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ON THE ROLE OF SEROTONIN_{2A/2C} RECEPTORS
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Apart from showing involvement of dopamine, recent studies also indicate a role of serotonin (5-HT) in the behavioral effects of cocaine in rodents. In the present study we investigated the role of 5-HT_{2A/2C} receptors in the development or expression of sensitization to cocaine in rats, using ketanserin, an antagonist at these receptors. Since ketanserin also shows a high affinity for alpha₁-adrenoceptors, prazosin, a comparative antagonist at those receptors was also examined. Male Wistar rats were treated repeatedly (for 5 days) with cocaine (10 mg/kg) in combination with either vehicle, or ketanserin (1-3 mg/kg) or prazosin (3 mg/kg); afterwards, on day 10, they received a challenge dose of cocaine (10 mg/kg). In another experiment, the animals were given either with vehicle or cocaine (10 mg/kg) for 5 days, and were then challenged with cocaine (10 mg/kg) in combination with vehicle, or ketanserin (1-3 mg/kg) or prazosin (3 mg/kg) on day 10. Acute administration of cocaine increased the locomotor activity in rats; that hyperactivation was inhibited by ketanserin (3 mg/kg), but not by prazosin. In animals treated repeatedly with cocaine, the locomotor hyperactivity induced by a challenge dose of the psychostimulant was ca. 2-3 times higher than that after its first administration. No difference was observed in the response to cocaine challenge in rats treated repeatedly with cocaine, ketanserin+cocaine, or prazosin+cocaine. In animals treated repeatedly with the psychostimulant, the behavioral response to a challenge dose of cocaine was dose-dependently decreased when the drug was combined with ketanserin, but not with prazosin. The above findings indicate a role of 5-HT_{2A/2C} receptors (but not alpha₁-adrenoceptors) in the acute locomotor hyperactivity, as well as in the expression (but not development) of cocaine sensitization. Since chronic use of cocaine by humans may lead to psychoses or craving for this drug of abuse, our findings also seem to indicate possible importance of 5-HT_{2A/2C} receptor antagonists in the therapy of cocaine addiction.

Key words: ketanserin, prazosin, cocaine, locomotor activity, sensitization, rats.

INTRODUCTION

Sensitization to cocaine is characterized — among others — by an augmentation of locomotor, stereotypy or positive reinforcing effects after the regimen of repeated, intermittent cocaine injections is discontinued (1, 2).

It seems of interest to study the mechanism of the above phenomenon, since sensitization to cocaine is thought to underlie certain aspects of drug addiction, i.e. paranoia, craving and relapse produced by chronic drug abuse in humans (1, 2). A number of studies have shown that the mesolimbic dopamine system is a major neurobiological substrate sustaining cocaine sensitization (3, 4, 5, 6, 7, 8); however, the influence of other neurotransmitter systems, e.g. excitatory amino acids or serotonin (5-HT), has also been reported (9).

As regards 5-HT, it has been reported that activation of 5-HT_{1A} or 5-HT_{1B} receptors and blockade of 5-HT₃ ones enhances and decreases, respectively, cocaine sensitization to its locomotor effect in rats (10, 11, 12, 13). Some findings indicate that also 5-HT₂ receptors may be regarded as a target for cocaine-induced behaviors. The above-mentioned receptors and their mRNA are located in different brain structures including the mesolimbic dopamine system (14, 15, 16); moreover, they have been found to regulate a tonic or a stimulated activity of the latter system (17, 18, 19, 20, 21). On the other hand, antagonists of 5-HT₂ receptors have been reported to decrease voluntary cocaine consumption in a two-choice paradigm (22) and to reduce the drug-induced reinforcing (23), discriminative (24, 25, 26) and locomotor effects (27, 28, 29). Sparse data from humans also indicate that an antagonist of 5-HT₂ receptors may decrease the subjective and reinforcing effects of cocaine, whereas a 5-HT₂ receptor agonist seems to be efficacious in enhancing cocaine reinforcement (30).

In the present paper we focussed our attention on the role of 5-HT₂ receptors in cocaine sensitization to its locomotor hyperactivity effect in rats using ketanserin, an antagonist of those receptors (31, 32), administered in a development or an expression phase of the phenomenon. Ketanserin binds to 5-HT_{2A} and 5-HT_{2C} subtypes of 5-HT₂ receptors and displays selectivity ca. a 8 times higher for 5-HT_{2A} receptors than for 5-HT_{2C} binding sites (33, 34). Since ketanserin also shows significant affinity for alpha₁-adrenergic binding sites and has antagonistic properties at these receptors (33), we used for comparison prazosin as a selective alpha₁-adrenergic antagonist to exclude involvement of the latter receptors.

