Effects of gabapentin on cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced nucleus accumbens dopamine in rats[☆]

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Abstract

Gabapentin is a γ-aminobutyric acid (GABA) analogue, with GABAmimetic pharmacological properties. Gabapentin is used for the treatment of seizures, anxiety and neuropathic pain. It has been proposed that gabapentin may be useful in the treatment of cocaine dependence. However, clinical trials with gabapentin have shown conflicting results, while preclinical studies are sparse. In the present study, we investigated the effects of gabapentin on intravenous cocaine self-administration and cocaine-triggered reinstatement of drug-seeking behavior, as well as on cocaine-enhanced dopamine (DA) in the nucleus accumbens (NAc). We found that gabapentin (25–200 mg/kg, i.p., 30 min or 2 h prior to cocaine) failed to inhibit intravenous cocaine (0.5 mg/kg/infusion) self-administration under a fixed-ratio reinforcement schedule or cocaine-triggered reinstatement of cocaine-seeking behavior. *In vivo* microdialysis showed that the same doses of gabapentin produced a modest increase ($\sim$50%, $p < 0.05$) in extracellular NAc GABA levels, but failed to alter either basal or cocaine-enhanced NAc DA. These data suggest that gabapentin is a weak GABA-mimic drug. At the doses tested, it has no effect in the addiction-related animal behavioral models here tested. This

is in striking contrast to positive findings in the same animal models shown by another GABAmimetic – γ-vinyl GABA (see companion piece to present article).

Keywords

Gabapentin; Cocaine; Dopamine; GABA; Self-administration; Relapse

1. Introduction

Cocaine addiction is a serious health problem, yet there are no effective medications for its treatment. The rewarding effects of cocaine have been thought to be mediated primarily by inhibition of dopamine (DA) re-uptake in the mesolimbic dopamine system, which originates from the ventral tegmental area (VTA) in the midbrain and projects to the nucleus accumbens (NAc) and other forebrain regions (Wise, 1996; Gardner, 2000). Given this, most current pharmacotherapeutic strategies for the treatment of cocaine addiction have focused on this DA system by either mimicking cocaine's inhibition of DA re-uptake (as a substitution type therapy) or by blocking DA transmission with various DA receptor antagonists (as a blocker type therapy to inhibit the enhanced DA produced by cocaine). However, these interventions have proven ineffective in many clinical trials to date (Nann-Vernotica et al., 2001; Haney et al., 2001; Grabowski et al., 2000; Gorelick et al., 2004).

In addition to modulating DA, cocaine also produces an inhibitory effect on GABAergic neurons in the VTA and NAc (Cameron and Williams, 1994; Henry and White, 1995; Kiyatkin and Rebec, 2000), which has been thought to play an important role in cocaine reward and relapse (Carlezon and Wise, 1996). Thus, it has been proposed that pharmacological elevation of brain GABA levels or augmentation of GABAergic neurotransmission would directly counteract cocaine's actions on GABAergic transmission, and thus on cocaine reward and relapse (Roberts et al., 1996; Dewey et al., 1997; Giorgetti et al., 1998). Several lines of evidence support this hypothesis. First, potentiation of $GABA_A$ receptor activity inhibits cocaine-induced seizures (Gasior et al., 1999) and cocaine-enhanced extracellular NAc DA (Giorgetti et al., 1998). Also, $GABA_B$ receptor agonists inhibit both cocaine self-administration (Roberts et al., 1996; Roberts, 2005) and cocaine-triggered reinstatement of drug-seeking behavior (Campbell et al., 1999; Di Ciano and Everitt, 2003). Second, elevation of extracellular GABA levels by inhibition of GABA degradation by γ-vinyl GABA (GVG) inhibits the rewarding effects of cocaine as assessed by intravenous self-administration, conditioned place preference and electrical brain stimulation reward (Kushner, 1997; Kushner et al., 1999; Dewey et al., 1998). GVG has also been reported to inhibit cocaine-enhanced NAc DA levels (Dewey et al., 1998; Schiffer et al., 2003). Furthermore, clinical trials with the $GABA_A$ receptor modulator topiramate, the $GABA_B$ receptor agonist baclofen, or the GABA enhancers GVG or tiagabine (a GABA-uptake inhibitor) have shown significant decreases in self-reported cocaine craving and urine-confirmed cocaine use (Kampman et al., 2004; Shoptaw et al., 2003; Johnson, 2005; Brodie et al., 2003; González et al., 2003).

