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Various GABA-mimetic drugs differently affect cocaine-evoked hyperlocomotion and sensitization

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Abstract

To substantiate the notion that cocaine behavioral effects may be influenced by γ-aminobutyric acid (GABA) neurotransmission male Wistar rats were injected with gabapentin (a cyclic GABA analogue), tiagabine (a GABA reuptake inhibitor), or vigabatrin (a GABA transaminase inhibitor) before acute or repeated treatment with cocaine evoking either locomotor hyperactivation or sensitization. Gabapentin (1–30 mg/kg), tiagabine (2.5–10 mg/kg) or vigabatrin (75–250 mg/kg) attenuated the cocaine (10 mg/kg)-induced hyperactivation and in the highest doses they also decreased basal locomotor activation. Vigabatrin (75–250 mg/kg) dose-dependently reduced the development of cocaine sensitization in rats treated repeatedly (days 1–5) with cocaine (10 mg/kg) and then challenged with cocaine (10 mg/kg) following 5-day withdrawal; the remaining drugs were ineffective. When injected acutely with a cocaine challenge dose, gabapentin (3–10 mg/kg) or vigabatrin (150 mg/kg), but not tiagabine, significantly attenuated the expression of cocaine sensitization. The present results show that enhanced GABA-ergic neurotransmission exerted inhibitory actions on acute responses to cocaine, however, only in a case of vigabatrin the inhibition seems to be unrelated to the inhibitory effect of the drugs on basal locomotor activity. The finding that vigabatrin protected against the development and the expression of cocaine sensitization further supports its therapeutic potential in the treatment of cocaine dependence.

Keywords: Cocaine; GABA neurotransmission; Locomotor activation; Behavioral sensitization; (Rat)

1. Introduction

In humans, cocaine exhibits rewarding properties that manifest themselves as positive subjective feelings which motivate people to use it repeatedly. In animals expression of cocaine-evoked behavioral responses includes, among others, hyperactivation and locomotor sensitization due to acute and repeated, intermittent drug exposure, respectively (Kalivas et al., 1998; Robinson and Berridge, 1993). 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 factors involved in relapse to drug use (De Vries et al., 1998; Kalivas et al., 1993, 1998; Robinson and Berridge, 2001).

Cocaine binds to dopamine, serotonin and norepinephrine transporters preventing the reuptake of these monoamines from synaptic cleft (Andrews and Lucki, 2001; Ritz et al., 1990). A number of data indicate that the locomotor and sensitizing properties of cocaine have been associated with its stimulation of the mesolimbic dopaminergic pathway (Di Chiara, 1995; Filip and Siwanowicz, 2001; Neisewander et al., 1995), consisting of the dopamine cell bodies in the ventral tegmental area and their projections to the nucleus accumbens (e.g. Dahlstrőm and Fuxe, 1964). Despite the principal involvement of dopamine in the above behavioral responses of cocaine, recent findings indicate a significant modulatory actions of other neurotransmitter systems, including γ-aminobutyric acid (GABA) (Koob, 1998; Pierce and Kalivas, 1997).

In fact, GABA is present in the mesolimbic dopaminergic pathway (Kalivas et al., 1993; Pierce and Kalivas, 1997) and GABA-induced stimulation inhibits dopaminergic tone (Churchill

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et al., 1992; Gerasimov et al., 2000; Kalivas et al., 1990; Morgan and Dewey, 1998). Recent preclinical laboratory findings show also an inhibitory influence of GABA systems on biochemical and behavioral effects of cocaine. For example increasing extracellular GABA levels following an inhibitor of GABA transaminase, i.e. vigabatrin (γ-vinyl-GABA; GVG), suppresses the accumbal dopamine release stimulated by cocaine (Ashby et al., 1999; Dewey et al., 1998; Gerasimov et al., 2000; Kusher et al., 1997; Morgan and Dewey, 1998). It was also shown that vigabatrin reduced cocaine-induced conditioned place preference (Dewey et al., 1998), self-administration (Kusher et al., 1999; Strőmberg et al., 2001) and lowering of brain stimulation reward thresholds (Kusher et al., 1997) in rats.

