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Effects of Cocaine and GBR-12909 on Brain Stimulation Reward

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MALDONADO-IRIZARRY, C. S., J. R. STELLAR AND A. E. KELLEY. *Effects of cocaine and GBR-12909 on brain stimulation reward.* PHARMACOL BIOCHEM BEHAV **48**(4) 915–920, 1994.—Cocaine and GBR-12909, two dopamine reuptake blockers, were administered in a multiple current rate-frequency curve-shift test of intracranial self-stimulation (ICSS) reward in rats with medial forebrain bundle (MFB) electrodes. Acute injections of cocaine (0, 5, 15, 30 mg/kg, IP) increased ICSS reward at all currents (501, 316, 200 μAmps) as measured by decrease half-maximal frequency threshold. Cocaine also increased operant motor performance but only at the low current. In addition, cocaine increased dynamic interval at the highest dose at all currents. Similar treatment with GBR-12909 (0, 5, 10, 20 mg/kg, IP) significantly increased ICSS reward (decreased threshold) especially at the medium dose in all currents and had no significant effects on operant motor performance or dynamic interval. The major novel finding of the present study is that the rewarding effects of both drugs was not dependent on the choice of stimulation current, which is discussed as simplifying future psychophysical testing of psychostimulant drugs in the ICSS rate-frequency curve-shift paradigm.

Cocaine GBR-12909 ICSS reward Stimulation Current Dopamine

IT IS well established that cocaine blocks the reuptake of monoamines (12,27), particularly dopamine (15,22,36). Microdialysis studies show that cocaine increases synaptic dopamine levels in the nucleus accumbens (1,15,23–25), a brain region implicated in drug self-administration (29,37) and in the rewarding effects of intracranial self-stimulation (ICSS) (5,8,11,18,26,29–31,34,37). Cocaine also is known to increase ICSS reward (7,10,17,20). A problem with studying the cocaine effects on ICSS reward is the well-known motor effects of this drug. This problem can be overcome in ICSS studies by using threshold or other rate-free measures, such as the rate-frequency curve-shift method (6,35).

In this method, subjects are allowed to lever press for bursts of ICSS that are composed of different pulse frequencies. The resulting rate-frequency curve can be analyzed like a dose–response curve in classical pharmacology into a half-maximal reward threshold that is similar to an ED_{50}, and is called the locus of rise (LOR). Numerous validation studies support the basic reward selectivity of the LOR, for curve shifts greater than 0.1 log Hz (6,9,19,35,37). Moreover, the LOR measure has been utilized in many studies of dopamine antagonist drugs (8,33,37).

Recently, results from several studies suggested that the size of LOR shifts produced by lesions appeared to depend on the ICSS current at which the subject was tested (21,32). If this were to be observed in drugs studies, then the arbitrary choice of ICSS current could become a determining factor in the outcome and interpretation of the experiment. A previous investigation of the effects of pimozide using the rate-frequency curve-shift method did not find systematic differences depending on current (13). To further establish that the choice of current is not an important factor in pharmacological studies of ICSS, the present study examined the effects of indirect dopamine agonists like cocaine and GBR-12909 on ICSS reward. In addition, this study investigates the changes in the dynamic interval of the rate-frequency curve which is defined as the range of ICSS pulse frequency over which behavior rises from low or zero levels to maximal responding. Changes in the dynamic interval would produce a different slope of the rate-frequency curve and would indicate that the

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neuronal rules of integration of the ICSS pulses into the operant reward stimulus had been changed.

METHOD

Subjects

Adults male Sprague-Dawley rats (Charles River, MA) were implanted under Nembutal (60 mg/kg, IP) anesthesia with monopolar electrodes (Plastics One, Inc.) aimed at the lateral hypothalamus. The level-skull electrode coordinates were: AP − 3.0 from bregma, ML + 1.7 from midsagittal sinus, and DV − 7.5 from cortex. A ground wire was attached to the skull screws to serve as a ground connection for the electrode. Dental acrylic was applied to the electrode and screws to create and secure the assembly. Subjects were housed individually in transparent plastic cages under day : night reversed cycle (12L : 12D) in a temperature- and humidity-controlled colony room. Food (Purina Lab Chow pellets) and water were available at all times.

