A}-receptor agonists and 5-HT_{2C}-receptor antagonist enhance the locomotor stimulant effect of cocaine (30, 34, 35). These results suggest that the central 5-HT system plays a role in cocaine-induced behavioral sensitization. However, all these studies were carried out in rats. Since there is a species difference pertaining to the behavioral effects that the 5-HT_{1A}-receptor agonist has on rats and mice (36–39), the similar studies in mice appear to be important. Our recent results in mice are shown in Table 1 (18). Cocaine-induced hyperlocomotion was augmented by repeated administration of cocaine (15 mg/kg) to mice, and this sensitization persisted even after a 7-day withdrawal period. Under the condition, osetozotan and ritanserin inhibited the development and expression of cocaine-induced behavioral sensitization in mice. In addition, azasetron inhibited the development of cocaine-induced behavioral sensitization in mice. However, none of these ligands reversed cocaine-induced behavioral sensitization, when each drug was administered for 7 days after repeated cocaine administration. This finding suggests that the involvement of

5-HT system in the maintenance of behavioral sensitization is different between cocaine and methamphetamine in mice. The important findings are that the modulation of cocaine-induced sensitization by 5-HT-receptor ligands is observed in mice and that there is the species difference between rats and mice in the effect of the 5-HT_{1A}-receptor agonist on cocaine-induced behavioral sensitization.

Neurochemical effects of repeated methamphetamine administration

The central DA system is well recognized to play an essential role in sensitization to psychostimulants for which the release and reuptake inhibition of DA are a primary mechanism mediating the motor behaviors (3). Most investigators have reported that an enhanced DA response in the nucleus accumbens (40), striatum (41, 42), and prefrontal cortex (43) may underlie behavioral sensitization, while some investigators have shown that behavioral sensitization can be obtained in the absence of an enhanced DA response in the DA projection regions (8–12). The apparent discrepancy may be due to differences in the conditions for induction of behavioral sensitization such as stimulant treatment and period of drug withdrawal (44).

With regards to the effects of chronic methamphetamine administration on monoamine release, we have recently demonstrated that chronic methamphetamine enhanced methamphetamine challenge-induced increases in extracellular 5-HT levels in the prefrontal cortex, but did not affect methamphetamine challenge-induced increases in extracellular DA and noradrenaline levels (17) (Fig. 1). This enhanced 5-HT response is not observed in the striatum and nucleus accumbens. In this line, Salomon et al. (45) have reported that chronic *d*-amphetamine injections induced an increased reactivity of serotonergic neurons as measured by cortical extra-

Fig. 1. Effects of single and repeated administration of methamphetamine (METH) on the in vivo release of DA, 5-HT, and noradrenaline (NA) in the prefrontal cortex of mice. Mice were administered saline or METH (1 mg/kg) repeatedly for 7 days. Saline-pretreated mice (open circles) and METH-pretreated mice withdrawn for 7 days (triangles) or 14 days (closed circles) from chronic METH administration were challenged with METH (1 mg/kg) at 0 time (arrow). Reproduced from ref. 17 with permission from Elsevier.

Fig. 2. Effects of osemozotan and WAY100635 during the maintenance phase on the methamphetamine (METH)-induced release of DA and 5-HT in the prefrontal cortex of mice. Mice were treated with METH (1 mg/kg) repeatedly for 7 days (days 1–7), administered vehicle (circles) or osemozotan at 0.3 mg/kg (triangles) twice daily for 7 days (days 8–14), and then challenged with METH (1 mg/kg) after a 7-day withdrawal period at 0 min (arrow) (on day 22). WAY100635 (0.1 mg/kg) was administered i.p. 30 min before osemozotan administration (squares). Reproduced from ref. 17 with permission from Elsevier.