On the other hand, cocaine addiction shifts the allosteric state of the GABA systems (Koob and Le Moal, 2001), this being reflected by a decrease in GABA levels in frontal lobe of cocaine-dependent subjects (Ke et al., 2004) and in the striatum of cocaine sensitized rats (Jung et al., 1999). Furthermore, chronic cocaine administration (by slow-releasing pellets) to rats decreases immunolabeling of GABA-ergic terminals in discrete brain regions (Meshul et al., 1998), while withdrawal state as well as the cocaine challenge dose in rats repeatedly treated with cocaine enhances GABA transmission in the nucleus accumbens (Xi et al., 2003) and the prefrontal cortex (Jayaram and Steketee, 2005).

In the present series of experiments we tested the hypothesis that enhancement of GABA-ergic transmission by drugs interfering with different steps within that neurotransmitter system may control sensitization to cocaine in male Wistar rats. We used three drugs that enhance GABA transmission by different mechanisms, but they do not have binding affinities, directly or indirectly, with GABA receptors: gabapentin, tiagabine and vigabatrin. Gabapentin is a cyclic analogue of GABA that either directly stimulates GABA release (Gotz et al., 1993) or indirectly increases GABA synthesis (Goldlust et al., 1995) and/or inhibits the alpha$_2$delta subunit-composed voltage-gated Ca^{2+} channels (Gee et al., 1996). Tiagabine is a selective type I GABA reuptake transporter inhibitor that results in an increase in the amount and dwell time of GABA in the synaptic cleft (Dhar et al., 1994). Vigabatrin is an irreversible inhibitor of GABA breakdown by GABA transaminase (Lippert et al., 1977; Palfreyman et al., 1981) as well as an effective inhibitor of the isoform 1 of GABA reuptake transporter (Eckstein-Ludwig et al., 1999; Leach et al., 1996). Gabapentin, tiagabine and vigabatrin were administered during the development or expression phases of sensitization in rats treated with cocaine for 5 days and then with a cocaine challenge dose following 5-daily withdrawal.

To extend the previous observations that vigabatrin blocks the development and expression of cocaine sensitization (Gardner et al., 2002), we also used this drug and tested it under our experimental protocol (above). The dose-range and pretreatment intervals of drugs were chosen on their functional in vivo activity to reach maximal values of basal extracellular GABA levels (Bohlen et al., 1979; Fink-Jensen et al., 1992; Jung et al., 1977; Kelly, 1998; Petroff and Rothman, 1998) or to reduce basal or stimulated dopamine levels in rats (Morgan and Dewey, 1998), or to attenuate some cocaine-induced behavioral responses in rodents (Gasior et al., 1999; Kusher et al., 1997, 1999; Strőmberg et al., 2001).

2. Materials and methods

2.1. Animals

Male Wistar rats (derived from licensed breeder, Warszawa, Poland) weighing 270–290 g were used. The rats were housed 8 per cage in standard plastic rodent cages (57 × 35 × 20 cm) in a colony room maintained at 21 ± 1 °C and at 50% humidity under a 12 h light–dark cycle (lights on at 6 a.m.) and had continuous access to tap water and rodent food. All experiments were approved by the Bioethics Commission as compliant with the Polish Law (of 21st August 1997) and carried out in accordance with the National Institutes of *Health Guide for the Care and Use of Laboratory Animals*.

2.2. Drugs

The following drugs were used: cocaine hydrochloride (Merck, Germany), gabapentin (Pfizer, USA), tiagabine (Gabitril®, Sanofi-Synthelabo, France) and vigabatrin (Sabril®, Marion Merrell Dow S.A., Bourgain-Jallien, France). Cocaine was diluted in saline, gabapentin was diluted in distilled water and tiagabine and vigabatrin were suspended in 0.5% Tween 80 (Sigma Aldrich, Steinheim, Germany). All the drugs were injected i.p. in a volume of 1 ml/kg. Gabapentin, tiagabine or vigabatrin were administered 60, 30 or 240 min before saline or cocaine.