Drug Preparation: GBR-12909, Cocaine

GBR-12909 (Novo Nordisk A/S, Denmark) was dissolved in 90°C distilled water and tartaric acid (five parts drug to one part acid). Fresh solutions were prepared daily. Cocaine-HCl (Sigma Chemical Co., St. Louis) was dissolved in isotonic saline.

Drug Treatment and Groups

In the first experiment, two groups of rats were injected with either 0, 5.0, 10.0, or 20.0 mg/kg IP of GBR-12909 (n = 5) or 0.0, 5.0, 15.0, or 30.0 mg/kg of cocaine-HCl (n = 7). GBR-12909 was given 30 min before behavioral testing and cocaine was given 10 min before testing. Within each group, each injection was administered in a counterbalanced order with two drug-free behavioral test days in between each drug injection.

Behavioral Testing

Seven days after electrode implantation, subjects were trained to lever-press for brain stimulation in a standard operant chamber. The stimulation parameters, data collection, experiment timing, and chamber lights were controlled by a Stimtek stimulator board driven by a Basicon microcontroller that was networked to an IBM-PC. Brain stimulation reinforcements consisted of a 1.0 s burst of 0.1 ms square-wave monophasic cathodal constant-current pulses.

During initial training, ICSS pulse frequency was set at 100 Hz, and a current was selected that gave the highest rate of responding with low signs of aversiveness (ex. vocalization, defecation, retreat from lever). Subjects were first trained on a CRF schedule, and eventually transferred to a VI 3 second schedule of reinforcement. ICSS testing was then divided into a series of 90 s trials. ICSS frequency was fixed within a trial and changed across trials. The data from the first 30 s of each trial were discarded to allow the rat to adjust its lever pressing rate to the new ICSS frequency. Following each trial was a 10-s blackout of the houselight during which the lever did not deliver stimulation. A reinforcement light was illuminated during the delivery of brain stimulation bursts.

After initial training, the animals were further trained on the rate-frequency procedure in which ICSS frequency was changed each trial over a range of 2.4–1.0 log Hz (251–10 Hz) in a descending pattern of 0.2 log Hz steps. This was first done at the optimal current selected in initial training. For each curve tested, data from the rate-frequency curves were analyzed into three points. First, the point where the animal reached behavioral maximal response (MAX), the locus of rise (LOR), or frequency required to support half-MAX according to the broken-line methods and the dynamic interval which is found by subtracting the threshold score from the saturation score (5). Threshold is defined as the ICSS frequency where the lower asymptote intersects the rising or diagonal line. Saturation is defined similarly as the ICSS frequency where the rising diagonal intersects the upper asymptote (or MAX). LOR and the dynamic interval are considered to be measuring the reward aspects and MAX the motor performance aspect of the rate-frequency curve.

In the actual test, subjects were given complete rate-frequency curves at three different ICSS currents over a range of 2.7–2.3 log μAmps (501–200 μAmps) in 0.2 log μAmps steps. Order of current was ascending for half the subjects and descending for the other half. The entire experiment took about 1 h, with rate frequency curves starting at 20-min intervals. Behavioral testing was continued until the LOR and MAX were stable (less than 20% natural scale daily change, no trend) for 10 days at each current tested, after which drug testing was begun.

Data Analysis

After stabilizing behavioral response for 7 days, running baseline was taken before each drug test day. From this running baseline, difference scores were calculated for LOR, MAX, and the dynamic interval on the drug day (including vehicle day). In addition, analysis of variance (ANOVA) was performed with current and dose as within-subject factors for each drug treatment (cocaine or GBR-12909). Dunnet's test or Newman-Keuls post hoc analysis were used when appropriate. Data are displayed as differences from baseline at various drug doses and ICSS currents for LOR, MAX, and dynamic interval.

Histology

At the end of each experiment, subjects were sacrified with an overdose of Nembutal and perfused transcardially with isotonic saline followed by 10% formalin. Brains were later sectioned at 40 μm and examined to localize electrode placements.