Fig. 3. Effect of ritanserin during the maintenance phase on the methamphetamine (METH)-induced release of DA and 5-HT in the prefrontal cortex of mice. Mice were treated with saline (open symbols) or METH 1 mg/kg (closed symbols) repeatedly for 7 days (days 1–7), administered vehicle (circles) or ritanserin 3 mg/kg (triangles) twice daily for 7 days (days 8–14), and then challenged with METH (1 mg/kg) after a 7-day withdrawal period at 0 min (arrow) (on day 22). ** $P < 0.01$, *** $P < 0.001$. n.s.: not significant. Reproduced from ref. 19 with permission.

cellular 5-HT levels after administration of *p*-chloroamphetamine, a 5-HT releaser. These findings suggest that the enhanced prefrontal 5-HT system is at least partly involved in psychostimulant-induced behavioral sensitization in mice.

Effects of 5-HT-receptor ligands on methamphetamine-induced changes in 5-HT and DA systems

To study the role of the enhanced prefrontal 5-HT system in the maintenance of methamphetamine-induced behavioral sensitization, we examined the effects of osemozotan and ritanserin on the neuronal sensitization in the prefrontal cortex (17, 19). Both osemozotan and ritanserin significantly attenuated the enhanced 5-HT response in methamphetamine-pretreated mice, but did not affect the methamphet-

amine-induced increase in extracellular DA levels (Figs. 2 and 3). Furthermore, this effect of osemozotan was blocked by the coadministration of low doses of WAY100635 (Fig. 2). The finding suggests that osemozotan-induced reversal of methamphetamine-induced behavioral sensitization is related to an inhibition of serotonergic activity through the activation of presynaptic 5-HT_{1A} receptors. Regarding the effect of ritanserin, previous studies demonstrate that the activation of postsynaptic 5-HT_{2A} receptors in the prefrontal cortex stimulates the activity of the serotonergic system through changes in the activity of pyramidal neurons projecting to the dorsal raphe nucleus in rats and mice (46, 47). These reports suggest that 5-HT_{2A} receptors play roles in regulating the serotonergic activity in an opposite direction of 5-HT_{1A} autoreceptors. Thus, down- and up-regulation of 5-HT_{1A}- and 5-HT_{2A}-receptor

Fig. 4. Possible mechanisms for methamphetamine-induced neurochemical sensitization and the reversal effects of 5-HT-receptor ligands. SERT, serotonin transporter; 5-HT_{1A} R, 5-HT_{1A} receptor; 5-HT_{2A} R, 5-HT_{2A} receptor.

function, respectively, may lead to methamphetamine-induced enhancement of 5-HT release in the prefrontal cortex, although the exact mechanism remains to be determined (Fig. 4). This idea may be in agreement with our findings that osemozotan and ritanserin attenuates the enhanced response of 5-HT release, although it is not known whether chronic methamphetamine affects the expression of 5-HT_{1A} and 5-HT_{2A} receptors. Furthermore, we observed that osemozotan and ritanserin inhibited acute methamphetamine-induced hyperlocomotion in mice and that these drugs also inhibited acute methamphetamine-induced increase in the extracellular 5-HT, but not DA, levels in the prefrontal cortex. These findings suggest that the prefrontal 5-HT system may play a key role in the effects of osemozotan and ritanserin on methamphetamine-induced hyperactivity in mice.

Concluding remarks

The present review focused on the effects of 5-HT-receptor ligands on methamphetamine- and cocaine-induced behavioral sensitization and neurochemical changes in prefrontal 5-HT and DA systems in mice. Although neuronal control of locomotor activity is more likely to be associated with neurochemical changes in the nucleus accumbens and striatum than in the prefrontal cortex, our findings suggest that the 5-HT system, including 5-HT_{1A} and 5-HT₂ receptors, is involved at least partly in methamphetamine-induced behavioral effects such as sensitization and the

locomotor stimulant effect in mice. In contrast, the 5-HT-related mechanisms underlying cocaine-induced behavioral sensitization remains to be determined because osemozotan, ritanserin, and azasetron did not affect the maintenance of the sensitization. Since the establishment and expression of sensitization is part of psychostimulant addiction and psychosis, these studies imply that 5-HT_{1A}-receptor agonists and 5-HT₂-receptor antagonists may have a potential therapeutic value for the treatment of methamphetamine abuse or psychosis.

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