2.3. Locomotor activity measurement

Locomotor activity was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, USA) linked online to a 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 as reported previously (Filip et al., 2004; Przegaliński et al., 2001). Interruptions of these photobeams resulted in horizontal activity defined as distance traveled (in cm). Rats were habituated in the experimental cages for two days (2 h/day) and for 1 h before testing; 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). Seven to eight animals per group were used.

2.4. Basal and cocaine-induced locomotor activation

Animals were tested only once, and separate groups of animals were pretreated with either the appropriate vehicle, gabapentin (1–30 mg/kg), tiagabine (2.5–10 mg/kg) or vigabatrin (75–250 mg/kg) before injection of either saline or cocaine (10 mg/kg). Measurements of locomotor activity began immediately after saline or cocaine injection.

2.5. Development of cocaine sensitization

During the first 5 days of experiment, the animals received the following injections: vehicle+saline, vehicle+cocaine (10 mg/kg), gabapentin (1–30 mg/kg)+cocaine (10 mg/kg),

tiagabine (2.5–10 mg/kg)+cocaine (10 mg/kg) or vigabatrin (75–250 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. Each rat underwent only one test session.

2.6. 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), gabapentin (1–30 mg/kg)+cocaine (10 mg/kg), tiagabine (2.5–10 mg/kg)+cocaine (10 mg/kg) or vigabatrin (75–250 mg/kg)+cocaine (10 mg/kg) and locomotor activity was recorded immediately after cocaine injection. Each rat underwent only one test session.

2.7. Statistical analyses

The data are expressed as mean total activity counts (±S.E.M.) 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.

3. Results

3.1. Basal locomotor activity

Following injection of either gabapentin (30 mg/kg, but not 1–10 mg/kg), tiagabine (10 mg/kg, but not 2.5–5 mg/kg), or vigabatrin (250 mg/kg, but not 75–150 mg/kg) significant decreases in rats' basal locomotor activity were observed (Table 1).

Table 1
Effects of gabapentin, tiagabine and vigabatrin on the basal locomotor activity in rats

Treatment	Horizontal distance traveled (cm)/60 min	ANOVA
Vehicle	404±116	
Gabapentin (1)	559±81	
Gabapentin (3)	572±108	
Gabapentin (10)	493±55	
Gabapentin (30)	197±81[a]	$F(4,30)=2.68$, $P<0.05$
Vehicle	422±99	
Tiagabine (2.5)	501±98	
Tiagabine (5)	391±37	
Tiagabine (10)	103±44[a]	$F(3,24)=4.07$, $P<0.05$
Vehicle	419±106	
Vigabatrin (75)	303±53	
Vigabatrin (150)	374±66	
Vigabatrin (250)	117±40[a]	$F(3,24)=3.25$, $P<0.05$

Doses are expressed in mg/kg. [a]$P<0.05$ vs vehicle (Dunnett's test).