MATERIALS AND METHODS

Animals

The experiment was performed on male Wistar rats (280–300 g). The animals had free access to food and water, and were kept at a room temperature of 20 ± 1°C on a 12-h light/dark cycle (the light on between 6.00–18.00 h). All the experiments were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Science in Kraków.

Drugs

The following drugs were used (pre-session injection times given in parentheses): cocaine hydrochloride (-5 min; Merck, Germany), ketanserin tartrate (-35 min; Tocris, UK) and prazosin hydrochloride (-35 min; Tocris, UK). Cocaine and ketanserin were dissolved in saline, while prazosin was suspended in a 1% aqueous solution of Tween 80. All the drugs were administered intraperitoneally (i.p.) in a volume of 1 ml/kg.

Locomotor activity measurements

The locomotor activity of rats was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, USA), linked on-line to a compatible IBM-PC. Each cage (43 x 44 cm) was equipped with 15 infra-red emitters, located on the *x* and *y* axes, and with an equivalent amount of receivers on the opposite walls of the cage. The rats' behavior was analyzed using Auto-track software (Columbus Instruments, USA). Locomotor activity associated with horizontal locomotion was defined as a trespass of three consecutive photo-beams.

Before recording the locomotor activity, the animals were allowed a 60-min habituation period after which they were taken out, injected with the drugs, and placed back in the boxes. Locomotor activity was recorded for 60 min. Six to eight animals per group were used.

Experimental design

Development of cocaine sensitization. During the first 5 days of the experiment, the animals received the following injections (30 min apart): vehicle + vehicle, vehicle + cocaine (10 mg/kg), ketanserin (1-3 mg/kg) + cocaine (10 mg/kg) or prazosin (3 mg/kg) + cocaine (10 mg/kg). On day 10, all the rats were challenged with cocaine (10 mg/kg). Locomotor activity was recorded on days 1 and 10.

Expression of cocaine sensitization. During the first 5 days of the experiment, the animals received the following injections (30 min apart): vehicle + vehicle or vehicle + cocaine (10 mg/kg). On day 10, the rats were challenged with vehicle + cocaine (10 mg/kg), ketanserin (1-3 mg/kg) + cocaine (10 mg/kg) or prazosin (3 mg/kg) + cocaine (10 mg/kg). Locomotor activity was recorded on days 1 and 10.

Data analysis

To evaluate behavioral sensitization, the response to cocaine on day 10 was compared with that to the first injection of cocaine (day 1) in the same animal, or with the response to the test drug injection (day 10) in animals treated with repeated vehicle, using a paired Student *t*-test or a one-way ANOVA, respectively. The one-way ANOVA, followed by *post hoc* Dunnett's test, were applied to evaluate the treatment group effect separately on days 1 and 10.

RESULTS

Development of cocaine sensitization (Fig. 1)

On day 1 of the experiment, cocaine induced a ca. four-fold increase in the locomotor activity of rats. Ketanserin (3 mg/kg, but not 1 mg/kg) significantly reduced the cocaine-evoked hyperactivity. Prazosin (3 mg/kg) did not change the hyperactivity induced by cocaine.

