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Review

Role of serotonin (5-HT)$_{1B}$ receptors in psychostimulant addiction

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Abstract:
Psychostimulant (cocaine, amphetamine and its derivatives) addiction is an important health problem with implications in social and economic life. Although mesocorticolimbic dopamine system plays a crucial role in the mechanism responsible for the rewarding effects of these drugs, recent data also show involvement of the brain serotonin (5-HT) system. In the present review we discuss the role of 5-HT$_{1B}$ receptors in the psychostimulant addiction on the base of the effects of 5-HT$_{1B}$ receptor ligands on the behavioral effects of the psychostimulants in experimental models (sensitization, intracranial self-stimulation, conditioned place preference, self-administration and extinction/reinstatement model) used to assess their addictive properties. Moreover, the effect of long-term treatment with psychostimulants on 5-HT$_{1B}$ receptors is also discussed.

Key words:
5-HT$_{1B}$ receptors, psychostimulants, behavioral models of drug addiction

Introduction

Drug abuse is an important health problem which also affects many sides of social and economic life. The commonly abused drugs are a group of psychostimulants including cocaine, amphetamine and its derivatives. Although the mesocorticolimbic dopamine system plays a crucial role in the mechanisms responsible for the behavioral effects of psychostimulants, including their reinforcing or rewarding activity [17, 21], recent data also show involvement of the brain serotonin (5-HT) system [11, 12]. In fact, psychostimulants not only inhibit the dopamine transporter and/or increase dopamine release [20, 45], but also inhibit 5-HT reuptake, which leads to an increase in extracellular 5-HT concentrations [2, 23]. Moreover, several lines of evidence indicate that manipulation of the brain 5-HT system modifies different behavioral effects of psychostimulants [11, 12, 22, 24, 27, 49].

5-HT neurotransmission is mediated by at least 14 different 5-HT receptor subtypes. Among them are 5-HT$_{1B}$ receptors located as autoreceptors on 5-HT nerve endings, which regulate 5-HT release [18, 47], as well as heteroreceptors located on dopaminergic, glutamatergic, GABA-ergic or cholinergic neurons and regulating the release of these neurotransmitters [26, 42, 50]. Importantly, 5-HT$_{1B}$ receptors are strongly expressed in the mesocorticolimbic system, which seems to be closely involved in the effects of psychostimulants [5, 43].

In the present review we discuss the impact of 5-HT$_{1B}$ receptor ligands on the behavioral effects of psychostimulants, mainly in experimental models used to assess their addictive properties. Moreover, the effect of long-term treatment with psychostimulants on 5-HT$_{1B}$ receptors is also discussed.

Locomotor activity and sensitization

While peripheral administration of the 5-HT$_{1B}$ receptor antagonist GR 127935 or SB 216641 was found to reduce the locomotor hyperactivity induced by single doses of cocaine in rats [7] or amphetamine in mice [35], the hyperlocomotion evoked by cocaine was reported to be enhanced in 5-HT$_{1B}$ receptor knock-out mice [41]. Although the cause of the above discrepancy is unclear, it cannot be excluded that it stems from the difference between the acute pharmacological blockade and the long-term genetic knock-out of 5-HT$_{1B}$ receptors. Interestingly, local injection of another 5-HT$_{1B}$ receptor antagonist GR 55566, into the ventral tegmental area (VTA) did not affect the locomotor hyperactivity induced by either cocaine or amphetamine in rats [31, 39].

Agonists of 5-HT$_{1B}$ receptors (CP 93129, CP 94253) administered systemically increased the cocaine-induced hyperlocomotion, but when injected locally into the VTA, they enhanced both the cocaine- and the amphetamine-induced locomotor hyperactivity [31, 34, 39]. The above observations are confirmed by the results obtained by Neumaier et al. [28], who showed that the cocaine-evoked locomotor hyperactivity was enhanced in rats with genetically induced elevation of the expression of 5-HT$_{1B}$ receptors.

Experiments into sensitization demonstrated that peripheral administration of 5-HT$_{1B}$ receptor antagonists did not affect the acquisition of cocaine sensitization in rats [34], but reduced the development of amphetamine sensitization in mice [35]. Inhibition of the development of cocaine sensitization in rats was demonstrated after local injection of 5-HT$_{1B}$ receptor antagonists into the VTA or nucleus accumbens shell [39, 40]. On the other hand, agonists of 5-HT$_{1B}$ receptors, administered systemically or locally into the VTA (but not into the nucleus accumbens), enhanced the development of sensitization evoked by cocaine or amphetamine in rodents [34, 35, 39, 40].

