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Effects of $GABA_B$ receptor agonists on cocaine hyperlocomotor and sensitizing effects in rats

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Abstract:
The present study was designed to find out whether pharmacological activation of $GABA_B$ receptors played a role in cocaine sensitization. To this end, male Wistar rats were injected with baclofen or 3-aminopropyl(methyl)phosphinic acid (SKF 97541), the potent and selective $GABA_B$ receptor agonists. The rats, which were repeatedly (for 5 days) administered with cocaine (10 mg/kg) and then challenged with cocaine (10 mg/kg) after 5-day withdrawal period, showed significantly higher locomotor hyperactivity in comparison with the effect observed in saline-pretreated and cocaine challenged rats. Baclofen (1.25, 2.5 and 5 mg/kg), administered for 5 days prior to cocaine, dose-dependently attenuated cocaine sensitization. When injected in the same treatment regimen, SKF 97541 (0.03 mg/kg) reduced the development of cocaine sensitization. To examine the effects of baclofen and SKF 97541 on the expression of cocaine sensitization, the drugs were given acutely before a challenge dose of cocaine (10 mg/kg) on day 10. Either baclofen (2.5 and 5 mg/kg) or SKF 97541 (0.1 mg/kg) decreased sensitization to cocaine. Our findings implicate a role of $GABA_B$ receptors in locomotor responses to cocaine. More specifically, they show that stimulation of $GABA_B$ receptors exerted inhibitory actions on acute locomotor responses to cocaine and on the expression of cocaine sensitization, what may offer a therapeutic potential of $GABA_B$ receptor agonists in the treatment of cocaine dependence.

Key words:
cocaine, baclofen, SKF 97541, behavioral sensitization, locomotor activity

Introduction

In humans, repeated abuse of cocaine and other psychostimulants lead to addiction and psychosis. In rodents, repeated exposure to such drugs induces among others enhancement of stimulating effects on locomotor activity (i.e., behavioral sensitization), the model thought to reflect neuroadaptations that contribute to addiction [27, 30]. A number of data indicate that the major role in cocaine locomotor responses including development of behavioral sensitization plays the mesocorticolimbic dopamine system [12, 20, 28] consisting of the dopamine cell bodies and terminals located in the ventral tegmental area and inter alia in the nucleus accumbens, respectively. Locomotor hyperactivity in rats may mimic cocaine-induced hyperexcitability in humans, while cocaine sensitization is believed to reflect the cocaine-induced paranoia in human cocaine addicts and to be one of the main cause of drug relapse [30, 37, 38]. Thus, finding drugs that modulate the development and/or expression of sensitization to cocaine might be theoretically and clinically important.

However, dopaminergic system is only one component of the neuronal circulatory that mediates cocaine

behavioral sensitization, recent finding indicate that a significant effects of other neurotransmitter systems, e.g., excitatory amino acids or γ-aminobutyric acid (GABA) [40, 42], in this phenomenon. Regarding the latest neurotransmitter, it is the major inhibitory transmitter in the mammalian central nervous system where acts on two receptor classes: ionotropic ($GABA_A$ and $GABA_C$) and metabotropic $GABA_B$ receptors. $GABA_B$ receptors have been found in every brain region including the mesocorticolimbic circulation [4, 5, 29] where play a primary role in decreasing dopamine release [8, 9, 29, 36]. In fact, preclinical findings show that the $GABA_B$ receptor stimulation in the ventral tegmental area decreases extracellular dopamine in the terminal areas [43, 44] and antagonizes cocaine-induced dopamine release in the nucleus accumbens [15]. Furthermore, in rodents the $GABA_B$ receptor agonist baclofen blocks cocaine-induced hyperlocomotion [27] and the drug developed conditioned hyperlocomotion [25]. Importantly, pharmacological stimulation of $GABA_B$ receptors attenuates cocaine-reinforced responding in a self-administration procedures [10, 11, 19, 39] as well as both cocaine-induced and cocaine-associated cue-induced reinstatement of seeking behavior [11, 13, 16]. Recent findings indicate several modulations (increases or decreases) in $GABA_B$ receptor binding in limbic regions during reinstatement of cocaine seeking behavior in rats [21].