RESULTS

Cocaine and GBR-12909 dose dependently decreased the average ICSS thresholds (dLOR) and did so without systematically different effects at different ICSS currents (Fig. 1). Cocaine and GBR-12909 did not significantly increase the average motor performance (dMAX), except at the low current where a dose-dependent increase was seen for cocaine (Fig. 2). In addition, cocaine and GBR-12909 had no systematic effects on the average dynamic interval except at the highest dose of cocaine which increased dynamic interval at all currents. Rate-frequency curves are shown for two representative animals that were given either cocaine or GBR-12909 (Fig. 4).

ANOVAs of GBR-12909 and cocaine dLOR scores from Fig. 1 found only an overall significant effect of dose respectively, $F(3, 55) = 3.68, p < 0.05$; $F(3, 77) = 6.24, p < 0.01$. In addition, no significant effects of ICSS current or current-dose interaction were found. Dunnet's test post hoc analysis for cocaine scores showed that the medium dose at all currents

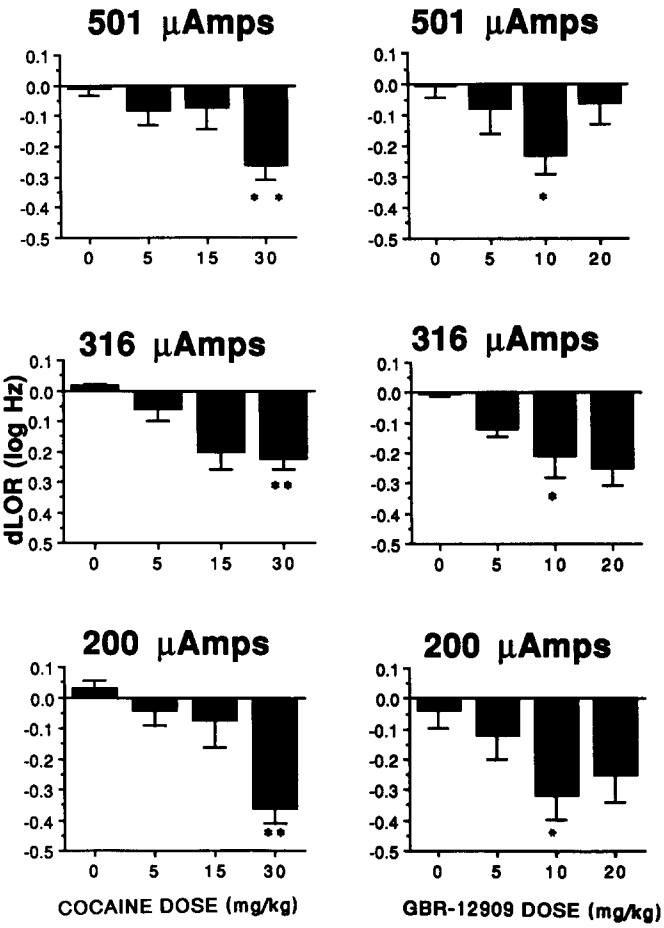

FIG. 1. The effects of saline vehicle and various IP doses of cocaine or GBR-12909 on ICSS reward threshold changes from baseline (dLOR) at three stimulation currents. Error bars represent the SEM of dLOR scores for each dose. $^{**}p < 0.01$ and $^{*}p < 0.05$, compared to saline.

reached statistical significance ($p < 0.05$). Also, Dunnet's test analysis of GBR-12909 data found the high dose to be significantly different from saline at all currents ($p < 0.01$).

ANOVAs for GBR-12909 and cocaine dMAX scores from Fig. 2, found factors of current and dose to be nonsignificant. However, for cocaine treatment, a significant interaction between current and dose effects on dMAX was found, $F(6, 36) = 2.42, p < 0.05$. To interpret this interaction, a simple main effect analysis was performed which showed significant differences only at low current. More specifically, Newman-Keuls analysis showed that at low current, the saline vehicle dMAX was significantly different from dMAX medium and high doses ($p < 0.05$).

