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Short communication

Gamma-vinyl γ-aminobutyric acid attenuates the synergistic elevations of nucleus accumbens dopamine produced by a cocaine/heroin (speedball) challenge

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Abstract

In the present study, we examined the effect of an acute administration of the selective suicide inhibitor of γ-aminobutyric acid (GABA)-transaminase, gamma-vinyl GABA on increases in nucleus accumbens dopamine produced by a cocaine/heroin challenge in freely moving animals. Cocaine (20 mg/kg, i.p.) produced an elevation in extracellular nucleus accumbens dopamine of approximately 380% above baseline, while heroin produced only a moderate increase of 70%. Coadministration of these two drugs, however, produced a synergistic elevation in nucleus accumbens dopamine of 1000%. This response was reduced by 50% in animals pretreated with gamma-vinyl GABA (300 mg/kg, i.p.) 2.5 h prior to challenge. This same dose of gamma-vinyl GABA inhibited cocaine-induced increases in nucleus accumbens dopamine by 25% and completely abolished heroin-induced increase. These findings indicate that gamma-vinyl GABA can interfere with the synergistic effects produced by the combination of an indirect dopamine releaser (heroin) and a dopamine reuptake blocker (cocaine).

Keywords: Speedball; Cocaine; Heroin; Dopamine; Microdialysis; Addiction

1. Introduction

Psychostimulants such as cocaine and opioid agonists such as heroin are often abused together in a drug combination known as a ''speedballing''. This trend is increasing at an alarming rate among patients in methadone and levo-α-acetylmethadol (LAAM) maintenance programs. Several descriptions of the simultaneous effects have been offered, including an enhancement of the magnitude and/or duration of the euphoria associated with each drug alone. For example, behavioral studies have demonstrated that conditioned place preference for cocaine was potentiated by morphine (Masukawa et al., 1992). Furthermore, self-administration of a cocaine/heroin combination produced a synergistic effect on the magnitude of increase in extracellular dopamine concentrations in the nucleus accumbens of freely moving animals (Hemby et al., 1998).

We have focused on developing a novel strategy of targeting the γ-aminobutyric acid (GABA)ergic system for the potential treatment of addiction. Systemic administration of gamma-vinyl GABA (Vigabatrin, Sabril®), a selective suicide inhibitor of GABA-transaminase, causes a dose-dependent and prolonged elevation of whole brain GABA levels (see Sabers and Gram, 1992 for review). Recently we examined the ability of gamma-vinyl GABA to attenuate the biochemical and behavioral effects of cocaine, heroin, nicotine, methamphetamine, and ethanol in the primate and rodent central nervous system (Dewey et al., 1998, 1999; Gerasimov et al., 1999). Acutely, at the highest dose tested, gamma-vinyl GABA significantly attenuated cocaine and methamphetamine-induced increases while it completely abolished heroin, nicotine and ethanol-induced increases in nucleus accumbens dopamine. In the present study, we extended these findings to include an investigation of the effects of gamma-vinyl GABA on the synergistic elevations known to result in nucleus accumbens dopamine following a cocaine/heroin (speedball) challenge.

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2. Materials and methods

Male Sprague–Dawley rats were used in all experiments (200–300 g, Taconic Farms, Germantown, NY). Each animal was housed individually on a 12/12 h light/dark cycle. All animals were used under an Institutional Animal Care and Use Committee approved protocol and with strict adherence to National Institutes of Health guidelines.