Gabapentin is another GABAergic modulator which facilitates GABAergic neurotransmission, possibly by increasing the synthesis and nonvesicular release of GABA as well as by preventing GABA catabolism (reviewed in Taylor et al., 1998). Early studies and small-scale (9–30 patient) open outpatient trials resulted in reports of reduced cocaine cravings and use after initiation of treatment with gabapentin (Raby, 2000; Raby and Coomaraswamy, 2004; Myrick et al., 2001; Hart et al., 2004; Haney et al., 2005). However, these findings were later challenged by other larger-scale, double-blind, placebo-controlled clinical trials demonstrating that gabapentin, at doses up to 2400–3200 mg/day for 6–12 weeks, had no effect on abstinence rates, craving or subjective effects of cocaine (Bisaga et al., 2006; Berger et al., 2005; González

et al., 2007; Hart et al., 2007). However, there is no evidence demonstrating whether pretreatment with gabapentin significantly alters cocaine's direct rewarding effects or cocaine-triggered reinstatement of drug-seeking behavior at preclinical levels in experimental animals. Therefore, in the present study, we first observed the effects of systemic administration of gabapentin (25–200 mg/kg) on intravenous cocaine self-administration and cocaine-induced reinstatement of cocaine-seeking behavior in laboratory rats, and then further observed the effects of gabapentin on NAc extracellular DA, GABA and cocaine-enhanced NAc DA levels.

2. Materials and methods

2.1. Animals

Male Long-Evans rats (Charles River Laboratories, Raleigh, NC) weighing 250–300 g were housed individually in a climate-controlled animal room on a reversed light–dark cycle with free access to food and water. All experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* of the U.S. National Academy of Sciences, and were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse.

2.2. Cocaine self-administration and reinstatement of drug-seeking behavior

Animals were surgically implanted with intravenous (i.v.) catheters under sodium pentobarbital anesthesia using aseptic surgical technique. After the right external jugular vein was separated from surrounding tissues and fascia by blunt dissection and catheterized, the free end of the catheter was passed subcutaneously to the top of the skull, where it exited into a connector (a modified 22 gauge cannula; Plastics One, Roanoke, VA) mounted to the skull with stainless steel skull screws (Small Parts Inc., Miami Lakes, FL) and dental acrylic. To help prevent clogging, the catheters were flushed daily with a gentamicin–heparin–saline solution (5 mg/kg gentamicin, 30 IU/ml heparin; ICN Biochemicals, Cleveland, OH). After full recovery from surgery, animals were placed into standard operant chambers for cocaine self-administration and reinstatement as described previously (Xi et al., 2005, 2006). Initially, animals pressed the active lever for cocaine (1 mg/kg/infusion) for 3 h per day under fixed-ratio 1 (FR1) reinforcement, and were then switched to 0.5 mg/kg/infusion under FR2 reinforcement. Cocaine infusions were associated with light and sound cues. Inactive lever-presses were counted, but had no consequence.

For those rats used to evaluate the effects of gabapentin on cocaine self-administration, stable cocaine-maintained responding (0.5 mg/kg/infusion) under a FR2 schedule was established before gabapentin testing was initiated. Less than 10% variability in inter-response interval and less than 10% variability in number of presses on the active lever for at least three consecutive days were required for inclusion in the study. Animals then randomly received vehicle (25% 2-hydroxypropyl-β-cyclodextrin) or one dose of gabapentin (25, 60, 100, 200 mg/kg, i.p). Thirty minutes or 2 h later, all rats were put into test chambers, and the numbers of cocaine infusions and active lever-presses were recorded for 3h.

For those rats used to evaluate the effects of gabapentin on cocaine-triggered relapse, stable self-administration (0.5 mg/kg/infusion) under a FR2 reinforcement schedule was established, and animals were then exposed to extinction conditions, during which cocaine was replaced by saline and the cocaine-associated cue-light and tone turned off. Daily extinction sessions continued until lever-pressing was less than 10 per 3 h session for three consecutive days. Then, animals were divided into experimental groups, and reinstatement testing was begun 24 h later. On the reinstatement test day, each group of rats received either vehicle or one dose of gabapentin (25, 60, 100, 200 mg/kg, i.p). Thirty minutes or 2 h later, all rats received a priming injection of cocaine (10 mg/kg i.p.) and active lever-presses were recorded for 3 h. Inactive lever-presses were also counted but had no consequence.

2.3. In vivo brain microdialysis

Four groups of rats were used to evaluate the effects of gabapentin (0, 25, 100, 200 mg/kg i.p.) on NAc GABA and DA levels. Additionally, two groups of rats were used to evaluate the effects of the same doses of gabapentin on cocaine-induced changes in NAc DA. Microdialysis procedures were as reported previously (Xi et al., 2006). Guide cannulae (20 gauge, Plastics One, Roanoke, VA) were surgically implanted into the NAc (AP +1.6 mm, ML ±1.8 mm, DV −4.3 mm, angled 6° from vertical) under sodium pentobarbital anesthesia. The guide cannulae were fixed to the skull with stainless steel skull screws (Small Parts Inc., Miami Lakes, FL) and dental acrylic. Animals were allowed to fully recover from surgery before experiments began. Microdialysis probes were inserted through the previously-implanted guide cannulae into the NAc 12 h before each experiment to minimize damage-induced neurotransmitter release. During each experiment, microdialysis buffer (5 mM glucose, 2.5 mM KCl, 140 mM NaCl, 1.4 mM $CaCl_2$, 1.2 mM $MgCl_2$, 0.15% phosphate buffered saline, pH 7.4) was perfused through the probe (2.0 μl/min) for at least 2 h before sampling began. Samples were collected every 20 min into 10 μl of 0.5 M perchloric acid (to prevent neurotransmitter degradation). After sample collection, all samples were frozen at −80 °C until analyzed.