ANOVA analysis of dynamic interval data in Fig. 3 show a significant effect of current, $F(2, 55) = 4.36, p < 0.05$, and dose, $F(3, 55) = 5.095, p < 0.05$, under cocaine treatment but not under GBR-12909 treatment. Dunnet's post hoc analysis of the dose factor showed the high dose of cocaine to be statistically significant at all currents. In addition, Newman-Keuls analysis of the current factor showed a trend ($p < 0.08$) when the medium and high currents where compared in this treatment.

Histological verification showed that the electrodes were located within the medial forebrain bundle at the level of the lateral hypothalamus.

DISCUSSION

Both GBR-12909 and cocaine treatments increased reward (decrease LOR) from ICSS in a rate-frequency paradigm as seen previously with cocaine in similar ICSS threshold procedures (7,10). With other results (29), these findings also establish an ICSS reward enhancing effect for GBR-12909, the more selective dopamine reuptake blocker (2,14). In addition, the present results are also consistent with a previous study, demonstrating a psychostimulant-like profile for GBR-12909 (16). Our findings further support the future use of GBR-12909 in studies investigating DA-mediated rewards.

Furthermore, the fact that the ICSS reward increases occurred without systematically different effects at different currents is a new finding. It suggests that future investigators interested in using the LOR reward measurement statistic of the rate-frequency curve need not be concerned with the exact choice of current in trying to avoid ceiling effects.

The significant effect of cocaine on dMAX scores only found at low current was somewhat surprising because psychostimulants are generally known to increase behavioral vigor in operant tasks as dose is increased. The MAX of the rate-frequency curve is associated with a number of variables

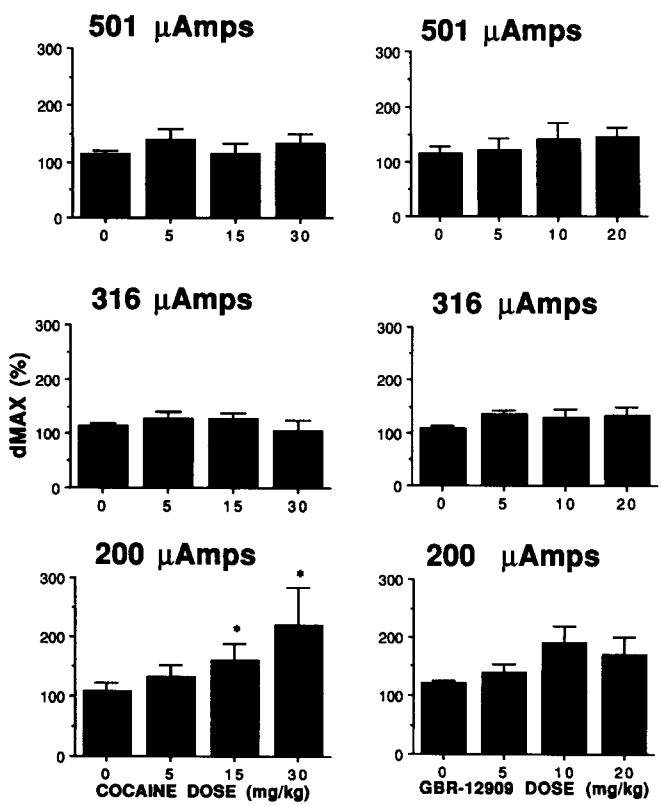

FIG. 2. The effects of saline vehicle and various IP doses of cocaine or GBR-12909 on motor performance changes from baseline (dMAX) at three stimulation currents (µAmps). Error bars represent the SEM of dMAX scores for each dose. $^{*}p < 0.05$, current × dose interaction compared to saline.