In vivo microdialysis studies were performed using adult male Sprague–Dawley rats (Taconic Farms). Animals were anesthetized and siliconized guide cannulae were stereotaxically implanted into the right nucleus accumbens (2.0 mm anterior and 1.0 mm lateral to bregma, and 7.0 mm ventral to the cortical surface) at least 4 days prior to study. Microdialysis probes (2.0 mm, Bioanalytical Systems, West Lafayette, IN) were positioned within the guide cannulae and artificial cerebrospinal fluid (155 mM NA^+, 1.1 mM Ca^{2+}, 2.9 mM K^+, 132.76 mM Cl^-, and 0.83 mM Mg^{2+}) was administered through the probe using a CMA/100 microinfusion pump at a flow rate of 2.0 μl/min. Animals were placed in bowls, and probes were inserted and flushed with ASCF overnight. On the day of study, a minimum of three samples were injected to determine baseline stability. Samples were collected for 20 min and injected on-line (CMA/160). The average dopamine concentration of these three stable samples was defined as control (100%), and all subsequent treatment values were transformed to a percentage of that control. Upon establishing a stable baseline, drugs were administered by intraperitoneal (i.p.) injection. The high-pressure liquid chromatography system consists of a reverse-phase column (3.0 μ C-18), an liquid chromatograph-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), and a dual pen chart recorder. The mobile phase (flow rate 1.0 ml/min) consisted of 7.0% methanol, 50 mM sodium phosphate monobasic, 1.0 mM sodium octyl sulfate, and 0.1 mM EDTA, pH 4.0. dopamine eluted at 7.5 min.

In all studies, gamma-vinyl GABA (300 mg/kg) was administered i.p. 2.5 h prior to administration of the challenge drug. Cocaine hydrochloride ($n = 6–8$) was administered at a dose of 20 mg/kg (i. p.), while heroin (diacetylmorphine hydrochloride, National Institute on Drug Abuse, Rockville, MD), ($n = 6–8$) was administered at a dose of 0.5 mg/kg (i.p.). In studies designed to investigate the synergistic effects of a cocaine/heroin mixture ($n = 6–8$), both drugs were administered at the identical dose used in the single drug studies.

Gamma-vinyl GABA was generously supplied by Hoechst Marion Roussel (Kansas City, MO).

3. Results

In each group of animals receiving gamma-vinyl GABA, extracellular nucleus accumbens dopamine levels decreased beginning 80 min following administration. This decrease reached a maximum effect of approximately 60% below baseline values 2.5 h following administration.

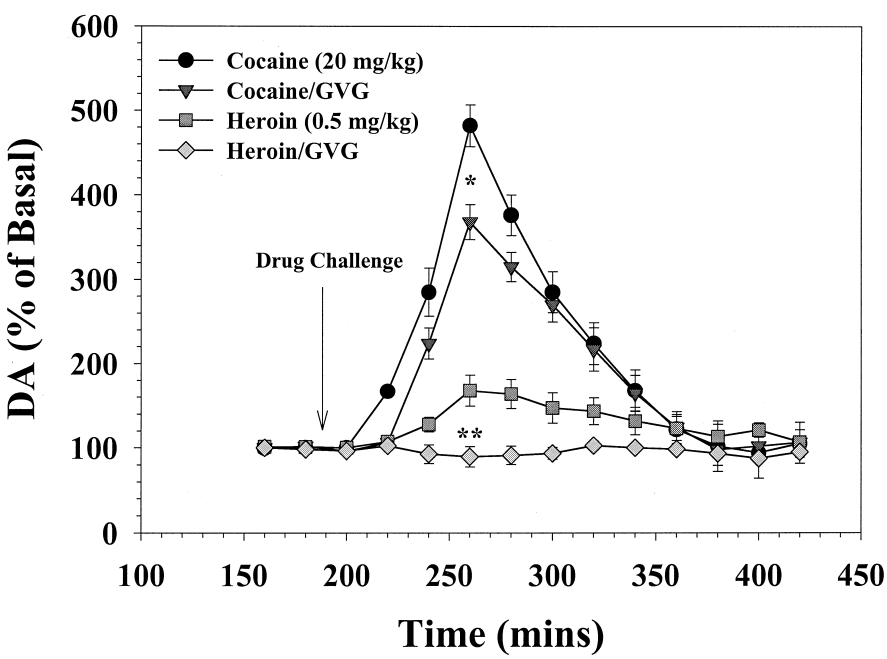

Fig. 1. In vivo microdialysis studies in freely moving rats ($n = 6–8$ per group). * Peak values are significantly different from those obtained from animals that received cocaine alone ($P < 0.01$, ANOVA and Student–Newman–Keuls test). ** Peak values are significantly different from those obtained from animals that received heroin alone ($P < 0.01$, ANOVA and Student–Newman–Keuls test).

