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γ-Aminobutyric acid mimetic drugs differentially inhibit the dopaminergic response to cocaine

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Abstract

Dopaminergic activity in the mesocorticolimbic system is associated with reinforcing properties of psychostimulant drugs. We previously demonstrated that increased γ-aminobutyric acid (GABA)-ergic activity produced by γ-vinyl GABA [D,L-4-amino-hex-5-enoic acid (Vigabatrin®)], an irreversible inhibitor of GABA-transaminase, attenuated cocaine, nicotine, heroin, alcohol, and methamphetamine-induced increases in extracellular nucleus accumbens dopamine as well as behaviors associated with these biochemical changes. In the present study, using in vivo microdialysis techniques, we compared three different strategies to increase GABAergic activity in order to modulate cocaine-induced increase in extracellular dopamine. Our data demonstrate that the anticonvulsant 1-(2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride (NNC-711), a GABA uptake inhibitor, dose and time dependently diminished increases in extracellular dopamine following acute cocaine challenge. Furthermore, we demonstrated that cyclized analogue of vigabatrin, a competitive reversible GABA-transaminase inhibitor, is a more potent inhibitor of cocaine-induced dopamine increase than vigabatrin. Our data suggest that in addition to irreversible inhibition of GABA transaminase, inhibition of GABA uptake represent another potentially effective, indirect strategy for the treatment of cocaine abuse.

Keywords: γ-Aminobutyric acid (GABA); Dopamine; Microdialysis; Cocaine; γ-Vinyl GABA (vigabatrin); γ-Aminobutyric acid (GABA) reuptake inhibitor

1. Introduction

Psychostimulants (cocaine, methylphenidate, and amphetamine) increase synaptic dopamine concentrations in the mesocorticolimbic system, a response thought to be involved in the rewarding and reinforcing characteristics of these potentially addictive drugs (Dewey et al., 1998; Gerrits and Van Ree, 1996; Pettit and Justice, 1991). Specifically, the reinforcing properties of cocaine are linked to its ability to bind to the dopamine transporter and prevent dopamine reuptake into the presynaptic terminal (Kuhar et al., 1991; Morgan et al., 1997). This increase in synaptic dopamine concentration is dependent on the rate and the amount of dopamine released from the intraneuronal stores. The firing rate of dopaminergic ventral tegmental and nucleus accumbens neurons is under inhibitory control by γ-aminobutyric acid (GABA)-releasing neurons (Kalivas et al., 1990). Indeed, several studies have demonstrated that pharmacologic potentiation of the GABA system has a significant effect on subcortical dopamine release (Dewey et al., 1992, 1997; Finlay et al., 1992; Gong et al., 1998) and dopamine cell firing (Engberg et al., 1993; Kalivas et al., 1990). Thus, it is likely that this inhibitory control can be directed at attenuating the rewarding and reinforcing actions of cocaine.

Downstream inhibition of dopaminergic activity can be potentiated by several pharmacologic manipulations of the GABAergic system. After being released into the synaptic cleft, where it activates specific receptors, GABA is then reabsorbed into synaptic nerve terminals and glia cells where it is catabolized by the enzyme GABA-transaminase

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(Sabers and Gram, 1992). Of the three types of GABA receptors ($GABA_A$, $GABA_B$, and $GABA_C$), only action at $GABA_A$ and $GABA_B$ sites has been shown to exert inhibitory control over dopamine release and cell firing. Benzodiazepines, positive allosteric modulators of GABA activity at $GABA_A$ receptors, significantly attenuate both the dopaminergic and behavioral response to a cocaine challenge (Dewey et al., 1997; Giorgetti et al., 1998; Meririnne et al., 1999). Similarly, GABA mimetic drugs such as baclofen, which through $GABA_B$ receptor activation diminish dopaminergic activity in the mesolimbic region (Gong et al., 1998; Xi and Stein, 1998) also decrease the behavioral response to cocaine (Campbell et al., 1999; Roberts et al., 1996).