The present study was undertaken to investigate whether $GABA_B$ receptor stimulation may also control expression of locomotor and sensitizing effects by cocaine in male Wistar rats. In pharmacological analyses we used baclofen [6, 17, 22] and 3-aminopropyl (methyl)phosphinic acid (SKF 97541) [17, 22], the potent (K_i = 4.57 nM and IC_{50} = 16 nM, respectively) and selective $GABA_B$ receptor agonists, and administered them either acutely in the cocaine-induced locomotor hyperactivation and before the cocaine challenge dose that induces cocaine sensitization (expression of locomotor sensitization) or concurrently with chronic cocaine treatment (development of locomotor sensitization).

Materials and Methods

Animals

The experiment was performed on male Wistar rats (derived from licensed breeder, Warszawa, Poland) weighing 280–300 g. The animals were kept at a room temperature of 20 ± 1°C and at 50% humidity under a 12-h light/dark cycle (the lights on at 6.00 a.m.), 8 per cage in standard plastic rodent cages (57 × 35 × 20 cm). The animals had free access to food (Labofeed pellets) and water during the 7-day habituation period. All experiments were conducted during the light phase of the light-dark cycle (between 8.00 a.m. –3.00 p.m.) and were carried out in compliance with the Animal Protection Bill of August 21, 1997 (published in Dziennik Ustaw no. 111/1997 item 724), and according to the NIH Guide for the Care and Use of Laboratory Animals. They also received approval from the Local Ethical Committee. Six to eight rats per group were used.

Drugs

The following drugs were used (in parentheses suppliers): cocaine hydrochloride (Sigma-Aldrich, USA), baclofen (Tocris Cookson, Bristol, UK) and SKF 97541 (Tocris Cookson, Bristol, UK). The drugs were dissolved in 0.9% NaCl and were injected in a volume of 1 ml/kg *ip*. Baclofen, SKF 97541 and their vehicles were given 30 min, while cocaine was given immediately before behavioral tests.

Locomotor activity measurement

The locomotor activity of rats was recorded individually for each animal as described previously [47]. Briefly, the rats' behavior was measured in Opto-Varimex cages (Columbus Instruments, USA) linked on-line to compatible IBM-PC. Each cage (43 × 44 × 25 cm) was surrounded with a 15 × 15 array of photocell beams located 3 cm from the floor surface. Horizontal locomotor activity, defined as distance travelled, was expressed in cm. Before locomotor activity was recorded, rats were habituated in the test cages for 2 h/day on each of the two days before the start of the experiment, and on the test day for 1 h before the start of the test session; afterwards they were taken out, injected with the drugs and put back into the cages. Locomotor activity was recorded for 1 h and analyzed using Auto-track software (Columbus Instruments, USA).

Basal and cocaine-induced locomotor activation

Animals were tested only once, and separate groups of animals were pretreated with either the appropriate vehicle, baclofen (1.25, 2.5 and 5 mg/kg) or SKF 97541 (0.01, 0.03 and 0.1 mg/kg) before injection of either saline or cocaine (10 mg/kg). Measurements of locomotor activity began immediately after saline or cocaine injection.

Development of cocaine sensitization

During the first 5 days of experiment, the animals received the following injections: vehicle + saline, vehicle + cocaine (10 mg/kg), baclofen (1.25, 2.5 and 5 mg/kg) + cocaine (10 mg/kg) or SKF 97541 (0.01, 0.03 and 0.1 mg/kg) + cocaine (10 mg/kg). On days 6–9, they remained drug-free in their home cages. On day 10, the animals received a challenge dose of cocaine (10 mg/kg) and locomotor activity was recorded immediately after cocaine injection.

Expression of cocaine sensitization

During the first 5 days of the experiment, the animals received saline or cocaine (10 mg/kg). On days 6–9, the animals remained drug-free in their home cages. On day 10 (a test for expression of sensitization), they received vehicle + cocaine (10 mg/kg), baclofen (1.25, 2.5 and 5 mg/kg) + cocaine (10 mg/kg) or SKF 97541 (0.01, 0.03 and 0.1 mg/kg) + cocaine (10 mg/kg) and locomotor activity was recorded immediately after cocaine injection.

Statistical analyses

The data are expressed as the mean total activity counts (± SEM) for the 1-h observation period. The one-way analysis of variance (ANOVA), followed by *post-hoc* Dunnett's test, was applied to evaluate the treatment group on day 1 (acute treatments) or on day 10 (repeated treatments). To evaluate behavioral sensitization, the response to cocaine on day 10 was compared with the response to the test drug injection (day 10) of animals treated with repeated saline, using a one-way ANOVA.