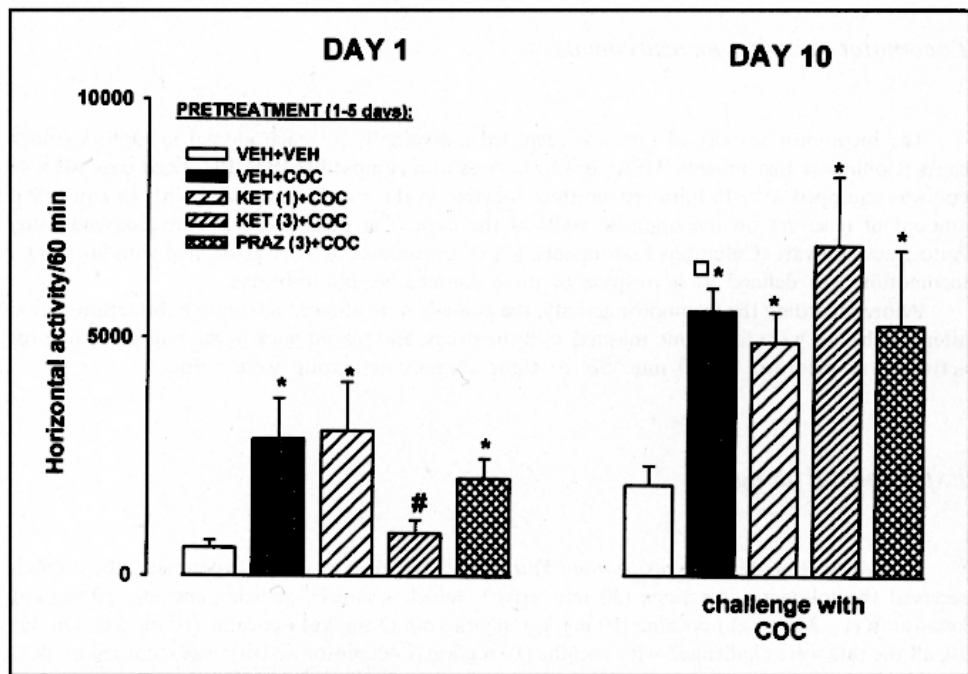


Fig. 1. Effects of ketanserin and prazosin on the development of cocaine sensitization.

Rats were treated repeatedly with vehicle (VEH), cocaine (COC; 10 mg/kg), or ketanserin (KET; 1–3 mg/kg)+cocaine (10 mg/kg) or prazosin (PRAZ; 3 mg/kg)+cocaine (10 mg/kg) daily for 5 days; on day 10 they were given a challenge dose of cocaine (10 mg/kg). Student's paired *t*-test showed a significance between the effect of cocaine on days 1 and 10 ($t = 4.29$, $\square P < 0.01$); ANOVA showed a significant treatment group effect on days 1 [$F(4,32) = 3.14$, $P < 0.05$] and 10 [$F(4,32) = 4.67$, $P < 0.01$], but not on day 8 [$F(4,32) = 0.59$, n.s.]. * $P < 0.001$ vs vehicle controls; # $P < 0.01$ vs cocaine groups.

On day 10 of the experiment, in rats treated repeatedly with cocaine (days 1–5), the challenge dose of the drug increased ca. 2–3 times their locomotor hyperactivity compared to the effect of the first injection of the psychostimulant (on day 1 in cocaine-treated animals, or on day 10 in vehicle-treated ones, respectively). Pretreatment with ketanserin (1 and 3 mg/kg) or prazosin

(3 mg/kg) before each of the 5 daily cocaine injections did not affect the cocaine-induced sensitization, tested 5 days after withdrawal (day 10).

Neither acute or repeated treatment with ketanserin or prazosin affected the basal locomotor activity of the animals (*acute* treatment — vehicle + vehicle: 347 ± 86.8 , ketanserin (3 mg/kg) + vehicle: 312 ± 90.6 , prazosin (3 mg/kg) + vehicle: 299 ± 77.1 ; *repeated* treatment — vehicle + vehicle: 286 ± 77.2 , ketanserin (3 mg/kg) + vehicle: 331 ± 79.6 , prazosin (3 mg/kg) + vehicle: 272 ± 62.5).

Expression of cocaine sensitization (Fig. 2)

On day 10, cocaine challenge of rats treated repeatedly with the psychostimulant (days 1–5) produced locomotor hyperactivity which was 104% higher than that observed in animals treated likewise with vehicle.