Indirect manipulation of GABAergic activity can be achieved through GABA transaminase inhibition using γ-vinyl GABA [D,L-4-amino-hex-5-enoic acid (Vigabatrin)], a highly specific irreversible inhibitor of the enzyme responsible for GABA catabolism. Vigabatrin has also demonstrated inhibitory control over mesocorticolimbic dopamine activity (Dewey et al., 1997, 1998; Morgan and Dewey, 1998) and the behavioral response to cocaine (Kushner et al., 1999). Finally, it is possible to increase synaptic GABA concentrations by inhibiting the presynaptic reuptake into neuronal and glial cells (i.e., via nipecotic acid and guvacine derivatives) (Fink-Jensen et al., 1992; Krogsgaard-Larsen and Johnston, 1975; Suzdak, 1993), much the same way cocaine blocks dopamine reuptake, although the effects of this modulation on psychostimulant-induced dopaminergic activity have yet to be reported. It is evident that increased GABAergic activity consistently produces a diminished dopaminergic response to psychostimulant challenge. However, the extent of this influence relative to the mechanism of action and temporal course, has not been fully characterized. In the present study, we explore the modulation of cocaine-induced increases in extracellular dopamine by the pharmacologic manipulation of biochemically and functionally distinct components of the GABAergic system: the reuptake site and the enzyme responsible for GABA catabolism.

In this study, we use in vivo microdialysis techniques in freely moving animals and several strategies to indirectly increase GABAergic activity in an effort to modulate cocaine-induced extracellular dopamine increases in the mesocorticolimbic system. To increase synaptic GABA by reuptake inhibition, we used 1-(2-(((diphenylmethylene)amino)oxy)ethyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride (NNC-711), a highly selective GABA reuptake inhibitor (Suzdak et al., 1992). To increase GABA concentrations by inhibition of GABA transaminase, we used vigabatrin, an irreversible enzyme inhibitor with a demonstrated prolonged effect on whole brain GABA levels (Jung et al., 1977) as well as a cyclized analog of vigabatrin, (1*R*,4*S*)-4-amino-cyclopent-2-enecarboxylic acid (1*R*,4*S*-ACC), which competitively inhibits GABAtransaminase in vitro (Qui et al., 2000).

2. Materials and methods

2.1. Animal housing and surgery

Male Sprague–Dawley rats were used in all experiments (200–300 g, Taconic Farms, Germantown, NY) and were given food and water ad libitum. Temperature and humidity were kept relatively constant. Each animal was housed individually on a 12/12 h light/dark cycle. All animals were used under an IACUC-approved protocol with strict adherence to NIH guidelines.

Animals were anesthetized with a ketamine/xylazine mixture and siliconized guide cannulae were stereotaxically implanted into the right nucleus accumbens (1.5 mm anterior and 1.0 mm lateral to bregma, and 5.6 mm ventral to the cortical surface) at least 3 days prior to study. These coordinates were calculated according to the Paxinos and Watson atlas for the rat brain (2nd edn., 1986).

2.2. Microdialysis experiments

Microdialysis probes (2.0 mm, Bioanalytical Systems, BAS, West Lafayette, IN) were positioned within the guide cannulae and artificial cerebrospinal fluid (aCSF: 155 mmol NA^+, 1.1 mmol Ca^{2+}, 2.9 mmol K^+, 132.76 mmol Cl^-, and 0.83 mmol Mg^{2+}) was perfused through the probe using a microinfusion pump (BAS) at a flow rate of 2.0 μl/min. Samples were collected for 20 min and injected on-line. On the day of study, a minimum of three samples were collected that varied by less than 10% which served to establish baseline neurotransmitter activity prior to administration of the drug.

The high-pressure liquid chromatography (HPLC) system consists of a BAS reverse-phase column (3.0 μ C-18), a BAS LC-4C electrochemical transducer with a dual glassy carbon electrode set at 650 mV, a computer that analyzes data on-line using a commercial software package (Chromgraph, BAS, Lafayette, IN), and a dual pen chart recorder. The mobile phase (flow rate 1.0 ml/min) consisted of 7.0% methanol, 50 mmol sodium phosphate monobasic, 1.0 mmol sodium octyl sulfate, and 0.1 mmol EDTA, pH 4.0. Appropriate standards indicated dopamine elution occurred at 15 min.

After all experiments, animals were euthanized with an overdose of chloral hydrate and brains dissected to verify probe placement.

2.3. Pharmacologic challenge regimens

All drugs were administered by intraperitoneal (i.p.) injection. In the control study, naive rats were pretreated with vehicle (saline, 0.5 ml) 0.5 h prior to a challenge with cocaine hydrochloride (20 mg/kg, Sigma Chemical, St. Louis, MO). In a separate group of experiments, animals were pretreated with one of the drugs tested according to the schedule described for each treatment (see Table 1).

All of the drugs were dissolved in saline. Each experiment included administration of one GABAergic compound followed by a cocaine challenge (Fig. 1). There were 15 groups for the entire experiment, five to seven animals in each group.