Tab. 1. Effects of baclofen and SKF 97541 on the basal locomotor activity in rats

Treatment	Horizontal distance traveled (cm)/60 min	ANOVA
Vehicle	416 ± 99	
Baclofen (1.25)	606 ± 154	
Baclofen (2.5)	516 ± 92	
Baclofen (5)	298 ± 98*	$F(3,28) = 4.02$, $p < 0.05$
Vehicle	450 ± 62	
SKF 97541 (0.01)	580 ± 102	
SKF 97541 (0.03)	409 ± 81	
SKF 97541 (0.1)	498 ± 76	$F(3,27) = 0.274$, NS

* $p < 0.05$ *vs.* vehicle

Results

Basal locomotor activity

Following injection of baclofen in a dose of 5 mg/kg (but not in doses of 1.25 or 2.5 mg/kg), a significant decrease in basal locomotor activity was observed, while SKF 97541 (0.01, 0.03 and 0.1 mg/kg) did not alter the basal locomotor activity in rats (Tab. 1).

Cocaine-induced hyperactivity

Cocaine (10 mg/kg) significantly (at least two-fold) enhanced the locomotor activity of rats as compared to the effect of saline-treated animals (Fig. 1).

A significant group effect was detected by ANOVA for pretreatment with baclofen ($F(4,30) = 2.63$, $p < 0.05$. Pretreatment with baclofen, 5 mg/kg (but not 1.25 or 2.5 mg/kg) significantly attenuated the hyperactivation of acute cocaine (Fig. 1, upper panel).

A significant group effect was detected by ANOVA for pretreatment with SKF 97541 ($F(4,30) = 4.12$, $p < 0.01$). Pretreatment with SKF 97541, 0.1 mg/kg (but not 0.01 or 0.03 mg/kg) significantly reduced the hyperactivation induced by acute cocaine (Fig. 1, lower panel).

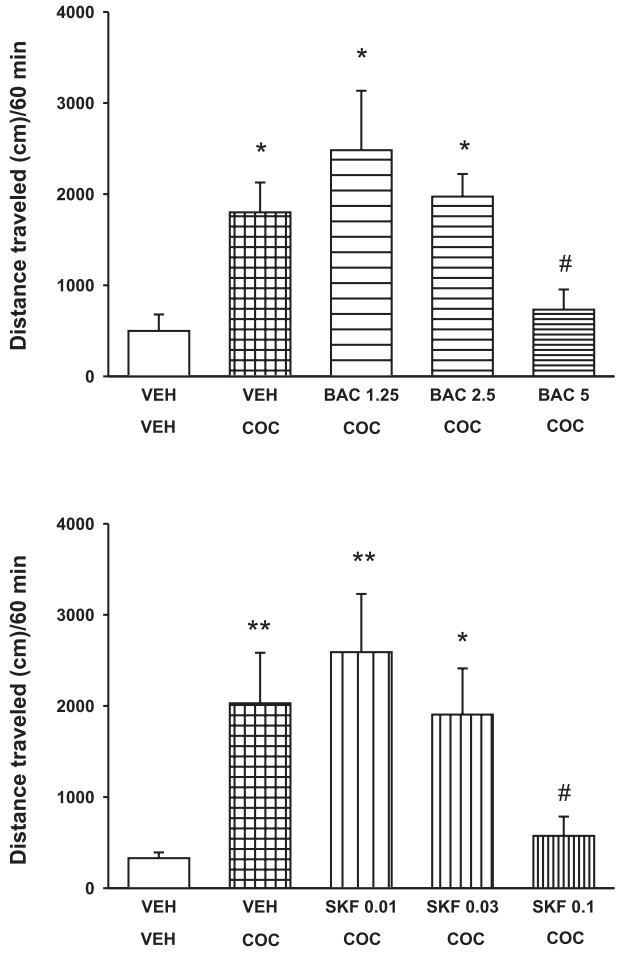

Fig. 1. Effects of baclofen (BAC) and SKF 97541 (SKF) on cocaine (COC; 10 mg/kg)-induced locomotor hyperactivity. * $p < 0.05$, ** $p < 0.01$ *vs.* corresponding vehicle + vehicle (VEH + VEH) group; # $p < 0.05$ *vs.* corresponding vehicle + cocaine group (Dunnett's test)