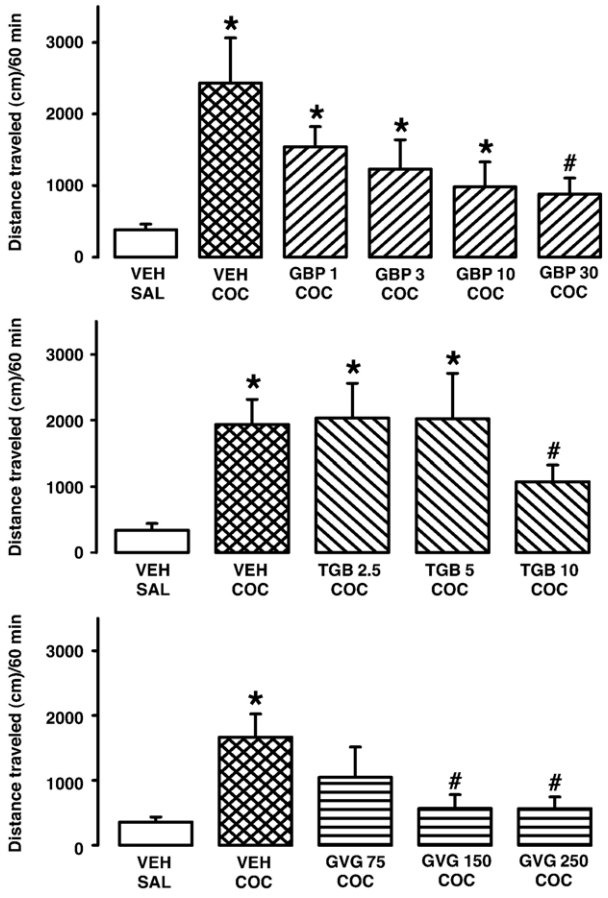

Fig. 1. Effects of gabapentin (GBP), tiagabine (TGB) and vigabatrin (GVG) on the cocaine (COC; 10 mg/kg)-stimulated locomotor activity. *$P<0.01$ vs corresponding vehicle (VEH)+saline (SAL) group; #$P<0.05$ vs corresponding vehicle+cocaine group (Dunnett's test).

3.2. Cocaine-induced hyperactivity

Cocaine (10 mg/kg) in combination with the respective vehicle significantly (at least two-fold) enhanced the total horizontal locomotor activity of rats as compared to the effect of vehicle+saline-treated animals (Fig. 1).

A significant group effect was detected by ANOVA for pretreatment with gabapentin ($F(5,38)=2.63$, $P<0.05$). Pretreatment with gabapentin (1–30 mg/kg) in a dose-dependent manner decreased the acute locomotor effect of cocaine. The significant effect was observed after 30 mg/kg of gabapentin (Fig. 1, upper).

A significant group effect was detected by ANOVA for pretreatment with tiagabine ($F(4,33)=3.14$, $P<0.05$). Pretreatment with tiagabine (2.5–10 mg/kg) attenuated the hyperactivation induced by acute cocaine; a significant decrease was observed following 10 mg/kg of tiagabine (Fig. 1, center).

A significant group effect was detected by ANOVA for pretreatment with vigabatrin ($F(4,30)=7.81$, $P<0.001$). Pretreatment with vigabatrin (150 or 250 mg/kg, but not 75 mg/kg) resulted in a significant reduction of locomotor hyperactivation induced by acute cocaine (Fig. 1, bottom).

3.3. Development of cocaine sensitization

Rats repeatedly (days 1–5) treated with cocaine (10 mg/kg) showed a 2–3.8-fold increase in the horizontal locomotor activity when challenged with cocaine (10 mg/kg) 5 days after the last treatment injection, as compared with 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 gabapentin ($F(5,38)=2.85$, $P<0.05$). The locomotor response to cocaine challenge was not altered by repeated treatment with gabapentin (1–30 mg/kg) given in combination with cocaine (days 1–5) (Fig. 2, upper).

A significant group effect was detected by ANOVA for pretreatment with tiagabine ($F(4,32)=3.25$, $P<0.05$). Repeated treatment with tiagabine (2.5–10 mg/kg) in combination with cocaine did not alter the locomotor response of cocaine challenge dose, as compared with the locomotor effect of cocaine challenge in vehicle and cocaine-treated animals (Fig. 2, center).