NNC-711 (RBI, Natick, MA) was administered 0.5 h (10 and 20 mg/kg, Groups 2 and 3) and 2.5 h (20 mg/kg, Group 4) prior to cocaine challenge.

Vigabatrin (Hoechst Marion Roussel, Kansas City, MO) was administered 0.5 and 2.5 h prior to cocaine challenge. Doses administered were 150 mg/kg (Groups 5 and 7) and 300 mg/kg (Groups 6 and 8).

1*R*,4*S*-ACC (ChiroTech Technology, Cambridge, UK) was administered 0.5 and 2.5 h prior to cocaine challenge. Doses administered were 75 (Groups 9 and 12), 150 (Groups 10 and 13), and 300 (Groups 11 and 14).

(1*S*,4*R*)-4-amino-cyclopent-2-ene-carboxylic acid (1*S*,4*R*-ACC) (ChiroTech Technology) was administered at 2.5 h (300 mg/kg) prior to cocaine challenge (Group 15).

2.4. Data analysis

The average dopamine concentration of three stable samples collected prior to any drug administration was defined as control and all subsequent treatment values were presented as a percentage of the control. A minimum of three samples obtained prior to any pretreatment or challenge administration provided basal dopamine values from which percentage change could be calculated. This way, possible prelowering effects due to increased GABAergic transmission do not factor into the percentage change. Each group was compared with a control group receiving cocaine alone through univariate analysis of changes in the outcome measure, in this case, percentage change in dopamine concentrations from basal levels represented in each group by the peak effects. All univariate analyses included a post hoc Student's Newman–Keuls test. Two-way analysis of variance (ANOVA) assessed differences between treatment groups. All values are expressed as mean percentage change ± S.E.M.

Table 1
Animal groups and pretreatment regimen

Group	Drug	Dose (mg/kg)	Pretreatment interval (h)
1	Cocaine alone	20	
2	NCC-711	10	0.5
3	NCC-711	20	0.5
4	NCC-711	20	2.5
5	GVG	150	0.5
6	GVG	300	0.5
7	GVG	150	2.5
8	GVG	300	2.5
9	1*R*,4*S*-ACC	75	0.5
10	1*R*,4*S*-ACC	150	0.5
11	1*R*,4*S*-ACC	300	0.5
12	1*R*,4*S*-ACC	75	2.5
13	1*R*,4*S*-ACC	150	2.5
14	1*R*,4*S*-ACC	300	2.5
15	1*S*,4*R*-ACC	300	2.5

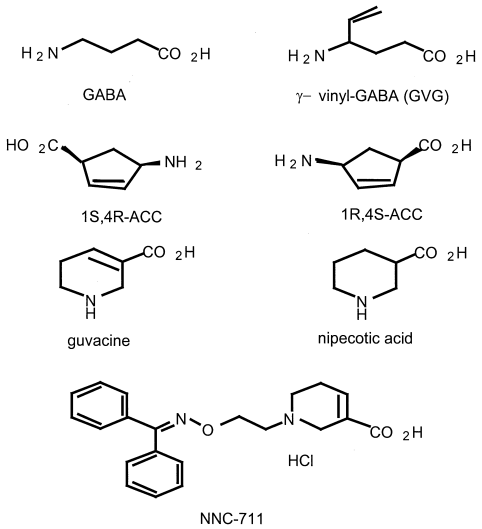

Fig. 1. Chemical structures of GABAergic compounds.

3. Results

3.1. Saline control

In vehicle pretreated animals cocaine increased extracellular dopamine 452% above baseline within 40 min with an estimated error of 10 min. In other studies with 20 min sampling, it has been shown that this increase occurs after the first injection, in the initial 20 min of the study (Segal and Kuczenski, 1992). Additionally, Parsons et al. demonstrated this increase to be at 45 min with 15 min sampling times (Parsons and Justice, 1993). When sampled every 10 min, Pettit et al. (1990) demonstrated a peak effect 30 min post cocaine administration (30 mg/kg). Our values returned to baseline approximately 200 min following challenge.

3.2. Dose–response for drug administration 30 min prior to cocaine

NNC-711 (20 mg/kg or 70 μmol/kg) decreased the cocaine-induced elevation of extracellular dopamine release by 69% (see Fig. 2) ($t = -6.43$, df = 8, $P < 0.001$). A dose of 10 mg/kg inhibited cocaine induced dopamine response by 55% ($t = -4.28$; df = 6; $P < 0.01$, data not shown).