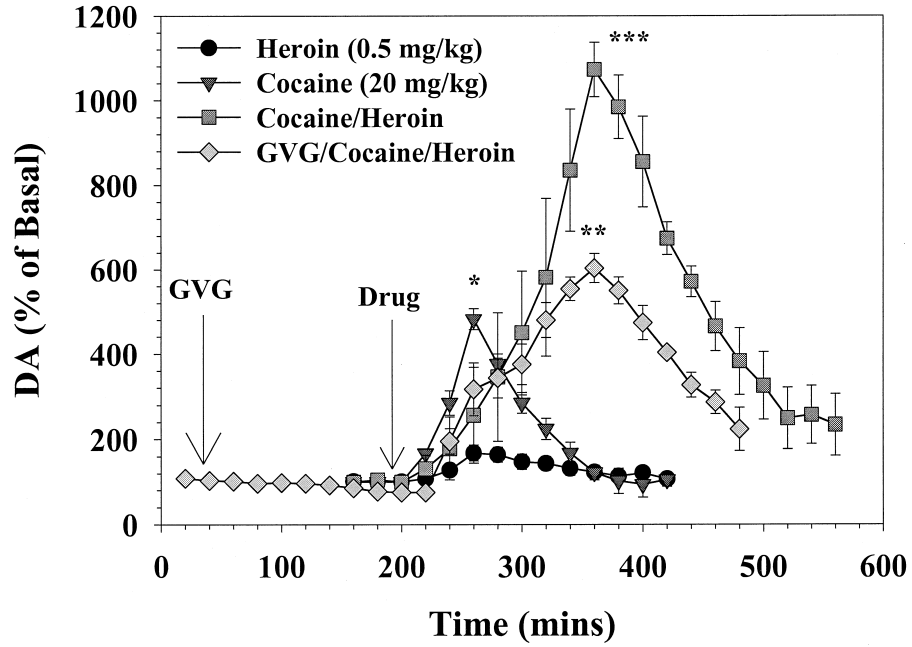

Fig. 2. In vivo microdialysis studies in freely moving rats ($n = 6–8$ per group). * Peak values are significantly different from those obtained from animals that received heroin alone ($P < 0.01$, ANOVA and Student–Newman–Keuls test). ** Peak values are significantly different from those obtained from animals that received a cocaine/heroin challenge ($P < 0.001$, ANOVA and Student–Newman–Keuls test) and statistically different from those animals that received cocaine alone ($P < 0.05$, ANOVA and Student–Newman–Keuls test). *** Peak values are significantly different from those obtained from animals that received cocaine or heroin alone ($P < 0.001$, ANOVA and Student–Newman–Keuls test).

Alone cocaine produced a marked elevation in extracellular dopamine of approximately 380% above baseline values 60 min following administration. Dopamine returned to baseline within 120 min gamma-vinyl GABA administration inhibited this response by approximately 25% (Fig. 1).

In marked contrast, heroin increased nucleus accumbens dopamine by only 70% 60 min following administration, returning to baseline within 140 min. Gamma-vinyl GABA completely abolished this effect (Fig. 1).

When combined, the two drugs produced an increase in nucleus accumbens dopamine of approximately 1000% 180 min following administration that had not returned to baseline values by 200 min after reaching peak values (Fig. 2). This increase was significantly different ($P < 0.001$) from cocaine or heroin alone. In animals that received gamma-vinyl GABA (300 mg/kg, i.p.) 2.5 h prior to challenge, nucleus accumbens dopamine increased by approximately 500% 180 min following challenge (Fig. 2). This increase was significantly different from both cocaine and heroin alone ($P < 0.05$ and 0.001, respectively) and cocaine/heroin combined ($P < 0.001$).