Microdialysate GABA was determined using high performance liquid chromatography (HPLC) with flourometric detection (Xi et al., 2006). Excitation (Exλ) and emission (Emλ) wavelengths were 336 nm and 420 nm, respectively. Concentrations of DA were measured by HPLC with an electrochemical (EC) detection system (ESA Associates, Chelmsford, MA) as described previously (Xi et al., 2006), upgraded with a Coulochem III EC detector (ESA Associates, Chelmsford, MA). Areas under the curve (AUC) for DA or GABA were measured.

2.4. Drugs

Cocaine HCl (Sigma-RBI., St. Louis, MO) was dissolved in physiological saline. Gabapentin was purchased from Tocris Bioscience (Ellisville, MO) or synthesized at the H.C. Brown Center for Borane Research, Department of Chemistry, Purdue University, West Lafayette, IN, and was dissolved in 25% 2-hydroxypropyl-β-cyclodextrin (Sigma-RBI, St. Louis, MO).

2.5. Histology

Following microdialysis, rats were euthanized by pentobarbital overdose (>100 mg/kg i.p.) and perfused transcardially with 0.9% saline followed by 10% formalin. Brains were removed and placed in 10% formalin for 1 week. The tissue was blocked around the NAc and coronal sections (100 μm thick) were made using a vibratome. The sections were stained with cresyl violet and examined by light microscopy.

2.6. Data analyses

All data are presented as means (±S.E.M.). AUC data were used for quantifying gabapentin's effects on basal extracellular NAc GABA, and basal or cocaine-enhanced extracellular NAc DA levels. The AUC (%) was calculated for each animal by subtracting 100 from the percent of baseline value for each data point, and subsequently summing all data points collected after drug administration. One-way analysis of variance (ANOVA) was used to analyze the effects of gabapentin on intravenous cocaine self-administration (Fig. 1), cocaine-induced reinstatement (Fig. 2), and basal or cocaine-induced neurochemical events (Figs. 3B, 3D, 4B, 4D). Two-way ANOVA with repeated measures over time was used to analyze the effects of gabapentin alone (Figs. 3A, C) or of gabapentin pretreatment on cocaine-induced changes in NAc neurotransmitter levels (Figs. 4A, 4C). Post-ANOVA pre-planned individual group comparisons were conducted using the Bonferroni procedure.

3. Results

3.1. Gabapentin had no effect on cocaine self-administration behavior

Fig. 1 shows the effects of gabapentin (25, 60, 100, 200 mg/kg) on cocaine self-administration rate under FR2 reinforcement conditions at a unit cocaine reinforcement dose of 0.5 mg/kg/infusion, when compared to vehicle treatment animals. One-way ANOVA for repeated measures over the gabapentin doses showed no statistically significant effect of gabapentin on cocaine self-administration, when gabapentin was administered either 30 min ($F_{4,33} = 0.67$, $p > 0.05$) or 2 h ($F_{3,15} = 0.21$, $p > 0.05$) prior to cocaine self-administration testing.

3.2. Gabapentin had no effect on cocaine-triggered reinstatement of drug-seeking behavior

Five additional groups of rats were used to evaluate the effects of gabapentin on cocaine-induced reinstatement of drug-seeking behavior. Rats in all five groups exhibited stable responses on the active lever during the last 5–7 days of cocaine self-administration. There was no statistically significant difference in mean numbers of cocaine infusions, active lever presses, or inactive lever presses between the different groups of rats during the last three sessions of cocaine self-administration or extinction. A single, noncontingent cocaine injection (10 mg/kg i.p.) produced robust reinstatement of lever-pressing behavior within 30–40 min after cocaine administration. Pretreatment with gabapentin (25, 60, 100, 200 mg/kg, i.p) had no significant effect on cocaine-induced reinstatement of drug-seeking behavior, when gabapentin was administered 30 min prior to cocaine priming (Fig. 2A: $F_{4,45} = 1.47$, $p > 0.05$). Similarly, gabapentin (200 mg/kg) also failed to alter cocaine-induced reinstatement, when it was administered 2 h prior to cocaine priming in an additional experiment (Fig. 2B: $F_{1,13} = 0.15$, $p > 0.05$).