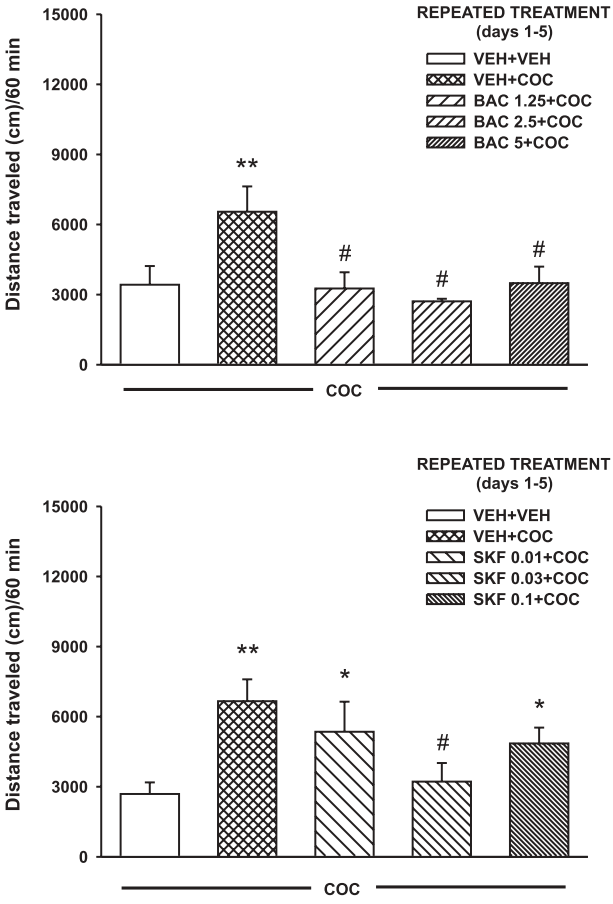

Fig. 2. Effects of baclofen (BAC) and SKF 97541 (SKF) on development of cocaine (COC) sensitization. Rats were treated repeatedly (days 1–5) with either vehicle (VEH + VEH), vehicle + cocaine (10 mg/kg), baclofen (1.25–5 mg/kg) + cocaine (10 mg/kg) or SKF 97541 (0.01–0.1 mg/kg) + cocaine (10 mg/kg). On day 10, the animals were given a challenge dose of cocaine (10 mg/kg). * $p < 0.05$, ** $p < 0.01$ *vs.* corresponding vehicle + vehicle-treated and cocaine-challenged group; # $p < 0.05$ *vs.* corresponding vehicle+cocaine-treated and cocaine-challenged group (Dunnett's test)

Development of cocaine sensitization

On day 10 of the experiment, the challenge dose of cocaine induced a 2–2.5-fold increase in the locomotor activity of rats treated repeatedly with cocaine (days 1–5) compared to the effect of acute cocaine in saline-treated animals (days 1–5) (Fig. 2).

A significant group effect was detected by ANOVA for pretreatment with baclofen ($F(4,30) = 7.65$, $p < 0.01$). A substantial decrease in the locomotor response to cocaine challenge was observed in rats treated repeatedly with baclofen (1.25, 2.5 or 5 mg/kg) in combination with cocaine (Fig. 2, upper panel).

Expression of cocaine sensitization

On day 10 of the experiment, cocaine challenge of rats treated repeatedly with cocaine (days 1–5) produced an increase in locomotor hyperactivity compared to the effect of acute cocaine in saline-treated (days 1–5) animals (Fig. 3).

A significant group effect was detected by ANOVA for pretreatment with baclofen ($F(4,34) = 10.28$, $p < 0.001$). Pretreatment with baclofen (1.25, 2.5 or 5 mg/kg) in a dose-dependent manner decreased the locomotor effects to a cocaine challenge in rats repeatedly treated with cocaine. A significant reduction almost to

