REVIEW

CNS Neuroscience & Therapeutics

Treatment of the Psychostimulant-Sensitized Animal Model of Schizophrenia

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Keywords
Behavioral sensitization; Dopamine; Schizophrenia.

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doi: 10.1111/j.1755-5949.2010.00218.x

SUMMARY

Behavioral sensitization to psychostimulants in rodents is associated with the alteration of dopaminergic neurotransmission, and has been proposed as a useful model of schizophrenia due to its progressively intensifying, easily relapsing, and long-lasting features. Pharmacological treatments that reverse the established sensitization may have potential therapeutic values for schizophrenia. The present aim is to review pharmacological treatments that induce the reversal of established sensitization to psychostimulants. In addition, we discuss possible mechanisms for the reversal of sensitization. Reversal of sensitization is induced by chronic dopamine D1 receptor agonism, D2 or D1/D2 receptor agonism combined with mild N-methyl-D-aspartate (NMDA) receptor antagonism or serotonin (5-HT_{2A} or 5-HT_3) receptor antagonism, 5-HT_{1A} receptor agonism, and 5-HT_{2A} or 5-HT_3 receptor antagonism. Chronic treatments with these drugs likely adjust altered dopaminergic neurotransmission in sensitized animals. Especially, chronic dopamine D1 receptor agonism, which may adjust mesolimbic hyperdopaminergic and mesocortical hypodopaminergic functions in sensitized animals, is an attractive therapeutic approach for schizophrenia.

Introduction

Repeated administration of psychostimulants such as methamphetamine (MAP), amphetamine (AMPH), and cocaine induces a progressive and enduring enhancement of locomotor activity in rodents, which is known as behavioral sensitization (development of sensitization). Behavioral sensitization easily reappears with the injection of small doses of psychostimulants (expression of sensitization) after a long period of abstinence following initial drug exposure [1,2]. Since the sensitized state is maintained for long time after psychostimulant withdrawal, it is important to find therapeutic agents that reverse the established behavioral sensitization.

Chronic exposure to psychostimulants in human can induce a psychotic state indistinguishable from paranoid schizophrenia. Moreover, acute AMPH administration can produce or enhance a psychotic reaction in patients with schizophrenia at doses that are ineffective in healthy controls [3,4]. The progressively intensifying, easily relapsing, and long-lasting features of behavioral sensitization in rodents are similar to clinical features in psychostimulant psychosis and schizophrenia [2]. In addition, alterations in dopaminergic neurotransmission induced by psychostimulants in rodents are similar to those hypothesized in schizophrenia [5–7]. Therefore, the psychostimulant-sensitized animal model is very useful to understand mechanisms of increased susceptibility to relapse and long duration of the vulnerability to relapse in schizophrenia [8]. Furthermore, psychostimulant sensitization, which is thought as a model of positive symptoms of schizophrenia associated with the mesolimbic hyperdopaminergic state, is now demonstrated to serve as a model of cognitive dysfunction of schizophrenia associated with the mesocortical hypodopaminergic state, based on the long-lasting cognitive deficits in domains of attention/vigilance and reasoning and problem solving observed in sensitized animals [9].

Most research in this field has focused on mechanisms underlying development and expression of sensitization. Development of sensitization is inhibited by dopamine D1 or D2 receptor antagonism, and expression of sensitization by psychostimulant challenge is inhibited by dopamine D2 receptor antagonism and in some cases by D1 receptor antagonism [7,10–14]. Dopamine D2 receptor antagonism suppresses the expression of sensitized behavior to psychostimulant challenge, but the sensitized state is maintained. For this meaning, it is necessary to develop therapeutic agents that reverse the established sensitization long time after withdrawal of therapeutic agents, resulting in cure rather than control of the sensitized state (Figure 1). Several drugs, previously shown to inhibit the development of sensitization, have been tested whether to reverse sensitization, but so far these attempts have failed. The drugs reported not