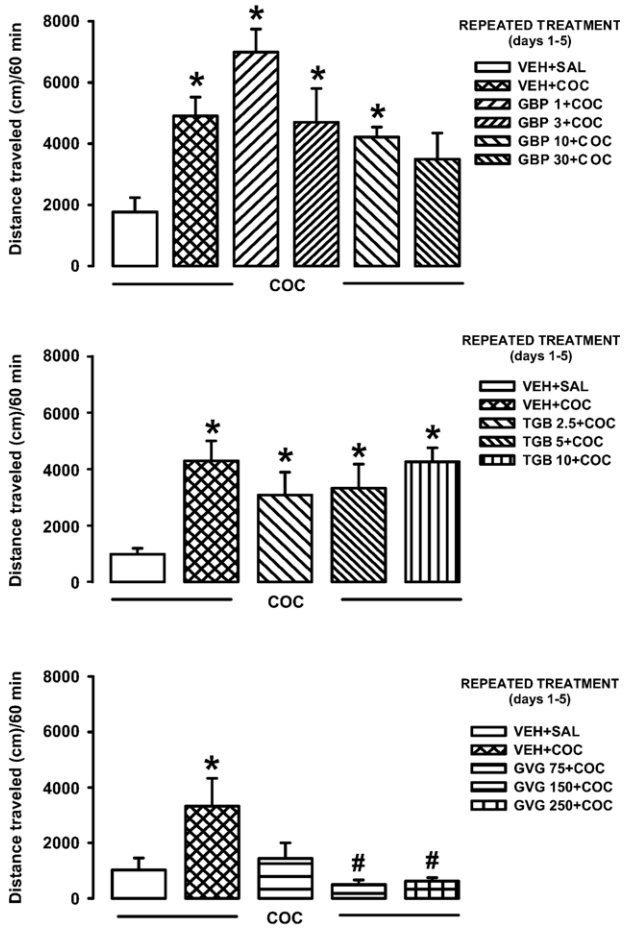

Fig. 2. Effects of gabapentin (GBP), tiagabine (TGB) and vigabatrin (GVG) on the development of cocaine (COC) sensitization. Rats were treated repeatedly (days 1–5) with either vehicle (VEH)+saline (SAL), vehicle+cocaine (10 mg/kg), gabapentin (1–30 mg/kg)+cocaine (10 mg/kg), tiagabine (2.5–10 mg/kg)+cocaine (10 mg/kg), or vigabatrin (75–250 mg/kg)+cocaine (10 mg/kg). On day 10, the animals were given a challenge dose of cocaine (10 mg/kg). *$P<0.01$ vs corresponding vehicle+saline-treated and cocaine-challenged group; #$P<0.01$ vs corresponding vehicle+cocaine-treated and cocaine-challenged group (Dunnett's test).

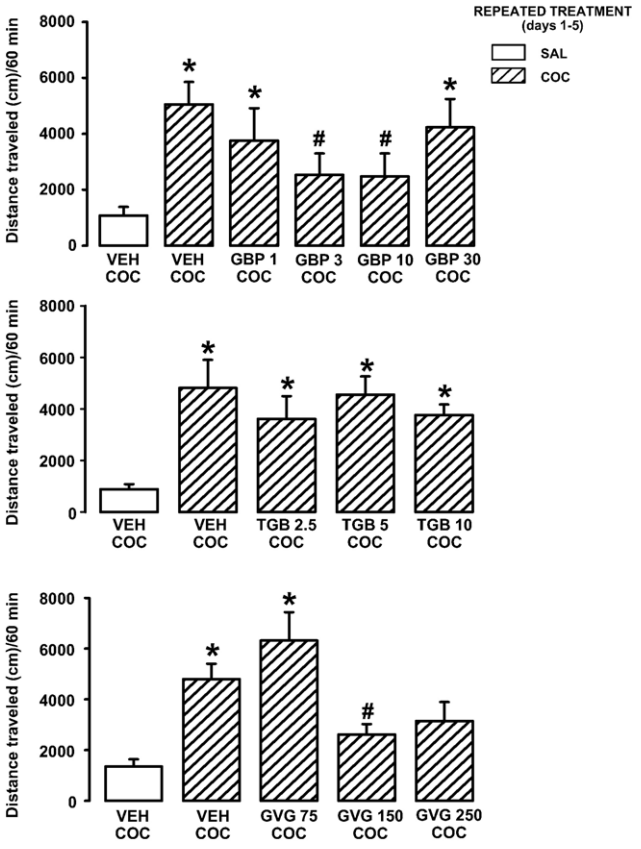

Fig. 3. Effects of gabapentin (GBP), tiagabine (TGB) and vigabatrin (GVG) on the expression of cocaine (COC) sensitization. Rats were treated repeatedly (days 1–5) with either saline (SAL) or cocaine (10 mg/kg). On day 10, the animals were challenged with either vehicle (VEH)+cocaine (10 mg/kg), gabapentin (1–30 mg/kg)+cocaine (10 mg/kg), tiagabine (2.5–10 mg/kg)+cocaine (10 mg/kg), or vigabatrin (75–250 mg/kg)+cocaine (10 mg/kg). *$P<0.01$ vs corresponding cocaine-treated and vehicle+cocaine-challenged group (Dunnett's test).