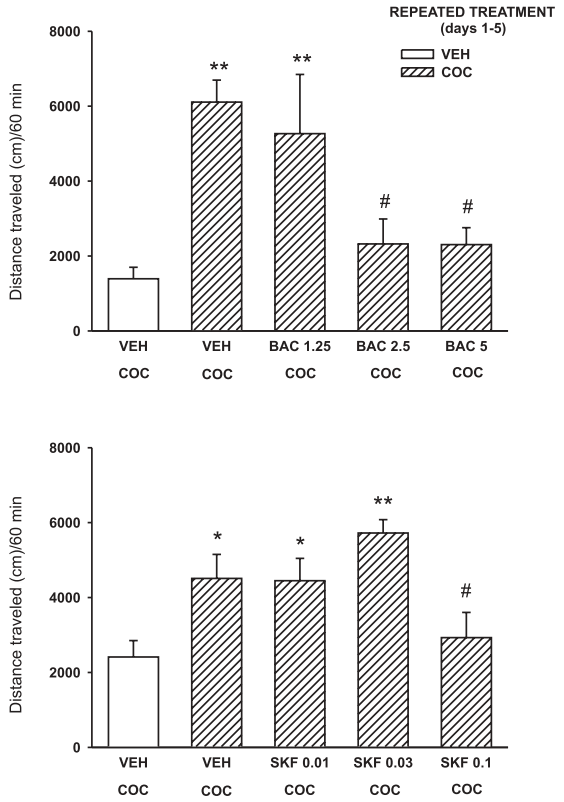

Fig. 3. Effects of baclofen (BAC) and SKF 97541 (SKF) on expression of cocaine (COC) sensitization. Rats were treated repeatedly (days 1–5) with either vehicle (VEH) or cocaine (10 mg/kg). On day 10, the animals were challenged with vehicle + cocaine (10 mg/kg), baclofen (1.25–5 mg/kg) + cocaine (10 mg/kg) or SKF 97541 (0.01–0.1 mg/kg) + cocaine (10 mg/kg). * $p < 0.05$, ** $p < 0.01$ *vs.* corresponding vehicle-treated and vehicle + cocaine-challenged group; # $p < 0.05$ *vs.* corresponding cocaine-treated and cocaine-challenged group (Dunnett's test)

the control level was seen following baclofen in doses of 2.5 and 5 mg/kg (Fig. 3, upper panel).

A significant group effect was detected by ANOVA for pretreatment with SKF 97541 ($F(4,32) = 4.25$, $p < 0.01$). A significant decrease in the locomotor response to cocaine challenge was found in rats treated repeatedly with cocaine after pretreatment with SKF 97541 in a dose of 0.1 mg/kg, but not in doses of 0.01 and 0.03 mg/kg (Fig. 3, lower panel).

Discussion

The findings of the present study indicate that mechanisms dependent on pharmacological stimulation of $GABA_B$ receptors seem to engaged in the locomotor behaviors induced by acute and repeated treatment with cocaine. In fact, the selective $GABA_B$ receptor agonists baclofen [6, 17, 22] and SKF 97541 [17, 22] attenuated the acute locomotor responses to cocaine and counteracted the development and expression of cocaine sensitization.

Our present results that $GABA_B$ receptor agonists attenuated both the development and expression of sensitization to cocaine extent previous data showing that baclofen [40] and the positive allosteric modulator of $GABA_B$ receptors GS 39783 [33] blocked the development of sensitization to cocaine. Moreover, the inhibitory action of baclofen is true also for locomotor responses induced by repeated exposure to other abused substances such as amphetamine [1, 2, 35] or morphine [3, 32, 46]. Current literature indicate also that several drugs that enhance synaptic GABA levels, i.e., γ-vinyl GABA (an irreversible inhibitor of GABA breakdown by GABA transaminase) and gabapentin (a cyclic analogue of GABA) inhibit the behavioral sensitization to cocaine in rodents [18, 23, 26], and such an inhibitory action of these drugs may be related to indirect stimulation of $GABA_B$ receptors. Sensitization is dependent on procedural variables, among which the dose and route of drug administration, as well as specific environmental cues (associated with repeated and challenge treatments) and the withdrawal time are of importance [41], and in this context it is worth to underlie that – independently of the way of its development – sensitization phenomenon is under control of $GABA_B$ receptors.

It should be noticed some differences in baclofen and SKF 97541 contributions to acute and repeated treatments with cocaine. Thus, co-treatment with baclofen during the repeated cocaine regimen (development of sensitization) or only its acute injection after this regimen before the challenge dose of cocaine (expression of sensitization) decreased locomotor hyperactivity induced by cocaine 5 days after termination of the sensitizing cocaine regimen. However, it should be underlined that when given alone baclofen in a dose of 5 mg/kg (but not 1.25 or 2.5 mg/kg) decreased basal locomotor activity of rats. The locomotor reducing effect of the $GABA_B$ receptor agonist alone may be inhibitory to stimulant effect of cocaine and may thus explain the observed decrease of behavioral responses after the baclofen treatment following acute treatment with cocaine or its expression of sensitization resulting from behavioral competition. However,

the fact that all used doses of baclofen given jointly with cocaine during development of cocaine sensitization decreased the locomotor effects of the challenge dose of cocaine after a 5-day withdrawal (i.e., also in the absence of baclofen) as well as a non-sedative dose (2.5 mg/kg) of baclofen reduced the expression of locomotor sensitizing effect to cocaine gives evidence that stimulation of $GABA_B$ receptors by this agonist inhibit both the development and the expression of cocaine sensitization.