3.3. Gabapentin modestly elevated extracellular GABA levels, but did not alter extracellular DA levels in the NAc

Fig. 3 shows the effects of gabapentin (25, 100, 200 mg/kg, i.p.) on NAc extracellular GABA and DA levels, demonstrating that gabapentin dose-dependently elevated extracellular NAc GABA levels, but had no effect on NAc DA levels. Two-way ANOVA for repeated measures over time for the data shown in Fig. 3A revealed a statistically significant treatment (gabapentin *vs.* vehicle) main effect ($F_{3,22} = 4.75$, $p < 0.05$), and a statistically significant time main effect ($F_{14,308} = 2.08$, $p < 0.05$), but no significant treatment × time interaction ($F_{42, 308} = 0.75$, $p > 0.05$). One-way ANOVA for the AUC data shown in Fig. 3B revealed a significant dose-dependent increase in NAc GABA after gabapentin administration ($F_{3,21} = 3.5$, $p < 0.05$). Individual comparisons with the Bonferroni *t*-test showed a significant increase in NAc GABA after 100 mg/kg ($t = 2.54$, $p < 0.05$) or 200 mg/kg ($t = 2.96$, $p < 0.05$), but not after 25 mg/kg ($t = 2.45$, $p > 0.05$), gabapentin. Two-way ANOVA for repeated measurements over time for the data shown in Fig. 3C did not reveal a statistically significant treatment main effect ($F_{3,21} = 2.69$, $p > 0.05$), time main effect ($F_{14,294} = 1.03$, $p > 0.05$), or treatment × time interaction ($F_{42, 294} = 1.13$, $p > 0.05$). Further, one-way ANOVA for the AUC data shown in Fig. 3D revealed no significant treatment main effect ($F_{3,44} = 1.22$, $p > 0.05$).

3.4. Gabapentin had no effect on cocaine-enhanced NAc DA

Fig. 4 shows that cocaine alone (10 mg/kg, i.p.) produced a significant increase (300–400% of baseline, $p < 0.05$) in extracellular DA in the NAc. Gabapentin pretreatment (100–200 mg/kg, i.p., 40 min prior to cocaine priming) did not significantly alter such cocaine-induced increases in DA. Two-way ANOVA for repeated measures over time for the data shown in Fig. 4A revealed a statistically significant time main effect ($F_{10,230} = 43.49$, $p < 0.001$) and a statistically significant treatment × time interaction ($F_{20,230} = 1.99$, $p < 0.01$), but no significant treatment main effect ($F_{2,23} = 1.24$, $p > 0.05$). One-way ANOVA for the AUC data shown in

Fig. 4B revealed no significant effect of gabapentin on cocaine-enhanced NAc DA ($F_{2,23} = 1.19$, $p > 0.05$). Similarly, gabapentin (200 mg/kg), when administered 2 h prior to cocaine injection, also failed to inhibit cocaine-induced increases in NAc extracellular DA in an additional experiment (Fig. 4C, D). Two-way ANOVA for repeated measures over time for the data shown in Fig. 4C revealed a statistically significant time main effect ($F_{11,176} = 14.23$, $p < 0.001$) and a statistically significant treatment × time interaction ($F_{11,176} = 17.85$, $p < 0.001$), but no significant treatment main effect ($F_{1,13} = 0.008$, $p > 0.05$). One-way ANOVA for the AUC data shown in Fig. 4D revealed no significant effect of gabapentin on cocaine-enhanced NAc DA ($F_{1,13} = 1.43$, $p > 0.05$).

Finally, histological examination indicated that the active membranes of the microdialysis probes were located within the NAc core and shell, but more within the core compartment (data not shown).

4. Discussion

The present study demonstrates that gabapentin, within the dose range 25–200 mg/kg, inhibited neither intravenous cocaine self-administration nor cocaine-induced reinstatement of cocaine-seeking behavior in experimental animals. Furthermore, the same doses of gabapentin only modestly (~50%) elevated NAc extracellular GABA levels, but had no effect on either basal levels of extracellular DA or cocaine-induced increases in extracellular DA in the NAc. These results suggest that gabapentin is a weak GABA-mimic drug, which, at the doses tested, has no effect on cocaine's reinforcing ability or on cocaine-triggered relapse to drug-seeking behavior.

Gabapentin is structurally analogous to GABA, but, unlike GABA, crosses the blood–brain barrier when administered systemically (Wang and Welty, 1996; Goa and Sorkin, 1993). Gabapentin has little affinity at ionotropic GABA$_A$ receptors or metabotropic GABA$_B$ receptors (Suman-Chauhan et al., 1993), but significantly increases GABA synthesis (Löscher et al., 1991) and release (Götz et al., 1993), most likely by reversal of the GABA transporter (Honmou et al., 1995). In addition, high concentrations of gabapentin also inhibit GABA uptake by blocking GABA binding to GABA transporters (Eckstein-Ludwig et al., 1999). Consistent with these findings observed *in vitro*, the present *in vivo* brain microdialysis study demonstrated that gabapentin (100–200 mg/kg) produced a modest (~50%), delayed (~2 h) increase in extracellular GABA levels, which lasted for at least 4 h. In contrast to this present finding, another *in vivo* microdialysis study reported that 100 mg/kg gabapentin alters neither basal levels of extracellular GABA, nor K$^+$-, glutamate- or nipecotic acid-induced increases in extracellular GABA in the substantia nigra (SN) (Timmerman et al., 2000). Such a difference in gabapentin's action on extracellular GABA could be related to the different doses (100 mg/kg *vs.* 200 mg/kg), the different brain regions sampled (NAc *vs.* SN) and/or the different sample sizes ($n = 10$ *vs.* $n = 4$). We also found that gabapentin neither lowers basal levels of extracellular NAc DA, nor inhibits cocaine-enhanced NAc DA, when gabapentin was administered either 40 min or 2 h prior to cocaine administration. Such pretreatment times were chosen based upon the finding that gabapentin-induced increases in NAc GABA are slow-onset and long-acting with significant increases occurring at around 2 h after gabapentin. These data suggest that gabapentin-induced increases in NAc GABA levels are not robust, and therefore likely not strong enough to inhibit NAc DA release.