Vigabatrin at 300 mg/kg (2.32 mmol/kg) reduced the dopaminergic response to cocaine by 39% (see Fig. 3) ($t = -2.59$, df = 9, $P < 0.05$). At a dose of 150 mg/kg (1.15 mmol), the response to cocaine after vigabatrin

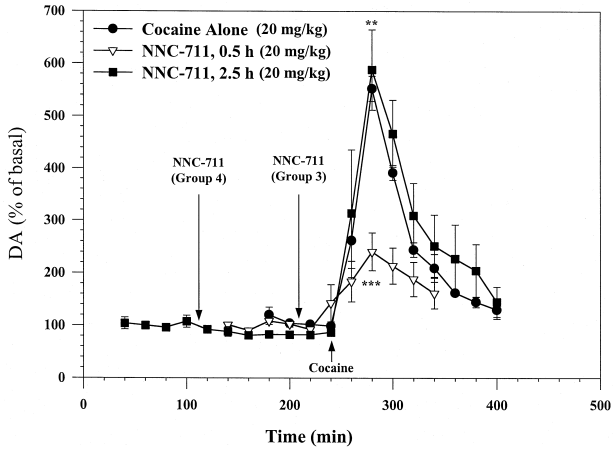

Fig. 2. Time activity of NNC-711 pretreatment on cocaine-induced nucleus accumbens dopamine release in freely moving animals. *** Peak values are significantly different from those obtained from animals that received cocaine alone ($P < 0.001$, ANOVA and Student Newman–Keuls post-hoc comparison) ** Peak values of NNC-711 0.5 h pretreatment and 2.5 h pretreatment are significantly different ($P < 0.01$, ANOVA and Student Newman–Keuls post-hoc comparison).

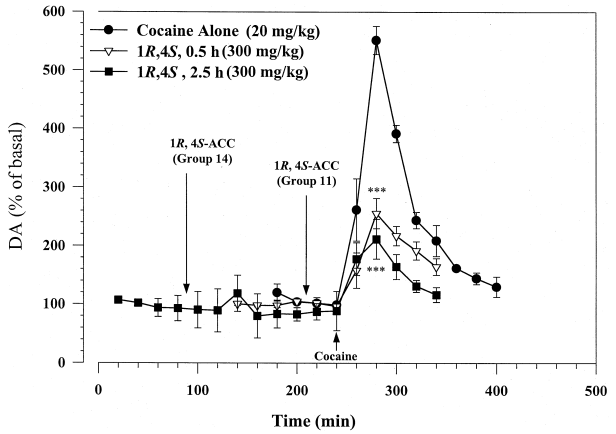

Fig. 4. Time activity of 1*R*,4*S*-ACC pretreatment on cocaine-induced nucleus accumbens dopamine release in freely moving animals. *** Peak values are significantly different from those obtained from animals that received cocaine alone ($P < 0.001$, ANOVA and Student Newman–Keuls post-hoc comparison). There is no significant effect of pretreatment interval on dopamine response to cocaine challenge after (1*R*,4*S*) pretreatment.

administration was not significantly different from vehicle pretreated controls (data not shown).

1*R*,4*S*-ACC was administered at 75 (0.57 mmol), 150 (1.15 mmol), and 300 mg/kg (2.32 mmol) (see Fig. 4) and inhibited the cocaine-induced dopamine response by 29%, 39%, and 65% ($t = -8.43$, df = 6; $P < 0.001$), respectively. Data is not shown for doses of 75 and 150 mg/kg.

3.3. Dose–response for drug administration 2.5 h prior to cocaine

NNC-711, at the highest dose tested (20 mg/kg), had no significant effect on cocaine's ability to elevate extracellular nucleus accumbens dopamine and demonstrated a significantly different response than the same dose administered at 0.5 h (see Fig. 2).

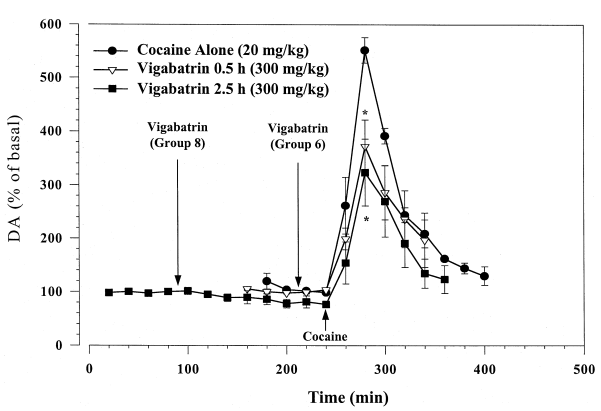

Fig. 3. Time activity of vigabatrin pretreatment on cocaine-induced nucleus accumbens dopamine release in freely moving animals. * Peak values are significantly different from those obtained from animals that received cocaine alone ($P < 0.05$, ANOVA and Student Newman–Keuls post hoc comparison). There is no significant effect of pretreatment interval on dopamine response to cocaine challenge after vigabatrin pretreatment.