As far as the expression of cocaine sensitization in rats or amphetamine sensitization in mice is concerned, all the examined 5-HT$_{1B}$ receptor antagonists were found to be ineffective [34, 35, 39, 40]. Agonists of those receptors, administered systemically, did not affect the expression of amphetamine sensitization in mice [35], but increased that phase of cocaine sensitization in rats [34]. An increase in the expression of cocaine sensitization in rats was also shown after 5-HT$_{1B}$ receptor agonists injected locally into the nucleus accumbens shell, but not into the VTA [39, 40].

Intracranial self-stimulation (ICSS) reward

There are only a few reports on the role of 5-HT$_{1B}$ receptors in the ICSS model. Harrison et al. [15] and Hayes et al. [16] found that the 5-HT$_{1B}$ receptor antagonist GR 127935 did not affect ICSS current thresholds in rats with electrodes implanted in the lateral hypothalamus or the VTA, respectively; furthermore the latter results indicated that impaired 5-HT neurotransmission through 5-HT$_{1B}$ receptors did not alter the reward-related ICSS behavior. On the other hand, the mixed 5-HT$_{1A/1B}$ receptor agonist RU 24969 [15] and the selective 5-HT$_{1B}$ receptor agonist CP 94253 [16] were reported to elevate ICSS thresholds. Since those threshold-elevating effects of either agonist were attenuated by GR 127935 [15, 16] pharmacological stimulation of 5-HT$_{1B}$ receptors seemed to be responsible for the inhibition of reward-related ICSS behavior. At the same time, Harrison et al. [15] also observed that RU 24969 blocked the threshold-lowering effect of cocaine – the outcome of two opposing drug effects canceling out each other rather than of specific pharmacological antagonism.

Conditioned place preference

Conditioned place preference is a widely used procedure for examining the rewarding effects of drugs [44]. As far as the role of 5-HT$_{1B}$ receptors in the effect of psychostimulants in this model is concerned, the first observations were reported by Belzung et al. [4], who demonstrated that 5-HT$_{1B}$ receptor knock-out mice did not show any reliable conditioned place preference for the stimuli paired with cocaine. On the other hand, however, the cocaine-induced place preference in rats was not affected by the 5-HT$_{1B}$ receptor antagonist GR 127 935 [8], which indicates differences between the acute pharmacological blockade and the long-term genetic knockout of 5-HT$_{1B}$ receptors in their effect on the rewarding properties of the psychostimulant; nonetheless the importance of the species difference (mice

vs. rats) cannot be excluded. At the same time, some convergent results were obtained in animals with the overexpression of 5-HT_{1B} receptors and following their pharmacological stimulation. For example, Neumaier et al. [28] and Barot et al. [3] studied the effect of cocaine in rats with overexpressed 5-HT_{1B} receptors (using a virally mediated gene transfer) in projections from the nucleus accumbens to the VTA. They found an increase in cocaine rewarding activity, shown as a shift to the left in the dose-response curve for cocaine-induced conditioned place preference [28]; moreover, the latter authors reported enhancement of both the rewarding and the aversive effects of cocaine depending on its dose and treatment schedule [3]. Cervo et al. [8] investigated the effect of the 5-HT_{1B} receptor agonist CP 94253 and found that it caused place aversion but also enhanced the action of the subthreshold doses of cocaine in the conditioned place preference paradigm, both those effects of CP 94253 being blocked by GR 127 935.

Self-administration

Another experimental model used to examine the rewarding effects of drugs is their self-administration paradigm [48]. Using that model, Rocha et al. [41] and Castanon et al. [7] reported that 5-HT_{1B} receptor knock-out mice showed an increased propensity to self-administer cocaine in a progressive ratio schedule, an effect suggesting a decrease in the reinforcing properties of the psychostimulant. On the other hand, acute pharmacological blockade of 5-HT_{1B} receptors was found to be ineffective towards cocaine self-administration in mice [7] and rats [32, 38], as well as towards amphetamine self-administration in rats [14]. The above results indicate that tonic activation of 5-HT_{1B} receptors is not involved in the rewarding effect of psychostimulants. Thus, like in the case of a conditioned place preference model, a difference between the acute pharmacological blockade and the long-term genetic knock-out of 5-HT_{1B} receptors was also observed in the self-administration paradigm. The latter findings seem to be supported by the results obtained by David et al. [9] who observed that subchronic (5-day) administration of a 5-HT_{1B} receptor antagonist disrupted intracranial (into VTA) cocaine self- administration.