A significant group effect was detected by ANOVA for pretreatment with vigabatrin ($F(4,30)=4.22$, $P<0.01$). A substantial decrease in the locomotor response to cocaine challenge was observed in rats treated repeatedly with vigabatrin (75–250 mg/kg) in combination with cocaine (Fig. 2, bottom).

3.4. Expression of cocaine sensitization

Rats repeatedly (days 1–5) treated with vehicle or cocaine (10 mg/kg), on day 10 of the experiment were challenged with vehicle or with GABA-mimetic drugs followed by cocaine (10 mg/kg) (Fig. 3).

A significant group effect was detected by ANOVA for pretreatment with gabapentin ($F(5,39)=4.50$, $P<0.01$). A significant decrease in the locomotor response to a cocaine challenge was found in rats treated repeatedly with cocaine after pretreatment with gabapentin in doses of 3 or 10 mg/kg, while the decreases were nonsignificant at 1 or 30 mg/kg (Fig. 3, upper).

A significant group effect was detected by ANOVA for pretreatment with tiagabine ($F(4,33)=3.58$, $P<0.05$). A pretreatment with tiagabine (2.5–10 mg/kg) did not alter the effects of a

challenge dose of cocaine on the locomotor activity compared to the cocaine-treated and cocaine-challenged group (Fig. 3, center).

A significant group effect was detected by ANOVA for pretreatment with vigabatrin ($F(4,30)=8.94$, $P<0.001$). A pretreatment with vigabatrin (150 or 250 mg/kg) resulted in a decrease in the locomotor response to a challenge dose of cocaine in rats repeatedly treated with cocaine; the significant effect being observed after 150 mg/kg of vigabatrin (Fig. 3, bottom).

4. Discussion

In the present study we report that activation of brain GABA systems alters the effects of acute and repeated administration of cocaine. In fact, gabapentin, tiagabine or vigabatrin significantly decreased the cocaine-induced locomotor hyperactivation. However, those drugs differentially affected the sensitization to cocaine. Thus, vigabatrin significantly reduced the development and expression of cocaine sensitization with the most effective dose of 150 mg/kg. Gabapentin reduced only the expression of cocaine sensitization, showing a U-shaped relationship with locomotor responding to cocaine challenge dose. Tiagabine was inactive toward development or expression of cocaine sensitization.

The first finding of the present study indicates that augmentation of GABA-ergic neurotransmission by different mechanism potently decreases the cocaine-induced locomotor activity in rats. In fact, we report that the highest doses of gabapentin (30 mg/kg), tiagabine (10 mg/kg) or vigabatrin (250 mg/kg) decreased the cocaine-induced hyperactivation. However, based on our pharmacological analysis, it should be noted that only vigabatrin's (150 mg/kg) action on cocaine hyperactivation seems to be independent of its own sedating effects and can be considered as a specific response. Blockade of cocaine's acute locomotor effect by gabapentin or tiagabine might rather result from behavioral competition since the effective doses of those drugs alone reduced the basal locomotor activity. These results differ from the previous reports showing that gabapentin in doses of 10–100 mg/kg given to mice (Itzhak and Martin, 2000) did not alter the basal locomotor responses. Moreover, vigabatrin in a dose of 250 mg/kg decreased locomotor activity in rats (present study), while Dewey et al. (1998) reported no changes in locomotion following vigabatrin's dose-range of 75–300 mg/kg. The reasons for the discrepancies between our present and other authors' reports are not readily apparent, but may be due to differences in animal species (rats vs mice for experiments with gabapentin) or their habituation to the experimental cages (long-time vs short-time vs lack). The observation on vigabatrin-induced reduction of locomotor responses to acute cocaine extends results of Dewey et al. (1998), however, in contrast to our studies on gabapentin, it has been found that the drug produced no decrease in locomotor activity induced by cocaine, but reduced such an effect of methamphetamine in mice (Itzhak and Martin, 2000).