Another important finding in the present study is that pretreatment with gabapentin (25–200 mg/kg) inhibits neither cocaine self-administration nor cocaine-triggered relapse to drug-seeking behavior, when administered either 30 min or 2 h prior to cocaine self-administration test. Intravenous cocaine self-administration and reinstatement of drug-seeking behavior are commonly used animal models to predict rewarding effects and relapse-provoking potential

of addictive drugs in humans (Shaham et al., 2003; Xi et al., 2005, 2006). Congruent with the present findings, Filip et al. (2007) recently reported that lower doses of gabapentin (10–30 mg/kg, 1 h prior to testing) failed to alter cocaine self-administration and cocaine-induced relapse in rats (Filip et al., 2007). Such low doses of gabapentin (1–30 mg/kg) also failed to alter acute cocaine-induced hyperactivity or repeated cocaine-induced behavioral sensitization in rats (Itzhak and Martin, 2000; but see Filip et al., 2006). In contrast, one study reported that gabapentin (10–100 mg/kg) dose-dependently protected against cocaine (75 mg/kg)-induced seizures in mice (Gasior et al., 1999), which may result from a pharmacologically distinct (i.e., non-GABAergic) underlying mechanism (Bossert and Franklin, 2003).

The present findings that gabapentin (25–200 mg/kg) failed to inhibit cocaine self-administration, cocaine-triggered relapse and cocaine-enhanced NAc DA suggest that gabapentin, at the doses tested, has little potential for altering cocaine's rewarding effects or cocaine craving and relapse at the human level. This is consistent with findings from recent large-scale clinical trials demonstrating that gabapentin (1600–3200 mg/day, 6–12 weeks) had no effect on cocaine craving or urine-confirmed cocaine use (Berger et al., 2005; Bisaga et al., 2006; Hart et al., 2007; González et al., 2007). Since large-scale, double-blind clinical trials have obvious advantages over the case reports described in the Introduction, we interpret these negative findings as being more reliable and conclusive. In addition to the above-noted negative or positive reports in human subjects, there are two more small-scale clinical reports (Hart et al., 2004; Haney et al., 2005) of mixed results with gabapentin (600–1200 mg/day, in 7–8 cocaine-dependent patients, for 7 weeks), in which gabapentin appeared to inhibit cocaine craving and subjective effects of smoked cocaine, but had no effect on either cocaine self-administration or on cognitive or cardiovascular effects of smoked cocaine. In addition, there are two case reports indicating that gabapentin itself appears to have abuse potential in cocaine addicts (Markowitz et al., 1997; Reccoppa et al., 2004).

The failure of gabapentin to inhibit acute cocaine's behavioral and neurochemical effects is unlikely due to too low doses being used in the present study. First, 100–200 mg/kg gabapentin did produce an increase (~50%, $p < 0.05$) in NAc extracellular GABA levels in the present study; Second, the doses used in the present experiments are equivalent to or higher than doses found to be effective in other behavioral tests in experimental animals. For example, it was reported that 10–30 mg/kg gabapentin significantly inhibits spontaneous activity and cocaine-induced behavioral sensitization (Filip et al., 2006), as well as nociceptive responses to noxious stimuli (Tanabe et al., 2006). In addition, 10–200 mg/kg gabapentin was reported to significantly inhibit cocaine- or pilocarpin-induced seizures (Gasior et al., 1999; Pereira et al., 2007). Third, by conversion of animal doses to human equivalent doses (i.e., rat dose in mg/kg × 0.16, as recommended by the U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research) (U.S. Department of Health and Human Services, 2005), the doses (25–200 mg/kg) of gabapentin we used in the present study in rats are equivalent to 4–30 mg/kg in humans. This is equivalent to the daily effective doses used for relieving pain (300–1200 mg/day, ≈5–20 mg/kg based on average body weight of 60 kg) (Mathiesen et al., 2007) or for controlling partial seizures (300–1800 mg/day, ≈5–30 mg/kg/day) (Morris, 1999) or for cocaine use (600–2400 mg/day, ≈10–40 mg/kg/day) in other clinical trials (Hart et al., 2004; Myrick et al., 2001; Raby, 2000; Raby and Coomaraswamy, 2004). It may be argued that such direct comparisons between a single animal dose and multiple human doses may be inaccurate or inappropriate. However, we point out that although the doses used in the present study are higher than the majority of doses reported in the literature for controlling pain and seizures (see review by Mathiesen et al., 2007), such high doses of gabapentin still had no effect on cocaine self-administration and cocaine-triggered reinstatement in experimental animals, and thus may be taken as an *a forteriori* demonstration of lack of effect.