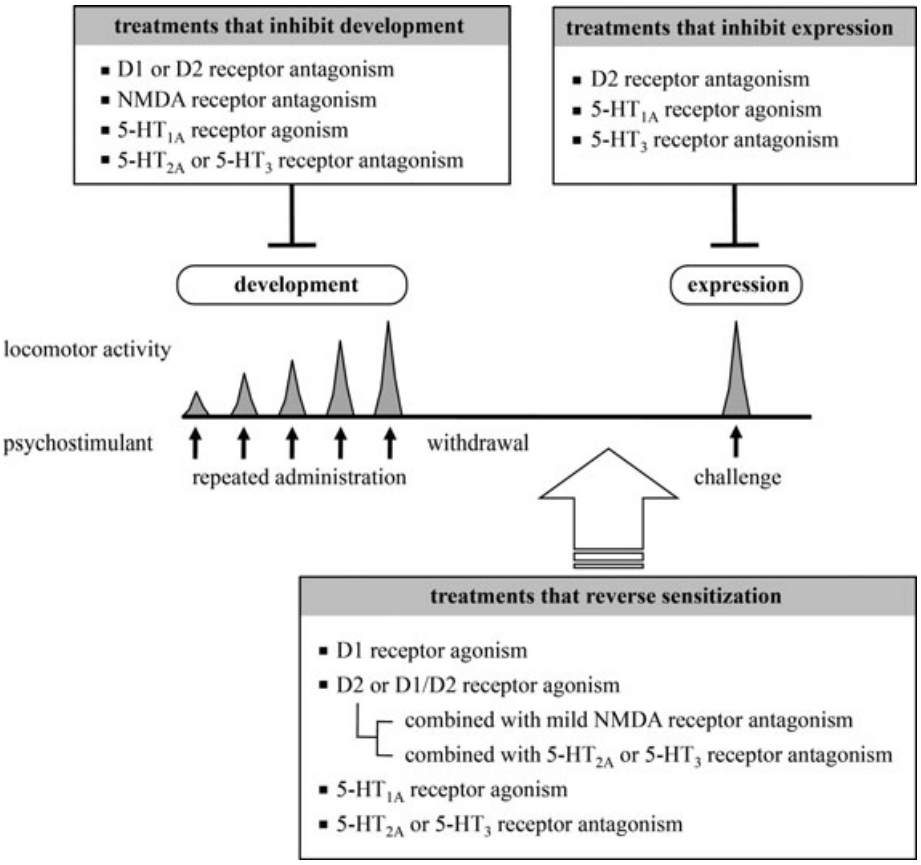

Figure 1 Pharmacological treatments that inhibit development and expression of sensitization and reverse established sensitization.

effective were a dopamine D1 receptor antagonist (SCH23390 [10,11,15]), dopamine D2 receptor antagonists (chlorpromazine [16], haloperidol [10], sulpiride [17], and nemonapride (YM-09151-2 [11,15,18]), and an N-methyl-D-aspartate (NMDA) receptor antagonist (MK-801 [19–21]).

Interestingly, administration of cocaine itself is demonstrated to reverse behavioral sensitization to cocaine, when cocaine administration is combined with the NMDA receptor antagonist [22]. Furthermore, there are several reports showing the reversal of psychostimulant-induced behavioral alterations in animal models, for example, drug-self-administration and seeking behaviors for cocaine, by dopamine D1 receptor agonists [23–25]. Based on these observations, many studies aiming the reversal of sensitization have focused on agonism of dopamine receptors. Activation of dopamine D1 receptors alone or activation of dopamine D2 or D1/D2 receptors in combination with NMDA receptor antagonists or serotonin receptor antagonists is shown to have therapeutic potentials, as summarized in Table 1. Drugs that modulate serotonergic neurotransmission are also shown to reverse behavioral sensitization. Since an excellent review on serotonergic drugs [26] is available and spaces are limited, we mainly focus on the reversal of behavioral sensitization by dopamine receptor agonism.

Effect of Dopamine D1 Receptor Agonism on Established Sensitization

Repeated administration of dopamine D1 receptor agonists has been demonstrated to reverse the established behavioral sensitization to MAP [27,28], AMPH [15], and cocaine [21] in rats (Table 1). We previously reported that intermittent administration of MAP (once every 3 days for a total of five times) induced the behavioral sensitization in rats [27]. After development of sensitization, the rats received a dopamine D1 agonist, R-(+)-SKF38393, once a day for seven consecutive days. The chronic administration of R-(+)-SKF38393 reversed MAP-induced behavioral sensitization, and the reversal was maintained at least for 14 days after the last injection of R-(+)-SKF38393 (Figure 2). Thus, chronic dopamine D1 receptor agonism reverses the established behavioral sensitization to MAP, lasting for at least 2 weeks.