In contrast to the data discussed above, an increase in the rewarding effect of psychostimulants was shown following stimulation of 5-HT_{1B} receptors. In fact, the agonists of 5-HT_{1B} receptors CP 93129, CP 94253 and RU 24969 dose-dependently reduced self-administration of cocaine, as shown by the descending arm of the fixed-ratio 5 (FR-5) cocaine dose-effect function, in a manner similar to the effect produced by an increased unit dose of the psychostimulant [32, 33, 38]. Those agonists also lowered the threshold dose of cocaine that supported its self-administration [32]. Moreover, they dose-dependently increased the highest completed ratio for cocaine self-administration in a progressive ratio schedule of reinforcement, the latter effect being also similar to that induced by an increased unit dose of cocaine [32]. Importantly, the specificity of the above effects of the 5-HT_{1B} receptor agonists can be confirmed by the following observations: 1) self-administration was not maintained when 5-HT_{1B} receptor agonists were substituted for cocaine, which indicates that they did not produce their own reinforcing effect [32]; 2) the increase in the rewarding effects of cocaine, induced by 5-HT_{1B} receptor agonists, was antagonized by the 5-HT_{1B} receptor antagonists GR 127935 [32] and SB 216641 [38]; 3) the 5-HT_{1B} receptor agonist CP 94253 did not affect food self-administration [33, 37].

Although the 5-HT_{1B} receptor agonist RU 24969 was shown to suppress amphetamine self-administration in rats on the FR-1 schedule of reinforcement – an effect antagonized by GR 127935 – the lack of the agonist-induced shift to the left in the amphetamine dose-response function suggests that it did not increase the rewarding properties of amphetamine [14]. Furthermore, the suppression of amphetamine self-administration following intra-accumbal injection of CP 93129 to rats on the progressive ratio schedule also seems to confirm the above conclusion [13].

Summing up, pharmacological stimulation of 5-HT_{1B} receptors seems to play a different role in the modulation of the rewarding activity of cocaine and amphetamine.

Extinction/reinstatement model

Psychostimulant abusers show a high rate of relapse into drug-seeking and drug-taking behavior, even after prolonged periods of abstinence [25]. In experimental animals, such an incentive motivation for psychostimulants is measured by an extinction/reinstatement model [10]. Using that experimental approach, Acosta et al. [1] reported that the 5-HT_{1B} receptor antagonist, GR 127935, administered in a dose of 3 mg/kg did not affect the cocaine- or cocaine-associated cue-induced reinstatement

of cocaine-seeking behavior. However, in our laboratory we found that GR 127935 administered in a higher dose (10 mg/kg), as well as another 5-HT$_{1B}$ receptor antagonist, SB 216641 (7.5 mg/kg), strongly reduced cocaine-primed the psychostimulant-seeking behavior [37]. Moreover, even when administered in a lower dose of 5 mg/kg, both those antagonists almost completely blocked the cue-induced cocaine-seeking behavior, but did not affect food-taking behavior [37, 38]. The relatively high doses of the 5-HT$_{1B}$ receptor antagonists, necessary to attenuate the cocaine-seeking behavior induced by cocaine priming, may be connected with the up-regulation [36] and functional supersensitivity [29] of 5-HT$_{1B}$ receptors during the withdrawal from repeated treatment with the psychostimulant (sensitization, discrimination or self-administration paradigms). In other words, our results indicate that tonic activation of 5-HT$_{1B}$ receptors plays a role in the cocaine- or cue-induced reinstatement of cocaine-seeking behavior [37].

Paradoxically, agonists of 5-HT$_{1B}$ receptors which increase the reinforcing effects of cocaine [32, 38] were found to attenuate the incentive motivation for cocaine, as measured by an extinction/reinstatement model [1, 33, 37]. In fact, RU 24969 [1] and CP 94253 [33, 37] were found to attenuate cocaine- or cocaine-associated cue-primed cocaine-seeking behavior. While Acosta et al. [1] found that the above-described inhibitory effect of RU 24969 was antagonized by GR 127935, in our experiment [37] we were not able to show any antagonistic effects of GR 127935 or SB 216641 on the CP 94253-induced inhibition of cocaine-seeking behavior. Since RU 24969 attenuated the cue-induced reinstatement of sucrose-seeking behavior [1], and in the light of the lack of effect of 5-HT$_{1B}$ receptor antagonists on the inhibitory effects of CP 94253 on cocaine-seeking behavior [37], a generalized impact on motivation (unrelated to the activation of 5-HT$_{1B}$ receptors?) rather than on the cocaine stimulus-induced motivational effects should be considered when inhibition of cocaine-seeking behavior by 5-HT$_{1B}$ receptor agonists is concerned.