In contrast to baclofen, SKF 97541 exerted an inhibitory influence on the development and expression of cocaine sensitization in the middle (0.03 mg/kg) and the highest dose (0.1 mg/kg), respectively, and such reduction may be considered as a specific response unrelated to its own effect on locomotion. Moreover, inhibition of the expression of behavioral sensitization to cocaine by SKF 97541 may stem from its similar effect on the locomotor hyperactivity produced by a single dose of the psychostimulant. In other words, the above observations indicate that the SKF 97541-induced activation of $GABA_B$ receptors contributes not only to the development of behavioral sensitization to cocaine, but also to the locomotor hyperactivity response to a single dose of the psychostimulant in drug-naive rats.

In line with a role of $GABA_B$ receptors in cocaine sensitization, several $GABA_B$ receptor agonists have been shown to reduce the reinstatement of cocaine seeking behaviors [13, 16] and reverse the reward impairment produced by cocaine withdrawal [8]. Furthermore, stimulation of $GABA_B$ receptors has been found to inhibit the initiation of cocaine self-administration [9, 11, 16, 36, 39].

The mechanism by which $GABA_B$ receptor agonists altered behavioral responses to cocaine following their acute and repeated administration is likely mediated through modulation of dopaminergic and/or glutamatergic neurotransmission. It was shown that the expression of both acute and sensitizing locomotor effects of cocaine are coincident with functional changes in mesolimbic dopaminergic neurotransmission [12, 20, 28] while activation of ventral tegmental dopamine neurons is strongly modulated by glutamatergic afferents and glutamate participates in involvement in behavioral sensitization [25]. The concentration of $GABA_B$ receptor mRNA and the density of $GABA_B$ receptors are found in the mesocorticolimbic system [7, 34, 45], and functional data indicate that GABA (through $GABA_B$ receptors) and dopamine interact in an antagonistic and reciprocal pattern. Thus, systematic or intra-tegmental application of $GABA_B$ receptor antagonists increased firing of the ventral tegmental dopamine neurons and/or increased extracellular dopamine levels [14, 24], while baclofen locally injected into the ventral tegmental area reduced somatodendritic [31] and terminal [43, 44] dopamine release. Furthermore, when co-treated with cocaine, baclofen simultaneously blocked cocaine-induced hyperlocomotion and decreased dopamine release in the nucleus accumbens [15]. The inhibitory effects of baclofen and SKF 97541 on cocaine-induced hyperlocomotor activity as well as behavioral sensitization seen in the present paper may be connected with decreasing tegmental dopamine excitability and decreasing release dopamine in the nucleus accumbens and/or the prefrontal cortex. On the other hand, systematic activation of $GABA_B$ receptor agonist by baclofen decreased glutamate release in the nucleus accumbens [25], the mechanism what may also be connected with the inhibitory effects of the drug-induced on cocaine behavioral responses.

In conclusion, the results of the present study implicate a role of $GABA_B$ receptors in locomotor responses to cocaine. More specifically, they show that stimulation of $GABA_B$ receptors exerted inhibitory actions on acute locomotor responses to cocaine and on the expression of cocaine sensitization, what may offer a therapeutic potential of $GABA_B$ receptor agonists in the treatment of cocaine dependence.

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References:

1. Bartoletti M, Gubellini C, Ricci F, Gaiardi M: Baclofen blocks the development of sensitization to the locomotor stimulant effect of amphetamine. Behav Pharmacol, 2005, 16, 553–558.
2. Bartoletti M, Gubellini C, Ricci F, Gaiardi M: The $GABA_B$ agonist baclofen blocks the expression of sensitisation to the locomotor stimulant effect of amphetamine. Behav Pharmacol, 2004, 15, 397–401.
3. Bartoletti M, Ricci F, Gaiardi M: A $GABA_B$ agonist reverses the behavioral sensitization to morphine in rats. Psychopharmacology, 2007, 192, 79–85.