Vigabatrin, at 300 mg/kg (2.32 mmol), attenuated cocaine induced dopamine release by 38% (see Fig. 3) ($t = 2.84$, df = 8, $P = 0.02$). At 150 mg/kg (1.15 mmol), vigabatrin had no significant effect on the dopaminergic response to cocaine (data not shown).

1*R*,4*S*-ACC, at 150 and 300 mg/kg (1.15 and 2.32 mmol), inhibited extracellular dopamine levels by 67% ($t = 4.27$, df = 6, $P < 0.01$, data not shown) and 75%, respectively ($t = 7.99$, df = 8, $P = 0.00044$), (see Fig. 4). At 75 mg/kg (0.57 mmol), there is no evident inhibition of the dopaminergic response to cocaine (data not shown).

The 1*S*,4*R* enantiomer of the cyclized vigabatrin analogue, tested at 300 mg/kg (2.32 mmol), had no effect on cocaine-induced increases in extracellular nucleus accumbens dopamine (data not shown).

4. Discussion

In the present study, we demonstrate the differential modulation of cocaine-induced dopamine increase by three compounds, each potentiating GABAergic transmission through a different, indirect, mechanism. The advantages of indirect manipulation of neurotransmitter activity through reuptake inhibition or enzymatic catabolism rely on the enhancement of existing endogenous reserves of GABA. Therefore, the physiologic action of GABA is retained without altering the GABA receptor complex itself. This is in marked contrast to direct selective stimulation of GABA receptors by GABA mimetic compounds

such as baclofen, progabide, or diazepam (Scatton et al., 1982), which interrupt natural compensatory processes and increase the risk of tolerance and abuse liability. Giorgetti et al. demonstrated that imidazenil, a partial positive allosteric modulator at $GABA_A$ receptors, reduces cocaine self-administration in rats without evidence of tolerance liability (Giorgetti et al., unpublished data). The authors attribute the absence of tolerance to incomplete activation of $GABA_A$ receptors. They propose that the system compensates by means of two interacting mechanisms, one involving endogenous activity and the other influenced by the GABAmimetic drug itself (Costa and Guidotti, 1996; Giorgetti et al., 1998). In a direct comparison of the two mechanisms, Takada and Yanagita assessed the dependence potential of vigabatrin in rhesus monkeys and rats and found that while the physical dependence potential of diazepam was clearly demonstrated, such potential was not shown for vigabatrin (Dam, 1989; Dewey et al., 1998; Takada and Yanagita, 1997).

In vivo investigations of GABA reuptake inhibitors have been impeded by the inability of first-generation GABA transport inhibitors like nipecotic acid and guvacine to cross the blood–brain barrier. The introduction of a lipophilic side chain on the amino acid nitrogen atom of nipecotic acid or guvacine has allowed newer GABA reuptake inhibitors like tiagabine (NO 328, a derivative of nipecotic acid) and NNC-711 (a derivative of guvacine) to be transported into the brain (Suzdak, 1993). This structural change also results in a 20- to 30-fold increase in potency, when tiagabine and NNC-711 are compared with their non-lipophilic parent compounds in vitro (Braestrup et al., 1990; Nielsen et al., 1991; Suzdak, 1993).

Prior studies showed that the systemic administration (11.5 and 21.0 mg/kg) of NO-328 (tiagabine), a selective GABA reuptake inhibitor similar to NNC-711, increased extracellular GABA levels to peak values of 210–310% 0.5 h following administration in the corpus striatum of awake, freely moving Sprague–Dawley rats. However, GABA levels returned to baseline 1–1.5 h following administration (Fink-Jensen et al., 1992). Furthermore, Braestrup et al. (1990) demonstrated that binding of tiagabine to the reuptake carrier is fully reversible, with maximal binding at 40 min. Here we have demonstrated that NNC-711, a potent GABA reuptake inhibitor with high selectivity for the human GABA transporter-1 (Borden et al., 1994), diminishes the dopaminergic response to cocaine when administered at 0.5, but not at 2.5 h prior to challenge.