Our next outcome is that vigabatrin in doses of 150–250 mg/kg given jointly with cocaine during development of cocaine sensitization potently counteracted the locomotor effects of the challenge dose of cocaine after 5-day withdrawal, while the reduction of expression of cocaine sensitization was seen after acute injection of 150 mg/kg of vigabatrin. It should be added that the protection of either development or expression of cocaine sensitization by vigabatrin occurs independently of sensitization protocol, i.e. injection of cocaine every day (this study) or every other day (Gardner et al., 2002), or withdrawal period (present results and those of Gardner et al., 2002).

The notion that the enhancement of GABA levels might be attributed to cocaine sensitization is partly supported by results with gabapentin. In fact, this drug given acutely reduced the locomotor effect of the cocaine challenge dose, but only in a narrow dose–response window: the dose–response curve was U-shaped and the drug was effective only in the 3–10 mg/kg dose-range. The reason for this is presently unknown, but the results correspond well with the in vitro findings of Gotz et al. (1993) who reported that only the therapeutically relevant concentration of gabapentin enhances the release of [^{3}H]GABA from the slices of rat neostriatum, while at lower and higher concentrations the drug was ineffective.

When assessing the mechanism by which GABA-mimetic drugs affect acute or repeated cocaine treatments several points should be considered:

1) Acute cocaine induces parallel increases in locomotor activation and accumbal dopamine levels (Broderick et al., 2004), while sensitizing cocaine treatment increases both dopamine and excitatory amino acid transmission in the nucleus accumbens in rats (Pierce et al., 1996);
2) Cocaine-induced sensitization, but not acute exposure to cocaine, is associated with a transient increase of GABA transmission in the medial prefrontal cortex (Jayaram and Steketee, 2005), while an overall decrease in pre- and postsynaptical GABA transmission was found in the striatum (Jung et al., 1999).

The GABA-mimetic drugs used in the present study act to increase GABA synaptic levels, however, they interfere with different mechanisms within the GABA-ergic system (see Introduction). If the elevation in the extracellular level of GABA by all the investigated drugs might counteract the dopamine-mediated acute response to cocaine, as found previously at the biochemical and behavioral levels (Ashby et al., 1999; Dewey et al., 1998; Gerasimov et al., 2000; Kusher et al., 1997, 1999; Morgan and Dewey, 1998; Strőmberg et al., 2001), it is not clear whether the anticocaine's effects observed during sensitization paradigm resulted from increased GABA content. In fact, gabapentin also alleviates glutamate synthesis (Goldlust et al., 1995) as well as its neurotransmission (Fink et al., 2000; Maneuf and McKnight, 2001) through a potent competitive inhibition of brain cytosolic branched-chain aminotransferase (Sweatt et al., 2004) and/or reduction of Ca^{2+} influx into glutamatergic terminals mediated by the voltage-gated Ca^{2+} channels, composed with the alpha$_2$delta subunit (Gee et al., 1996) while vigabatrin (in a dose of 150 mg/kg) dampens the activity of the glutamine synthetase that leads to reduction in cortical glutamine and glutamate levels (Waniewski and Mertin, 1995). Consequently, it may be postulated that gabapentin and vigabatrin by increased GABA levels and/or by protection against

excessive glutamate neurotransmission seen during repeated cocaine treatment (Pierce et al., 1996) reduced expression of cocaine sensitization (present study). This hypothesis is supported by the finding that behavioral sensitization to cocaine is associated with increased alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamatergic receptor expression in the nucleus accumbens (Boudreau and Wolf, 2005). And that this expression of sensitization is blocked by an intra-accumbal administration of AMPA glutamatergic receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (Pierce et al., 1996).