4. Bettler B, Kaupmann K, Mosbacher J, Gassmann M: Molecular structure and physiological functions of $GABA_B$ receptors. Physiol Rev, 2004, 84, 835–867.
5. Bischoff S, Leonhard S, Reymann N, Schuler V, Shigemoto R, Kaupmann K, Bettler B: Spatial distribution of $GABA_BR1$ receptor mRNA and binding sites in the rat brain. J Comp Neurol, 1999, 412, 1–16.
6. Bowery NG: $GABA_B$ receptors and their significance in mammalian pharmacology. Trends Pharmacol Sci, 1989, 10, 401–407.
7. Bowery NG, Hudson AL, Price GW: $GABA_A$ and $GABA_B$ receptor site distribution in the rat central nervous system. Neuroscience, 1987, 20, 365–383.
8. Brebner K, Childress AR, Roberts DC: A potential role for $GABA_B$ agonists in the treatment of psychostimulant addiction. Alcohol Alcohol, 2002, 37, 478–484.
9. Brebner K, Froestl W, Roberts DC: The $GABA_B$ antagonist CGP56433A attenuates the effect of baclofen on cocaine but not heroin self-administration in the rat. Psychopharmacology, 2002, 160, 49–55.
10. Brebner K, Phelan R, Roberts DC: Intra-VTA baclofen attenuates cocaine self-administration on a progressive ratio schedule of reinforcement. Pharmacol Biochem Behav, 2000, 66, 857–862.
11. Campbell UC, Lac ST, Carroll ME: Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. Psychopharmacology, 1999, 143, 209–214.
12. Di Chiara G: The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend, 1995, 38, 95–137.
13. Di Ciano P, Everitt BJ: The $GABA_B$ receptor agonist baclofen attenuates cocaine- and heroin-seeking behavior by rats. Neuropsychopharmacology, 2003, 28, 510–518.
14. Erhardt S, Mathé JM, Chergui K, Engberg G, Svensson TH: $GABA_B$ receptor-mediated modulation of the firing pattern of ventral tegmental area dopamine neurons in vivo. Naunyn-Schmiedeberg's Arch Pharmacol, 2002, 365, 173–180.
15. Fadda P, Scherma M, Fresu A, Collu M, Fratta W: Baclofen antagonizes nicotine-, cocaine-, and morphine-induced dopamine release in the nucleus accumbens of rat. Synapse, 2003, 50, 1–6.
16. Filip M, Frankowska M: Effects of $GABA_B$ receptor agents on cocaine priming, discrete contextual cue and food induced relapses. Eur J Pharmacol, 2007, 571, 166–173.
17. Filip M, Frankowska M: $GABA_B$ receptors in drug addiction. Pharmacol Rep, 2008, 60, 755–770.
18. Filip M, Frankowska M, Gołda A, Zaniewska M, Vetulani J, Przegaliński E: Various GABA-mimetic drugs differently affect cocaine-evoked hyperlocomotion and sensitization. Eur J Pharmacol, 2006, 541, 163–170.
19. Filip M, Frankowska M, Przegaliński E: Effects of $GABA_B$ receptor antagonist, agonists and allosteric positive modulator on the cocaine-induced self-administration and drug discrimination. Eur J Pharmacol, 2007, 574, 148–157.
20. Filip M, Siwanowicz J: Implication of the nucleus accumbens shell, but not core, in the acute and sensitizing effects of cocaine in rats. Pol J Pharmacol, 2001, 53, 459–466.
21. Frankowska M, Wydra K, Faron-Górecka A, Zaniewska M, Kuśmider M, Dziedzicka-Wasylewska M, Filip M: Alterations in γ-aminobutyric $acid_B$ receptor binding in the rat brain after reinstatement of cocaine-seeking behavior. Pharmacol Rep, 2008, 60, 834–843.
22. Froestl W, Mickel SJ, Hall RG, von Sprecher G, Strub D, Baumann PA, Brugger F et al.: Phosphinic acid analogues of GABA. 1. New potent and selective GABA agonists. J Med Chem, 1995, 38, 3297–3312.
23. Gardner EL, Schiffer WK, Horan BA, Highfield D, Dewey SL, Brodie JD, Ashby CR Jr: Gamma-vinyl GABA, an irreversible inhibitor of GABA transaminase, alters the acquisition and expression of cocaine-induced sensitization in male rats. Synapse, 2002, 46, 240–250.
24. Giorgetti M, Hotsenpiller G, Froestl W, Wolf ME: In vivo modulation of ventral tegmental area dopamine and glutamate efflux by local $GABA_B$ receptors is altered after repeated amphetamine treatment. Neuroscience, 2002, 109, 585–595.
25. Hotsenpiller G, Wolf ME: Baclofen attenuates conditioned locomotion to cues associated with cocaine administration and stabilizes extracellular glutamate levels in rat nucleus accumbens. Neuroscience, 2003, 118, 123–134.
26. Itzhak Y, Martin JL: Effect of riluzole and gabapentin on cocaine- and methamphetamine-induced behavioral sensitization in mice. Psychopharmacology, 2000, 151, 226–233.
27. Kalivas PW, Duffy P, Eberhardt H: Modulation of A10 dopamine neurons by gamma-aminobutyric acid agonists. J Pharmacol Exp Ther, 1990, 253, 858–866.
28. Kalivas PW, Nakamura M: Neural systems for behavioral activation and reward. Curr Opin Neurobiol, 1999, 9, 223–227.
29. Kalivas PW, Pierce RC, Cornish J, Sorg BA: A role for sensitization in craving and relapse in cocaine addiction. J Psychopharmacol, 1998, 12, 49–53.
30. Kalivas PW, Stewart J: Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev, 1991, 16, 223–244.
31. Leite-Morris KA, Fukudome EY, Shoeb MH, Kaplan GB: $GABA_B$ receptor activation in the ventral tegmental area inhibits the acquisition and expression of opiate-induced motor sensitization. J Pharmacol Exp Ther, 2004, 308, 667–678.
32. Lhuillier L, Mombereau C, Cryan JF, Kaupmann K: $GABA_B$ receptor-positive modulation decreases selective molecular and behavioral effects of cocaine. Neuropsychopharmacology, 2007, 32, 388–398.
33. Liang F, Hatanaka Y, Saito H, Yamamori T, Hashikawa T: Differential expression of γ-aminobutyric acid type B receptor-1a and -1b mRNA variants in GABA and non-GABAergic neurons of the rat brain. J Comp Neurol, 2000, 416, 475–495.
34. Phillis BD, Ong J, White JM, Bonnielle C: Modification of d-amphetamine-induced responses by baclofen in rats. Psychopharmacology, 2001, 153, 277–284.
35. Roberts DC, Brebner K: GABA modulation of cocaine self-administration. Ann NY Acad Sci, 2000, 909, 145–158.
36. Robinson TE, Berridge KC: Addiction. Ann Rev Psychol, 2003, 54, 25–53.