These findings support our hypothesis that the potentiated GABAergic activity produced by reuptake inhibition effectively attenuates cocaine-induced increases in nucleus accumbens dopamine. To our knowledge, this is the first study demonstrating that reuptake inhibition attenuates mesolimbic dopamine increases produced by psychostimulant drugs. The discrepancy between the short lasting effect of GABA uptake inhibitors observed in rats and superior efficacy of tiagabine demonstrated in trials with patients suffering from partial seizures (Kälviäinen, 1998) has been attributed to differences between species. Specifically, tiagabine and NCC-711 have a 1000-fold higher affinity for human GABA transporter-1 than for rat transporter (Borden et al., 1994). The dissimilar properties of reuptake inhibitors in humans target these anticonvulsants as a potential treatment for substance abuse.

Vigabatrin effectively raises whole brain GABA levels in humans and in rodents (Jung et al., 1977; Petroff et al., 1996) through inhibition of the enzyme responsible for its catabolism. We previously reported that systemic administration of vigabatrin attenuates or completely abolishes the biochemical effects of cocaine, nicotine, methamphetamine, heroin, or ethanol on nucleus accumbens dopamine in rodents (Dewey et al., 1999; Gerasimov et al., 1999; Morgan and Dewey, 1998). In sharp contrast to the substantial but short lasting increase in synaptic GABA levels elicited by NNC-711, the GABA enhancing effect of vigabatrin is maintained for at least 24 h, followed by a slow decline over time (Jung et al., 1977; Petroff et al., 1996). This significantly prolonged effect of vigabatrin is attributed to the irreversible nature of GABA transaminase inhibition, which requires de novo synthesis of the enzyme to surmount the effects of the drug.

In this investigation, we explored the effects of the competitive, reversible inhibition of GABA transaminase on cocaine-induced dopamine release. 1*R*,4*S*-ACC is a compound containing a GABA backbone with conformation restricted by a cyclopentene ring with β,γ unsaturation, therefore representing the cyclized analogue of vigabatrin. This compound competitively inhibits GABA transaminase in vitro (Qui et al., 2000). Our results indicate that the conformationally restricted 1*R*,4*S*-ACC form of vigabatrin not only penetrates the blood brain barrier quickly, but has a lasting effect on mesolimbic dopamine activity. 1*R*,4*S*-ACC inhibited cocaine-induced increases in extracellular nucleus accumbens dopamine by approximately 75% at the highest dose tested (300 mg/kg, 2.32 mmol) following either 0.5 or 2.5 h pretreatment (see Fig. 4). The degree of inhibition is also noteworthy, considering that acute administration of vigabatrin (300 mg/kg, 2.32 mmol) produces only 38% inhibition of the cocaine-induced effects.

Additionally, we observed stereospecificity of this effect, as the other enantiomer tested (1*S*,4*R*) had no effect on cocaine-induced increases in nucleus accumbens dopamine, a finding consistent with the lack of affinity of this enantiomer for GABA transaminase, demonstrated in vitro (Qui et al., 2000).

Data presented here indicate that, at the highest dose tested, the temporal course of the attenuation of cocaine-induced dopamine release is similar for both vigabatrin and 1*R*,4*S*-ACC. Both compounds effectively inhibit the dopaminergic response to cocaine after 0.5 or 2.5 h pretreatment intervals. It has been proposed that the early

onset of increased GABAergic activity after pretreatment with vigabatrin is due to the reported ability of vigabatrin to also inhibit GABA reuptake (Christensen et al., 1991; Jolkkonen et al., 1992). Since both the parent compound (vigabatrin) and 1*R*,4*S*-ACC are recognized as substrates by the same enzyme, it is possible that the efficacy of 1*R*,4*S*-ACC at 30 min could be due to the inhibition of GABA uptake, similar to what has been suggested about the mechanism of action of vigabatrin.

In summary, the potent and selective GABA reuptake inhibitor NNC-711 effectively attenuated cocaine-induced increases in nucleus accumbens dopamine. While this mechanism demonstrated limited temporal effects, it has been implied that the time course of reuptake inhibition is species-specific. Additionally, the new conformationally restricted analogue of vigabatrin more effectively inhibited the dopaminergic response to cocaine than the parent compound, although within our experimental period, the time dependent effects appear similar. Behavioral tests including conditioned place preference (CPP) and self-administration of cocaine seem to be warranted. Combined with our previous results (Dewey et al., 1998), the present data further support the strategy of indirectly targeting the GABA system for the treatment of substance abuse.

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