We have also demonstrated that vigabatrin, but not gabapentin or tiagabine, inhibits the development of sensitization to cocaine. Vigabatrin differs from the remaining drugs used in this study in evoking increases in basal presynaptical GABA level (Jung et al., 1977; Loscher et al., 1989), apart from increases in the basal level of extracellular GABA (Abdul-Ghani et al., 1981; Neal et al., 1989). It is not clear whether the anticocaine's effects of vigabatrin result from increased GABA content from presynaptical pool or extracellular pool, or both. The different activity of gabapentin may be related to the fact that the development of cocaine sensitization is linked with the psychostimulant-induced functional disturbances of glutamic acid decarboxylase mRNA level (Sorg et al., 1995), the enzyme being one of the important targets of gabapentin's action (Goldlust et al., 1995). Pharmacological manipulation of glutamic acid decarboxylase activity by repeated cocaine might lead to reduction of the cytoplasmic GABA concentration in presynaptic terminals, the mechanism that influences also vesicular GABA release (Golan and Grossman, 1996; Hensch et al., 1998; Tian et al., 1999).

The ineffectiveness of tiagabine in both phases of cocaine sensitization – even in its dose that produced marked decreases in basal locomotor activity and decreased cocaine's acute effect – is difficult to interpret. Since there is no data on the influence of tiagabine on the excitatory neurotransmission it may be speculated that this lack limited the drug's protective responses in the sensitization model in the present study.

Partly supporting our preclinical data on repeated cocaine administration in the sensitization model, the elevation of GABA level by gabapentin or tiagabine seems to be ineffective to decrease cocaine choice (Hart et al., 2004) or to prevent continued cocaine use by blocking its acute, abuse-related effects (Lile et al., 2004). On the other hand, both tiagabine and vigabatrin prolonged abstinence from cocaine measured as cocaine-free urines in cocaine-dependent patients (Brodie et al., 2005; Gonzalez et al., 2003; Winhusen et al., 2005) while the findings for gabapentin were not univocal (Berger et al., 2005, Bisaga et al., 2006; Raby and Coomaraswamy, 2004).

In light of indirect GABA stimulation that reduced cocaine's sensitizing effects (present study), the recent findings indicate a significance of GABA interventions directly at postsynaptic targets (i.e. $GABA_A$ and $GABA_B$ receptors) in modulating the abuse-related effects of cocaine. In fact, several GABA drugs including $GABA_A$ and $GABA_B$ receptor direct agonists (e.g. Barrett et al., 2005; Di Ciano and Everitt, 2003; Frankowska et al., 2004; Roberts et al., 1996) as well as allosteric modulators amplifying the action of the endogenous GABA neurotransmission (Barrett et al., 2005; Goeders et al., 1989, 1993; Smith et al., 2004) decreased cocaine self-administration, however, the decreases evoked only by the modulators were selective in comparison with food-maintained responding (Barrett et al., 2005). Similarly, the high efficacy $GABA_A$ modulators (Barrett et al., 2005; Negus et al., 2000) or a positive allosteric $GABA_B$ modulator (Go3da et al., 2005) attenuated the expression of cocaine subjective effects in drug discrimination paradigm, while direct $GABA_A$ and $GABA_B$ receptor agonists were inactive in this respect (Barrett et al., 2005; Munzar et al., 2000; Negus et al., 2000; but see also Gołda et al., 2005).

Summing up, we show that enhanced GABA-ergic neurotransmission exerted inhibitory actions on acute responses to cocaine, but only in the case of vigabatrin the inhibition seems to be specific. The present finding that vigabatrin protects against the development and the expression of cocaine sensitization in rats further supports its therapeutic potential in the treatment of cocaine dependence. These observations lead to revisiting the proposition about drugs indirectly targeting brain GABA-ergic systems as potentially effective pharmacological treatments for relapse reinstated by acute exposure to cocaine.

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