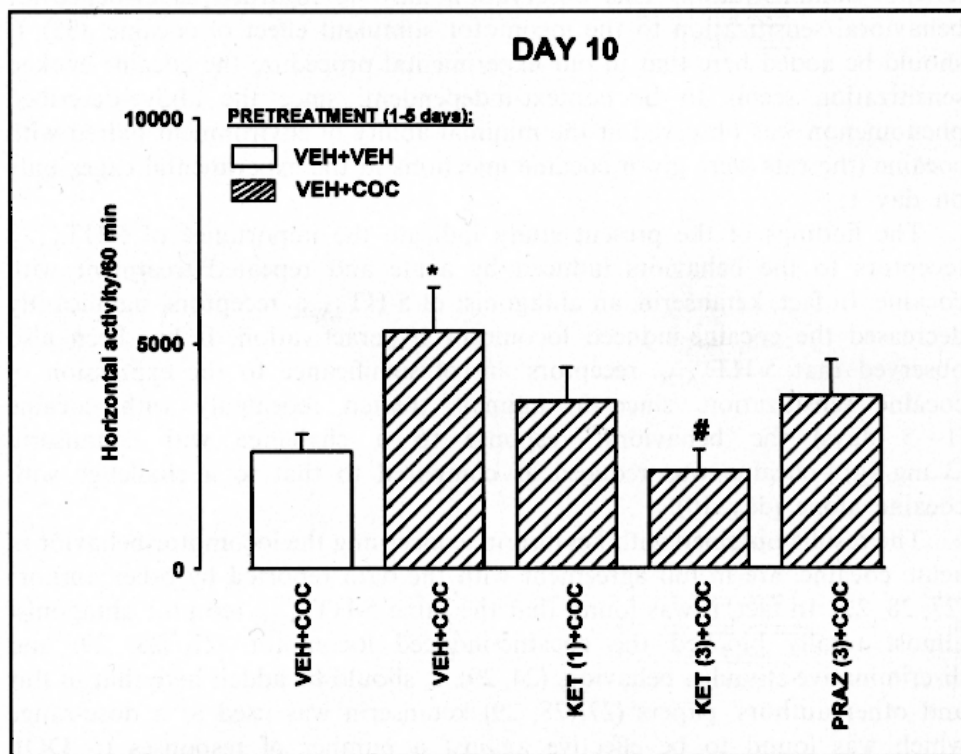


Fig. 2. Effects of ketanserin and prazosin on the expression of cocaine sensitization.

Rats were treated repeatedly with vehicle (VEH) or cocaine (COC; 10 mg/kg) daily for 5 days. On day 10 they were challenged with cocaine (10 mg/kg), or ketanserin (KET; 1–3 mg/kg) + cocaine (10 mg/kg) or prazosin (PRAZ; 3 mg/kg) + cocaine (10 mg/kg). ANOVA showed a significant treatment group effect [$F(4,32) = 15.19$, $P < 0.001$] * $P < 0.01$ vs vehicle-treated and cocaine-challenged group; # $P < 0.05$ vs cocaine-treated and cocaine-challenged group.

Successive investigations were conducted on rats treated repeatedly (days 1—5) with cocaine. When those animals were given a challenge dose of cocaine in combination with ketanserin (1—3 mg/kg), a dose-dependent reduction of the locomotor response to the psychostimulant challenge was observed; however, a significant effect (a decrease by about 61%) was produced by the highest dose of ketanserin only. Such an effect was not found when the challenge dose of cocaine was combined with prazosin (3 mg/kg).

DISCUSSION

In rats treated for 5 days with a dose of 10 mg/kg of cocaine, the locomotor hyperactivity induced by the same challenge dose of the psychostimulant — tested after 5-day withdrawal — was about 2—3 times as high as that after its first administration. This observation may be regarded as evidence for behavioral sensitization to the locomotor stimulant effect of cocaine. (35). It should be added here that in our experimental procedure the cocaine-evoked sensitization seems to be context-independent, since the above-described phenomenon was observed at the minimal ability of environment paired with cocaine (the rats were given cocaine injections in the experimental cages only on day 1).

The findings of the present study indicate the importance of 5-HT_{2A/2C} receptors to the behaviors induced by acute and repeated treatment with cocaine. In fact, ketanserin, an antagonist of 5-HT_{2A/2C} receptors, significantly decreased the cocaine-induced locomotor hyperactivation. It has been also observed that 5-HT_{2A/2C} receptors are of significance to the expression of cocaine sensitization, since in animals treated repeatedly with cocaine (1—5 days) the behavioral response to a challenge with ketanserin (3 mg/kg)+cocaine was reduced as compared to that to a challenge with cocaine alone (day 10).

The results obtained with ketanserin, concerning the locomotor behavior of acute cocaine, are in full agreement with the data reported by other authors (27, 28, 29). In fact, it was found that the same 5-HT_{2A/2C} receptor antagonist almost totally blocked the cocaine-induced locomotor (27, 28, 29) and discriminative stimulus behaviors (24, 29). It should be added here that in this and other authors' papers (27, 28, 29) ketanserin was used at a dose-range which was found to be effective against a number of responses to DOI, a preferential 5-HT_{2A/2C} receptor agonist (36, 37). In line with our results obtained with ketanserin regarding the expression of cocaine sensitization, McMillen *et al.* (22) found that amperozide, a 5-HT₂ receptor antagonist, also attenuated the craving for cocaine measured in another paradigm, i.e. the psychostimulant voluntary consumption assessed by a two-choice test.

Our finding showing that the blockade of 5-HT_{2A/2C} receptors attenuated the expression of cocaine sensitization may suggest that chronic cocaine alters the 5-HT_{2A/2C} receptor function, and that such a disturbance may change the experience of abstinent cocaine addicts. In line with the above suggestion, some pre-clinical experiments demonstrated that chronic exposure to cocaine potentiated the behavioral and endocrine effects of 5-HT_{2A/2C} receptor stimulation by DOI (38, 39, 40). While enhancing the functional sensitivity of 5-HT_{2A/2C} receptors, repeated administration of cocaine alters neither the number (β max) nor the affinity (K_D) of [³H] ketanserin binding sites in the rat brain (41), nor the 5-HT_{2A/2C} receptor availability in chronic cocaine abusers (42). In other words, it seems that repeated administration of cocaine leads to an increased functional reactivity of 5-HT_{2A/2C} receptors only.