The mechanisms for the expression and maintenance of MAP sensitization have been intensively investigated, and alterations of presynaptic and postsynaptic dopaminergic neurotransmission have been reported [2,29]. Analysis of dopamine release in the striatum by *in vivo* microdialysis revealed that the behavioral sensitization to MAP is in part mediated through the enhanced release of dopamine in response to MAP (Figure 3A) [27]. The findings are

Table 1 Summary of pharmacological treatments that reverse behavioral sensitization to psychostimulants

Reversal treatment	Inducer of sensitization	Animal	Study
D1 receptor agonism			
SKF81297	Cocaine	Rat	[21]
R-(+)-SKF38393	Methamphetamine	Rat	[27,28]
SKF38393	Amphetamine	Rat	[15]
D2 or D1/D2 receptor agonism combined with mild NMDA receptor antagonism			
Cocaine + MK-801	Cocaine	Rat	[21,22]
Quinpirole + MK-801	Cocaine	Rat	[21]
Quinpirole + CGS19755	Cocaine	Rat	[21]
Pergolide + memantine	Cocaine	Rat	[21]
D1/D2 receptor agonism combined with 5-HT_{2A} receptor antagonism			
Cocaine + clozapine	Cocaine	Rat	[67]
Cocaine + mianserin	Cocaine	Rat	[67]
Cocaine + ketanserin	Cocaine	Rat	[67]
Aripiprazole	Methamphetamine	Mouse	[17]
D1/D2 receptor agonism combined with 5-HT_3 receptor antagonism			
Cocaine + ondansetron	Cocaine	Rat	[62]
Pergolide + ondansetron	Cocaine	Rat	[64,65]
Pergolide + ondansetron	Methamphetamine	Rat	[63]
5-HT_{1A} receptor agonism			
Osemozotan	Methamphetamine	Mouse	[87]
5-HT_{2A} receptor antagonism			
Ritanserin	Methamphetamine	Mouse	[88]
Clozapine	Cocaine	Mouse	[91]
5-HT_3 receptor antagonism			
ondansetron	cocaine	Rat	[89,90]
Selective serotonin receptor reuptake inhibitor			
Fluoxetine	Methamphetamine	Mouse	[97]
Paroxetine	Methamphetamine	Mouse	[97]
Opioid receptor-like 1 (ORL1) receptor agonism			
Orphanin FQ/nociceptin	Cocaine	Mouse	[98]
Environmental conditions			
Environmental enrichment	Cocaine	Mouse	[99]

in agreement with previous reports [30,31]. Chronic administration of R-(+)-SKF38393 reversed the enhanced dopamine release in the striatum, and the reversal lasted for 2 weeks (Figure 3B). The results suggest that chronic dopamine D1 receptor agonism adjusts the enhanced dopamine release in the striatum of MAP-sensitized rats.

As a postsynaptic mechanism, we reported the alteration of dopamine receptor affinity states in MAP-sensitized rats. The dopamine receptor exists in high- and low-affinity states. High-affinity states of dopamine D1 ($D1^{High}$) and D2 ($D2^{High}$) receptors have ~1000-fold greater affinity for dopamine than low-affinity states of dopamine D1 and D2 receptors [32,33], and dopamine $D1^{High}$ and $D2^{High}$ receptors have been proposed as functional states of dopamine receptors [34]. In our study, repeated administration of MAP increased the proportions of $D1^{High}$ and $D2^{High}$ receptors in the rat striatum by 2.4-fold and 2.6-fold, respectively [28], as previously reported [35]. Behavioral sensitization can be explained by the increased proportion of $D1^{High}$ and $D2^{High}$ receptors in the striatum, which may result in supersensitivity to dopaminergic drugs and psychostimulants [36,37]. Chronic administration of R-(+)-SKF38393 after development of sensitization reversed the increased proportions of both $D1^{High}$ and $D2^{High}$ receptors. In agreement with our findings, an electrophysiological study revealed that chronic administration of a dopamine D1 receptor agonist SKF81297 reversed the dopamine D1 receptor supersensitivity in NAc neurons of cocaine-sensitized rats [21]. Thus, adjustment of the high affinity states of D1 and D2 receptors in striatal neurons and the dopamine D1 receptor supersensitivity in NAc neurons as well as the enhanced dopamine release by chronic D1 receptor agonism likely result in the attenuation of sensitized behavior to MAP or cocaine.