Importantly, the inhibitory effect of RU 24969 and CP 94253 on cocaine-seeking behavior was found when a submaximal cocaine priming dose (10 mg/kg) was used [1, 33, 37]. In contrast, controversial results were reported when a threshold cocaine priming dose (2.5 mg/kg) was used. While Pentkowski et al. [33] observed an inhibitory effect of CP 94253, our study revealed that the 5-HT$_{1B}$ receptor agonist in question potentiated cocaine-seeking behavior when combined with the threshold priming dose of cocaine, that effect of CP 94253 being antagonized by SB 216641 [37]. The latter effect of CP 94253 is in line with the increased effect of 5-HT$_{1B}$ receptor agonists on the reinforcing activity of cocaine [1, 33, 37].

Changes in 5-HT$_{1B}$ receptors following chronic exposure to psychostimulants

Using a quantitative autoradiographic analysis, we have found that a 5-HT$_{1B}$ receptor ligand binding was enhanced in several brain structures after withdrawal from chronic exposure to cocaine in both the discrimination and the sensitization paradigms in rats. In fact, such an effect was shown in the areas containing dopamine cell bodies (the VTA, the substantia nigra) and terminals (the nucleus accumbens shall and core, but not in the caudate putamen). At the same time, neither acute cocaine administration nor cocaine challenge following chronic exposure to the psychostimulant affected the 5-HT$_{1B}$ receptor ligand binding [36]. Importantly, an increase in 5-HT$_{1B}$ receptor mRNA in the nucleus accumbens shall and dorsal striatum was found after chronic, but not acute, binge cocaine administration to rats [19]. In line with our results [36], O'Dell et al. [30] reported functional changes in 5-HT$_{1B}$ receptors during abstinence from cocaine self-administration in rats. Actually, they found subsensitivity of the receptors following 6 hours of abstinence, and their supersensitivity to the locomotor response induced by a 5-HT$_{1B}$ receptor agonist following 14 days of abstinence. Interestingly, alterations in 5-HT$_{1B}$ receptor function were more severe after extended – when compared to limited – exposure to cocaine intake. Furthermore, the functional supersensitivity of 5-HT$_{1B}$ receptors, measured as a locomotor response to their agonist, was also observed in rats following 5-day abstinence from the subchronic treatment with cocaine [34].

A transient increase in 5-HT$_{1B}$ receptor binding sites in the striatum, but not in other structures, without alterations in 5-HT$_{1B}$ receptor mRNA [46], as well as functional desensitization of the 5-HT$_{1B}$ receptor-mediated motor behavior [6] were found following subchronic treatment with 3,4-methylenedioxymethamphetamine ("ecstasy"), which suggests that this drug may alter the activity of 5-HT$_{1B}$ receptors without changing 5-HT$_{1B}$ receptor mRNA or binding levels in majority of brain structures.

Conclusions

The inhibitory effect of 5-HT_{1B} receptor antagonists on cocaine- or cue-induced cocaine-seeking behavior indicates a role of the tonic activation of these receptors in the behavioral response studied. Importantly, this effect of 5-HT_{1B} receptor antagonists seems to be specific, as they affect neither other responses to cocaine (sensitization, conditioned place preference, maintenance of self-administration), nor food-taking behavior in rats. Hence, the above observations seem to indicate that 5-HT_{1B} receptor antagonists may be useful in treating cocaine addiction. It should be stressed, however, that the effects showing a decrease in the reinforcing properties of cocaine have been found in 5-HT_{1B} receptor knock-out mice in a conditioned place preference and a self-administration models. The cause of the discrepancy between the effects of acute pharmacological blockade and long-term genetic knock-out of 5-HT_{1B} receptors is still unknown and requires further studies.

Pharmacological stimulation of 5-HT_{1B} receptors seems to increase the rewarding activity of cocaine, but not amphetamine; there are only a few data on the latter drug in the literature, though. As regards cocaine, such an effect has been demonstrated using a conditioned place preference and a self-administration models, but not an intracranial self-stimulation model. Unexpectedly, the agonists of 5-HT_{1B} receptors – like their antagonists – have been found to reduce the reinstatement of cocaine-seeking behavior; however, it cannot be excluded that this effect of the agonists is not related to the activation of 5-HT_{1B} receptors.

In conclusion, 5-HT_{1B} receptors seem to be a potential target of further studies with new agents that are effective in the pharmacotherapy of psychostimulant addiction.

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