Taken together, all these data suggest that gabapentin is a weak GABA enhancer. The therapeutic effects of gabapentin in the treatment of seizures or other psychiatric diseases could be related to its actions on other neurotransmitters or ion channels, in addition to mild augmentation of GABAergic transmission (Timmerman et al., 2000; Goa and Sorkin, 1993).

In conclusion, the present data – and their preliminary presentations in abstract form (Peng et al., 2004; Li et al., 2006) – show, for the first time, that gabapentin neither alters cocaine self-administration nor cocaine-triggered reinstatement of drug-seeking behavior in laboratory animals, suggesting a limited potential in treating cocaine dependence in humans. This could be related to its weak GABA-mimic potency, which does not appear strong enough to effectively inhibit cocaine-induced increases in extracellular DA in the NAc. The present findings with gabapentin are thus in contrast to our findings with γ-vinyl GABA (GVG), another GABAmimetic compound that *does* show effectiveness in some of the same addiction-related preclinical animal models used in the present study (see companion piece to present article). We therefore conclude that there are significant differences among putative GABAmimetic compounds with respect to their potential utility as anti-addiction therapeutic agents at the human level.

Acknowledgements

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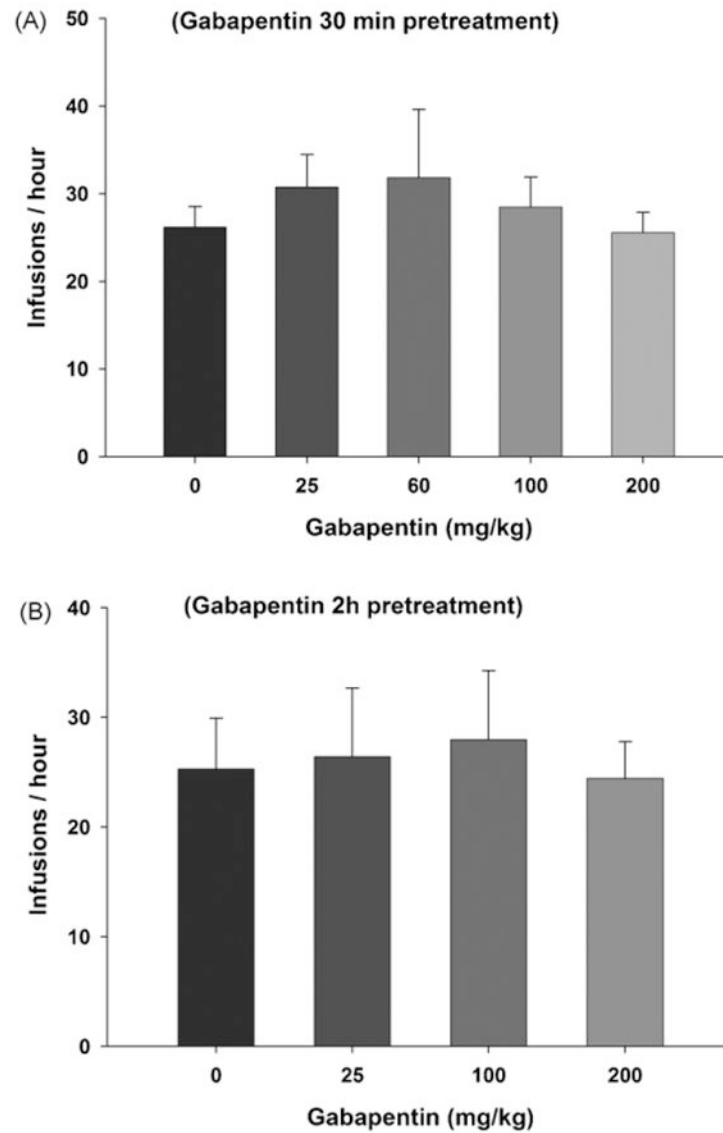
Fig. 1.
Effects of gabapentin (25–200 mg/kg) on intravenous cocaine (0.5 mg/kg/infusion) self-administration under a fixed-ratio 2 (FR2) reinforcement schedule, when gabapentin was administered either 30 min (Panel A) or 2 h (Panel B) prior to cocaine self-administration tests.
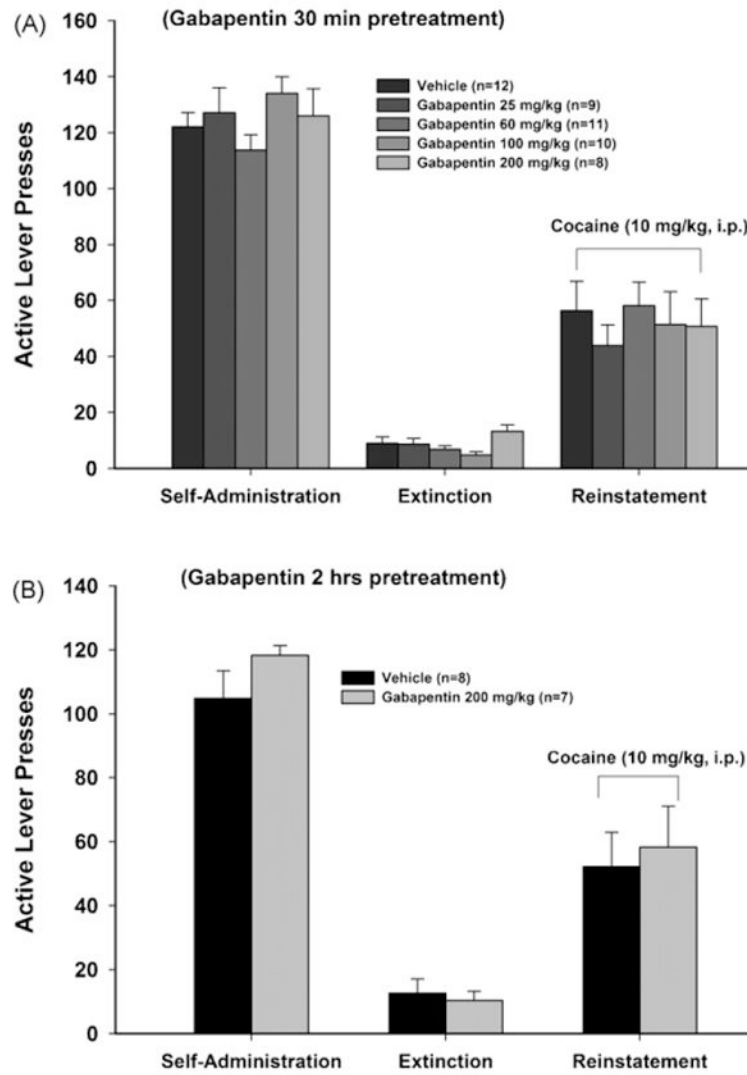
Fig. 2.
Effects of gabapentin (25–200 mg/kg) on cocaine (10 mg/kg)-induced reinstatement of drug-seeking behavior in rats, when gabapentin was administered either 30 min (Panel A) or 2 h (Panel B) prior to reinstatement tests.