The mechanisms by which dopamine D1 receptor agonism reverses the increased release of dopamine and the increased proportions of $D1^{High}$ and $D2^{High}$ receptors in MAP-sensitized rats

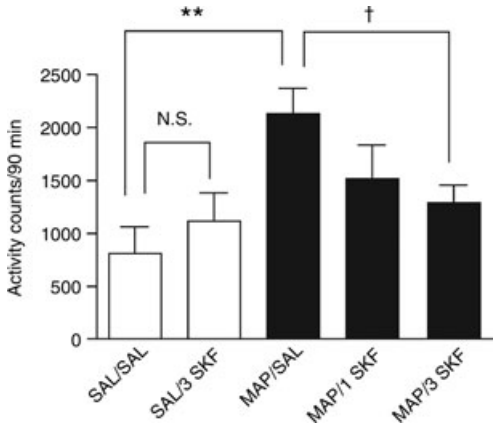

Figure 2 Effect of chronic dopamine D1 receptor agonism on methamphetamine (MAP)-induced behavioral sensitization. Rats were injected with MAP 1.0 mg/kg or saline (SAL) once every 3 days for total of 5 times (days 1–13), and then challenged with MAP 0.5 mg/kg after a 7-day withdrawal period (on day 20) to verify the development of sensitization. The rats subsequently received R-(+)-SKF38393 at 1.0 mg/kg (1 SKF) or 3.0 mg/kg (3 SKF) or SAL once a day for 7 days (on days 21–27), and then challenged with MAP 0.5 mg/kg. After a 14-day withdrawal period (on day 41), locomotor activity was recorded. Rats were subdivided into five groups (treatment on days 1–13/treatment on days 21–27), and number of rats was indicated in parentheses: SAL/SAL (5), SAL/3 SKF (6), MAP/SAL (9), MAP/1 SKF (5), MAP/3 SKF (7). Bars represent means ± S.E.M. ***$P < 0.05$ versus SAL/SAL group; †$P < 0.05$ versus MAP/SAL group. (Reproduced from Ref. [27] with permission.)

are currently unknown. Dopamine release from axon terminals of nigrostriatal dopaminergic neurons is negatively regulated by stiratonigral GABAergic neurons [38]. Activation of striatonigral GABAergic neurons by dopamine D1 receptor agonism likely inhibits nigrostriatal dopaminergic neurons and dopamine release in the striatum. Alternatively, the inhibition of glutamate release from corticostriatal glutamatergic neurons via activation of the striatonigral GABAergic neurons by dopamine D1 receptor agonism and subsequent changes in activity of nigro-thalamo-cortical loop [39] may result in the attenuation of dopamine release in the striatum. Thus, dopamine release from axon terminals of nigrostriatal dopaminergic neurons seems to be indirectly downregulated via activation of striatonigral GABAergic neurons by dopamine D1 receptor agonism, but mechanisms for its reversal lasting for a long time need to be clarified.

There are several reports suggesting attenuated intracellular signaling of dopamine D1 receptors in sensitized rats. Whereas a dopamine D2 receptor agonist induces augmented behavioral responses in sensitized rats, a dopamine D1 receptor agonist fails to induce augmented responses [36,37]. It is possible that activity of the dopamine D1 receptor/cAMP/PKA signaling cascade in the striatum is downregulated after the establishment of sensitization, in spite of the increased proportion of dopamine $D1^{High}$ receptors [28] and the supersensitivity of dopamine D1 receptors [21]. The fact that PKA activity is reduced in the NAc of AMPH- and cocaine-sensitized rats [40] supports the hypothesis. In addition, the phosphorylation of dopamine and cAMP-regulated phosphoprotein of M_r 32 kDa (DARPP-32) at Thr34 by PKA is reduced in the striatum of MAP-sensitized rats and cocaine-sensitized mice [41]. These findings raise a plausible mechanism that chronic dopamine D1 receptor agonism counteracts the decreased dopamine D1 receptor/cAMP/PKA signaling in the sensitized state, leading to the reversal of sensitization.

Dopamine D1 receptors are required for the development of behavioral sensitization, but dopamine D1 receptor agonism shows ability to reverse the sensitized state. It has been proposed that mesocortical hypodopaminergic function (causing negative symptoms), induced by lesioning of dopaminergic neurons, results in mesolimbic hyperdopaminergic function (causing positive symptoms), which is important in the etiology of schizophrenia [42–44]. Systemic administration or local administration to