37. Robinson TE, Berridge KC: Incentive-sensitization and addiction. Addiction, 2001, 96, 103–114.
38. Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW: The $GABA_B$ agonist baclofen modifies cocaine self-administration in rats. Behav Pharmacol, 1998, 9, 195–206.
39. Steketee JD, Kalivas PW: Sensitization to psychostimulants and stress after injection of pertussis toxin into the A10 dopamine region. J Pharmacol Exp Ther, 1991, 259, 916–924.
40. Stewart J, Badiani A: Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol, 1993, 4, 289–312.
41. Vanderschuren LJ, Kalivas PW: Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology, 2000, 151, 99–120.
42. Westerink BH, Enrico P, Feimann J, De Vries JB: The pharmacology of mesocortical dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and prefrontal cortex of the rat brain. J Pharmacol Exp Ther, 1998, 285, 143–154.
43. Westerink BH, Kwint HF, de Vries JB: Eating-induced dopamine release from mesolimbic neurons is mediated by NMDA receptors in the ventral tegmental area: a dual-probe microdialysis study. J Neurochem, 1997, 69, 662–668.
44. Wirtshafter D, Sheppard AC: Localization of $GABA_B$ receptors in midbrain monoamine containing neurons in the rat. Brain Res Bull, 2001, 56, 1–5.
45. Woo SH, Kim HS, Yun JS, Lee MK, Oh KW, Seong YH, Oh SK, Jang CG: Inhibition of baclofen on morphine-induced hyperactivity, reverse tolerance and postsynaptic dopamine receptor supersensitivity. Pharmacol Res, 2001, 43, 335–340.
46. Zaniewska M, McCreary AC, Sezer G, Przegaliński E, Filip M: Effects of agmatine on nicotine-evoked behavioral responses in rats. Pharmacol Rep, 2008, 60, 645–654.

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