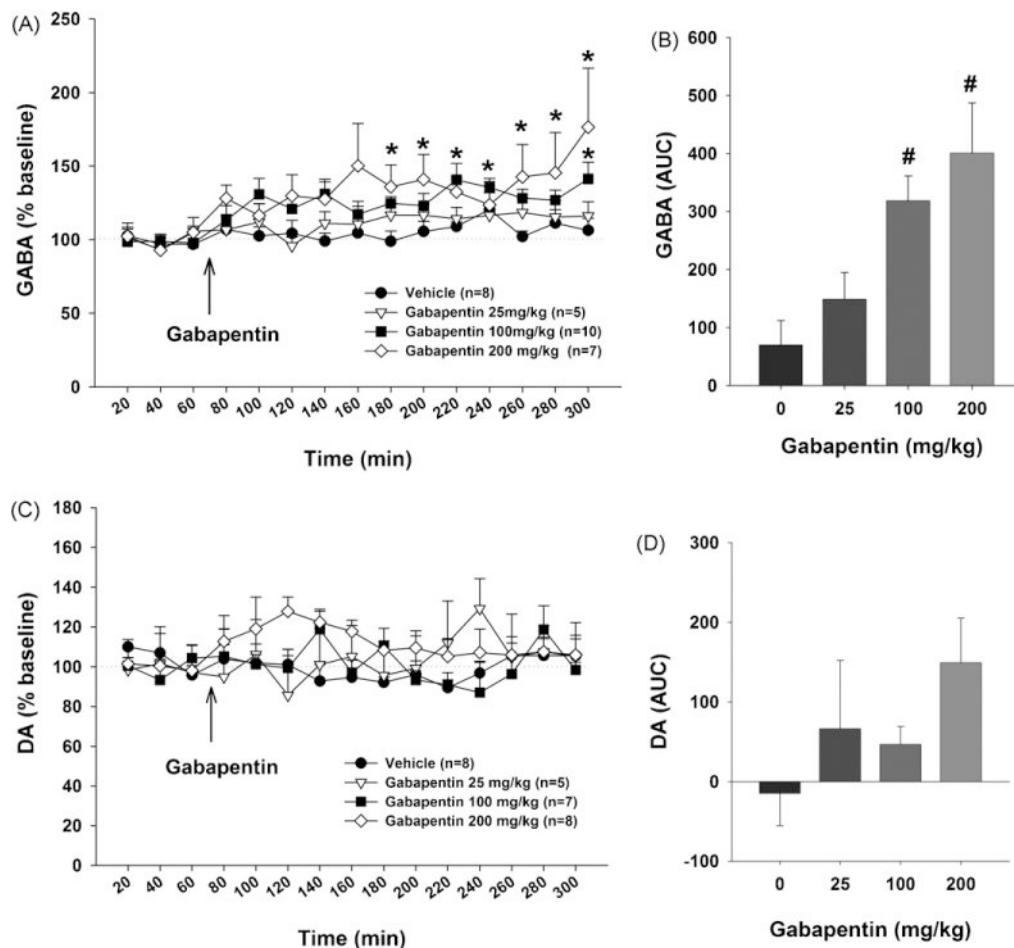
Fig. 3.
Effects of gabapentin on basal extracellular GABA and DA levels in the NAc. Systemic administration of gabapentin (25–200 mg/kg, i.p.) modestly elevated extracellular GABA levels in the NAc (Panels A and B), but failed to alter extracellular DA levels in the NAc (Panels C and D). *$p < 0.05$, compared with the baseline in each group; #$p < 0.05$, compared with the vehicle treatment group.
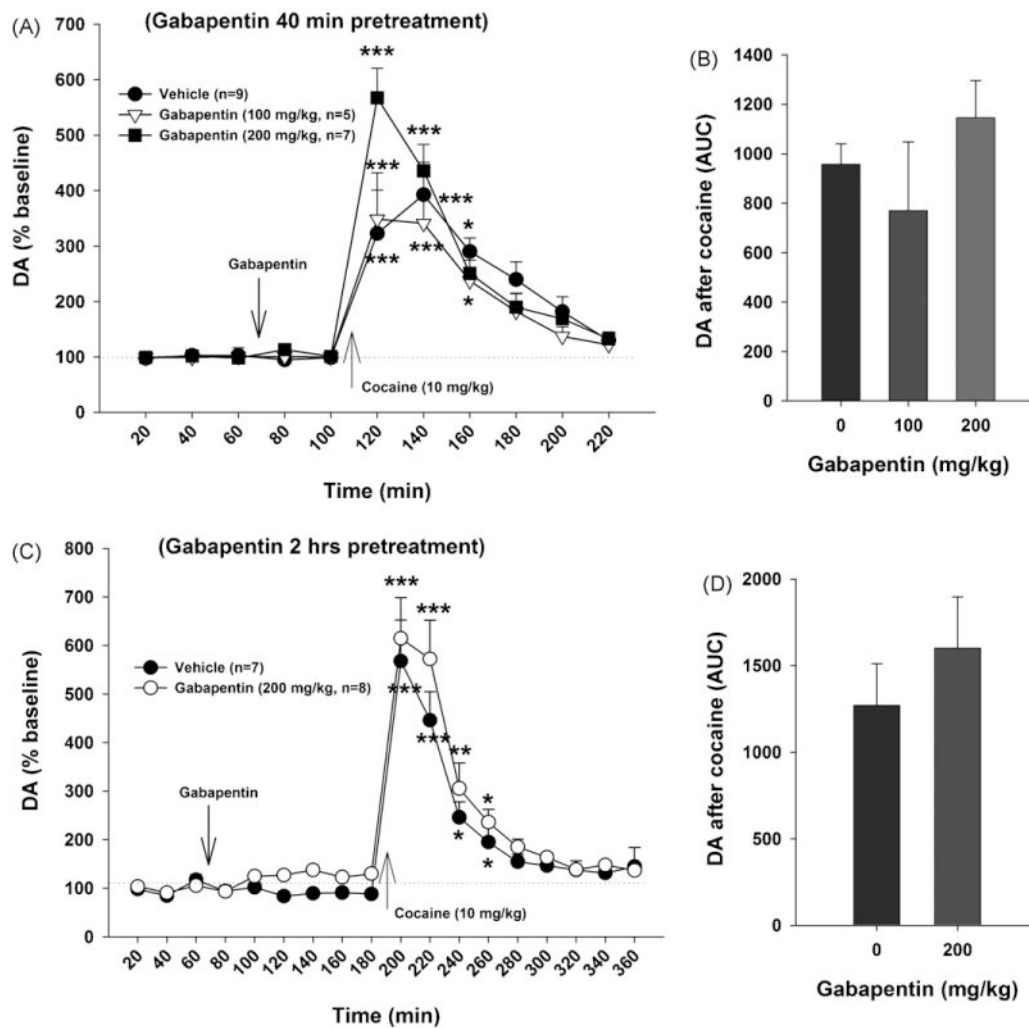
Fig. 4.
Effects of gabapentin on cocaine-induced increases in extracellular DA in the NAc. Systemic administration of cocaine (10 mg/kg, i.p.) significantly elevated extracellular DA in the NAc, while pretreatment with gabapentin (100–200 mg/kg, i.p.) failed to inhibit cocaine-enhanced DA in the NAc, when gabapentin was administered either 40 min (Panels A and B) or 2 h (Panels C and D) prior to cocaine priming. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, compared with the baseline in each group.