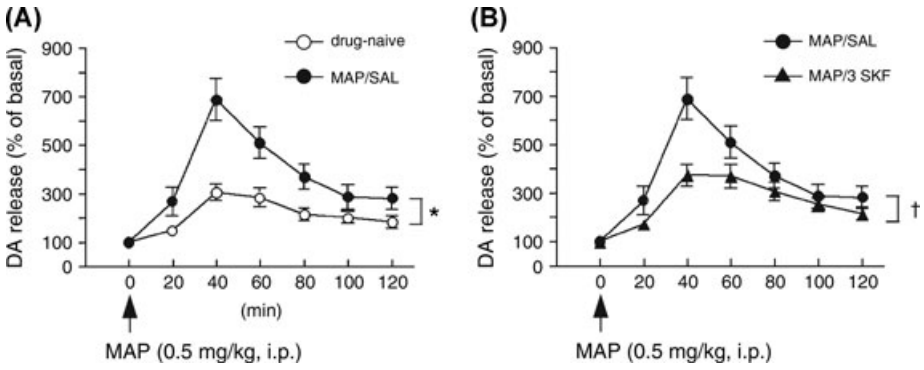

Figure 3 Effect of chronic dopamine D1 receptor agonism on the enhanced dopamine release in the striatum of MAP-sensitized rats. Dopamine release in the striatum after MAP 0.5 mg/kg challenge was analyzed using *in vivo* microdialysis on day 41, and compared between drug naïve and MAP/SAL groups (**A**) and between MAP/SAL and MAP/3 SKF groups (**B**). Dopamine release after MAP challenge was calculated relative to the basal values in each group (100%). Basal values in MAP/SAL or MAP/3 SKF group were not different from that in drug naïve group. Each point is the mean ± S.E.M., and number of rats was: drug naïve (6), MAP/SAL (8), MAP/3 SKF (10). *$P < 0.05$ versus drug naïve group; †$P < 0.01$ versus MAP/SAL-treated group. (Reproduced from Ref. [27] with permission.)

prefrontal cortex (PFC) of the dopamine D1 receptor agonist is shown to improve the behavioral impairments related to the function of PFC such as the AMPH-induced impairment of attentional set shifting [45] and the phencyclidine (PCP)-induced impairments in the novel object recognition test and the reversal learning test [46], suggesting the dysfunction of dopamine D1 receptors in the PFC of sensitized animals. Thus, chronic dopamine D1 receptor agonism, targeting hypofunctional D1 receptor signaling in the PFC as well as the striatum, is an attractive therapeutic approach, and may adjust the altered dopaminergic neurotransmission in sensitized animal models of schizophrenia.

Effect of Dopamine D2 or D1/D2 Receptor Agonism on Established Sensitization

Dopamine D2 receptor antagonism is an essential future of antipsychotics alleviating or controlling positive symptoms of schizophrenia, but less effective for negative symptoms or cognitive dysfunction. In sensitized animal models of schizophrenia, dopamine D2 receptor antagonism blocks the development and expression of behavioral sensitization, but fails to reverse the sensitized state, suggesting the limitation of dopamine D2 receptor antagonism for the treatment of sensitization.

Dopamine D2 receptor agonism or dopamine D1/D2 receptor agonism are also tried, but the agonism alone does not show the ability to reverse the established sensitization. However, when dopamine D2 or D1/D2 receptor agonism is combined with additional manipulations, reversal of sensitization is achieved, as described below.

Combination with Mild NMDA Receptor Antagonism

Glutamate as well as dopamine plays critical roles in the development of sensitization [47]. This notion is based on the finding that the NMDA receptor antagonist prevents the development of sensitization to cocaine or AMPH [48]. Glutamate signaling may be altered in the established sensitization, and NMDA receptors can be therapeutic targets for the reversal of sensitization.

Chronic dopamine D2 receptor agonism by quinpirole and chronic dopamine D1/D2 receptor agonism by cocaine or pergolide are shown to reverse the established sensitization to cocaine, when the function of NMDA receptors are partially suppressed by low doses of MK-801 or CGS19755 and by a relatively weak NMDA receptor antagonist, memantine [21]. The combined treatments also reverse the dopamine D1 receptor supersensitivity in the NAc of cocaine-sensitized rats [21].