4. Discussion

We have previously demonstrated the ability of gamma-vinyl GABA to inhibit increases in extracellular nucleus accumbens dopamine induced by various addictive drugs: ethanol, methamphetamine, nicotine, heroin and cocaine. The present report extends these findings with gamma-vinyl GABA and a single drug challenge.

The coadministration of the μ-opioid receptor agonist (heroin) and dopamine reuptake inhibitor (cocaine) produced a synergistic elevation of extracellular nucleus accumbens dopamine. The neurochemical synergy, as compared to an additive effect, was evident not only in the magnitude of the increase in nucleus accumbens dopamine, but also in the time it took to reach the peak elevation and return to baseline values. Individually, each drug produced a maximum increase within 60 min following challenge. When combined, however, this maximum increase took nearly three times longer to achieve than either drug alone. Furthermore, it took considerably longer to return to baseline values when compared to each drug separately. These results are consistent with previous anecdotal reports in humans suggesting that the duration of the euphoria is much longer when both drugs are used in combination as opposed to separately.

With respect to the absolute magnitude of the response, gamma-vinyl GABA completely abolished the synergistic effects following the combined drug challenge. That is, the data obtained following pretreatment with gamma-vinyl GABA and a ''speedball'' challenge are similar to an additive effect of both cocaine (380%) and heroin (70%) separately, compared to a synergistic effect. Of particular note is the finding that the dose of gamma-vinyl GABA used (300 mg/kg) completely abolished the response to

heroin and attenuated the effect of cocaine alone by only 25%, but inhibited the response to the combined cocaine/heroin challenge by 50%.

While abolishing the synergistic effect of both drugs with respect to the absolute magnitude of the increase, gamma-vinyl GABA did not effect the temporal aspects of the response. Following gamma-vinyl GABA administration and a subsequent cocaine/heroin challenge, nucleus accumbens dopamine reached a maximum concentration within 180 min which is identical to the response measured in animals that did not receive gamma-vinyl GABA prior to challenge.

We have previously commented on the possibility that other nondopaminergic neurotransmitter systems may play a significant role in the reinforcing properties of addictive drugs (Dewey et al., 1999). The hypothesis that pharmacologic systems mediating the stimulus properties of cocaine and heroin might be functionally independent is supported by the finding that destruction of dopamine terminals in the nucleus accumbens did not affect initiation of heroin self-administration, but significantly decreased the total intake of cocaine during the self-administration session (Gerrits and van Ree, 1996). The synergistic effect as well as the unexpected delay in reaching the peak values observed in the present study could be due to a currently ill-defined interaction between increases in dopamine neurotransmission due to blockade of reuptake sites by cocaine and opioid receptor dependent disinhibition of GABA interneurons. To test this hypothesis, additional studies using the combination of a direct dopamine releaser with heroin are warranted, since one might expect then to produce merely an additive effect.

In the present study, gamma-vinyl GABA extinguished the synergistic effects of a cocaine/heroin challenge on the magnitude of increases in nucleus accumbens dopamine. It is conceivable that gamma-vinyl GABA-induced decreases in nucleus accumbens dopamine prior to the drug challenge successfully interfere with the mechanism responsible for the synergistic effect produced, following the combination of an indirect dopamine releaser (heroin) and a dopamine reuptake inhibitor (cocaine). We are currently investigating the ability of gamma-vinyl GABA to block the behavioral effects of cocaine/heroin combination using a conditioned place preference paradigm.

In conclusion, our results indicate that gamma-vinyl GABA effectively attenuates the synergistic elevations in nucleus accumbens dopamine produced by a cocaine/heroin challenge. Combined with our previous studies, this finding suggests the potential effectiveness of gamma-vinyl GABA for the treatment of poly-drug abuse.

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