The mechanism responsible for the decrease in cocaine hyperactivation and sensitization by ketanserin may be related to the 5-HT_{2A/2C} receptor-mediated blockade of dopamine release in the nucleus accumbens, the terminal area of mesolimbic dopamine system playing a crucial role in the cocaine-related hyperlocomotion and expression of its sensitization (6, 9). Further support to this observation comes from the presence of 5-HT_{2A/2C} receptors in the nucleus accumbens (15, 16), as well as from the increases in extracellular dopamine concentrations after local activation of 5-HT_{2A/2C} receptors (43). In line with the latter suggestion, results of several electrophysiological studies indicate that 5-HT induces depolarization of medium spiny accumbal neurons, this effect being completely antagonized by ketanserin (44). Similarly, systemic (45, 46) or local (43) stimulation of 5-HT_{2A/2C} receptors by their agonist DOI enhances the dopamine release in the nucleus accumbens, this effect being reduced by perfusion of ketanserin or another selective 5-HT_{2A/2C} receptor antagonist, LY-53,877 (43).

Another interesting observation of this paper was that ketanserin given jointly with cocaine during development of cocaine sensitization did not modify the effects of the challenge dose of cocaine, tested after 5-day withdrawal. These data seem to exclude a role of 5-HT_{2A/2C} receptors in the process(es) related to the development of sensitization to cocaine. Since a lot of studies indicate that the development of sensitization comes from dopamine cell bodies in the ventral tegmental area, the origin of the mesolimbic system, reported in the present study lack of effect of ketanserin may indicate that the tegmental 5-HT_{2A/2C} receptors do not control this cocaine-related process. Indeed, as has been shown in some electrophysiological experiments, selective inhibition of 5-HT_{2A/2C} receptors does not affect dopamine cell firing in that brain structure (17, 47, 48). Similarly, ketanserin injected locally into the ventral tegmental area does not block the sensitization to another psychostimulant, amphetamine (49).

It is noteworthy that, besides 5-HT_{2A/2C} receptors, ketanserin shows a high affinity for α_1 -adrenoceptors and is regarded as their antagonist (33).

Recent microdialysis studies have showed that 5-HT_{2A} and 5-HT_{2C} receptors modulate the adrenergic neurotransmission, with a phasic-facilitatory and a tonic-inhibitory influence of 5-HT_{2A} receptors and 5-HT_{2C} receptors, respectively (46). Similar pattern of 5-HT_{2A/2C} receptor-mediated regulation on the firing rate activity of locus coeruleus, the area rich in adrenergic cell bodies, was found in electrophysiological experiments (48). However, alpha₁-adrenoceptor properties of ketanserin do not seem to be important to its antagonism toward the locomotor and sensitizing effects of cocaine, since the effects of cocaine are not affected by the selective alpha₁-adrenoceptor antagonist prazosin. In the context of weak receptor selectivity of ketanserin, a recent study by Wurch *et al.* (50) dealing with this antagonist has shown its high affinity for rat 5-HT_{1D} receptors ($K_i = 10$ nM). Involvement of 5-HT_{1D} rather than 5-HT_{2A/2C} receptors in the effect of ketanserin seems feasible, since there are only some 5-HT_{1D} receptors in rat brain (51); moreover ketanserin shows affinity ca. 5 times lower for 5-HT_{1D} than for 5-HT₂ binding sites (34, 50). On the other hand, the antagonistic activity of ketanserin towards 5-HT_{1D} receptors (52), as well as the character of 5-HT_{1D} receptors which act as 5-HT autoreceptors in rat dorsal raphe nucleus where inhibit 5-HT release (53, 54) — the latter effect enhancing sensitization to cocaine (12) — may speak for a role of 5-HT_{1D} receptors in sensitization to cocaine. The issue whether the latter 5-HT receptors are involved in sensitization to cocaine cannot be solved in this paper, and needs further studies with selective antagonists of 5-HT_{1D} receptors.

In conclusion, the results of the present study suggest that 5-HT_{2A/2C} receptors are involved in the expression (but not development) of cocaine sensitization; furthermore they corroborate some earlier reports that these receptors may be engaged in the locomotor hyperactivity induced by acute administration of the psychostimulant to rats. Since chronic use of cocaine may result in psychoses or craving for this drug of abuse, our findings also seem to indicate importance of 5-HT₂ receptor antagonists to the therapy of cocaine addiction.

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