Stimulation of dopamine D1/D2 receptors by systemic administration of cocaine is known to increase glutamate levels in the NAc [49]. Although highly speculative, combination of glutamatergic signal activated by dopamine D1/D2 receptor agonism and mild NMDA receptor antagonism may be required for the reversal of sensitization. Electrophysiological studies at corticostriatal synapses demonstrate that mild NMDA receptor activation and a subsequent, relatively small increase in intracellular Ca^{2+} induce long-term depression (LTD) [50,51]. The inhibition of glutamatergic neurotransmission via LTD may counteract long-term potentiation (LTP)-like plasticity, which is induced during development of sensitization [52–56]. The finding that D2 receptors are required for induction of LTD at corticostriatal synapses [57,58], supports the hypothesis that dopamine D2 or D1/D2 receptor agonism combined with mild NMDA receptor antagonism may adjust LTP-like plasticity of glutamatergic neurotransmission in sensitized animals via LTD-mediated mechanisms.

Combination with Serotonin Receptor Antagonism

Serotonin receptors (5-HT_{1A}, 5-HT_{2A} and 5-HT_3 receptors) are implicated in the development and/or expression of sensitization [59–61], indicating that serotonin receptors are also therapeutic targets for the reversal of sensitization. Chronic 5-HT_3 receptor antagonism (ondansetron) [62–66] and chronic 5-HT_{2A} receptor antagonism (clozapine, mianserin, and ketanserin) [67], combined with dopamine D1/D2 receptor agonism (cocaine or pergolide), reverse sensitization. Interestingly, an antipsychotic drug, aripiprazole, with properties of the partial dopamine D2 receptor agonist and 5-HT_{2A} receptor antagonist [68], but not risperidone with properties of the dopamine D2 receptor antagonist and 5-HT_{2A} receptor antagonist, is reported to reverse MAP sensitization [17].

The mechanism by which 5-HT_{2A} or 5-HT_3 receptor antagonism reverses sensitization is still poorly understood. Chronic administration of 5-HT_3 antagonists reduces activity of dopaminergic neurons in the ventral tegmental area (VTA) [69–74] and basal extracellular dopamine levels in the NAc, but not in the PFC [71,75]. Atypical antipsychotics with a property of 5-HT_{2A} receptor antagonist are known to induce the profound increase in dopamine release in the PFC presumably by interacting with 5-HT_{1A} receptor signaling [76–80], although the effects of the selective 5-HT_{2A} receptor agonist or antagonist on dopamine release in the PFC are controversial [81,82]. Thus, chronic 5-HT_3 or 5-HT_{2A} receptor antagonism may induce neuroadaptive changes in mesolimbic hyperdopaminergic and/or mesocortical hypodopaminergic function in sensitized animals [83].

The regulatory roles of 5-HT_2 and 5-HT_3 receptors are also implicated in glutamatergic neurotransmission. Activation of 5-HT_2 receptors enhances NMDA receptor function via phosphoinositol hydrolysis and subsequent stimulation of protein kinase C [84]. Activation of 5-HT_3 receptors induces Ca^{2+} influx at presynaptic nerve terminals and then enhances the release of neurotransmitters including glutamate [83,85,86]. These findings obtained with 5-HT_2 and 5-HT_3 receptor agonists suggest that chronic 5-HT_{2A} or 5-HT_3 receptor antagonism combined with dopamine D1/D2 receptor agonism may also induce LTD and adjust LTP-like plasticity of glutamatergic neurotransmission in sensitized animals.

Effect of Serotonin Receptor Agonism or Antagonism alone on Established Sensitization

A 5-HT_{1A} receptor agonist (osemozotan) [87], a 5-HT_{2A} receptor antagonist (ritanserin) [88], a 5-HT_3 receptor antagonist (ondansetron) [89,90], and an atypical antipsychotic with a property of 5-HT_2 receptor antagonist (clozapine) [91] were demonstrated

to reverse the established sensitization by themselves. Osemozotan and ritanserin were also shown to reverse the enhanced serotonin release in the PFC of MAP-sensitized mice [26,87,88].

Conclusions

Reversal of sensitization is likely achieved by treatments that adjust mesolimbic hyperdopaminergic and mesocortical hypodopaminergic functions in sensitized animals. As means of treatment for schizophrenia in human, dopamine D1 receptor agonists and drugs that regulate serotonergic receptors may have potential therapeutic values, since D2 receptor agonists [92] or NMDA receptor antagonists [45,93–96], which would exacerbate symptoms of schizophrenia, can not be used. We have demonstrated that chronic D1 receptor agonism reverses the established sensitization via presynaptic and postsynaptic mechanisms [27, 28]. Future studies are required to elucidate mechanisms for long-lasting reversal of sensitization by chronic D1 receptor agonism, possibly involving the remodeling of neuronal circuits mediated through neurogenesis and epigenetic modification.

Conflict of Interest

The authors have no conflict of interest.

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