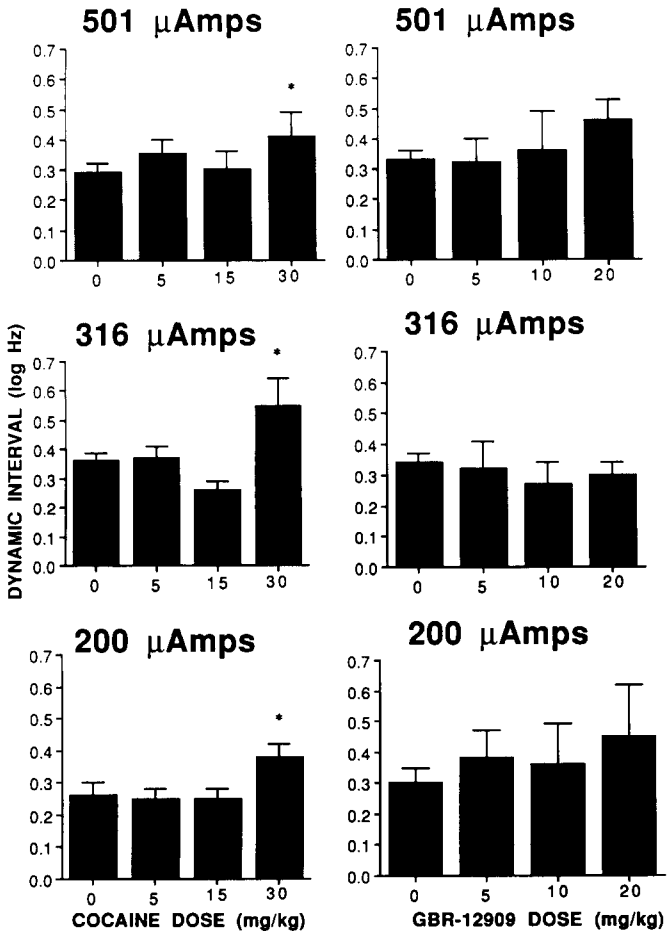

FIG. 3. The effects of saline vehicle and various IP doses of cocaine or GBR-12909 on the dynamic interval. Error bars represent the SEM for each dose.

reflective of behavioral vigor such as motor capacity, motivation, and task difficulty (35,37). One might suggest that the lack of an effect on dMAX is due to the fact that the MAX score is taken from rapid rate-operant responding at high ICSS pulse frequencies near the behavioral ceiling. However, inspection of individual data from Fig. 4 and our own analysis of the raw data suggest that even at low currents MAX is about the same as at high currents. In addition, DA agonists are known to produce stereotypical behaviors that may compete with increases in MAX, particularly at high doses. It is possible that the high currents combined with the cocaine produce greater dopamine release than low currents even though the higher frequencies used at lower currents brought response rate to the same operant behavioral levels. Such arguments will have to be addressed with multiple current, curve-shift, rate-frequency experiments of dopamine release and ICSS behavioral response.

When the dynamic interval scores were analyzed, the effects of the high dose of cocaine was statistically significant in all currents. As discussed previously, the dynamic interval of the rate-frequency curve is defined as the range of ICSS pulse frequencies over which the behavior rises from a minimal level (threshold frequency) to a maximal level (saturation frequency) (21). Under the simplest possible assumptions, the dynamic interval should not change as the rate-frequency curve shifts to lower stimulation pulse frequencies, provided that the drug only increases the effectiveness of the ICSS pulses and does not alter the basic rules by which the pulses are integrated to produce the reward effect. Under these circumstances, the LOR is an accurate and quantitative reflection of the alteration in effectiveness of ICSS pulses in producing the operant reward effects by the drug. However, if the dynamic interval is altered by the drug, then the fundamental rules of ICSS pulse integration are altered, and the LOR statistic contains a potential error. More to the point, by tracking the dynamic interval, one can make an estimate of the largest potential error in LOR measurement.

Within a test condition and excepting the highest dose of cocaine, the dynamic intervals fell within a range of variation about 0.1 Log Hz (Fig. 3). This was also the largest dynamic interval shift observed across ICSS currents in the baseline condition. These observations suggest the under the worst conditions where all the change in dynamic interval was absorbed by either the threshold or the saturation point alone, LOR would miss-estimate the true half-maximal threshold by at most 0.5 Log Hz. Generally, a LOR shift of 0.1 Log Hz is

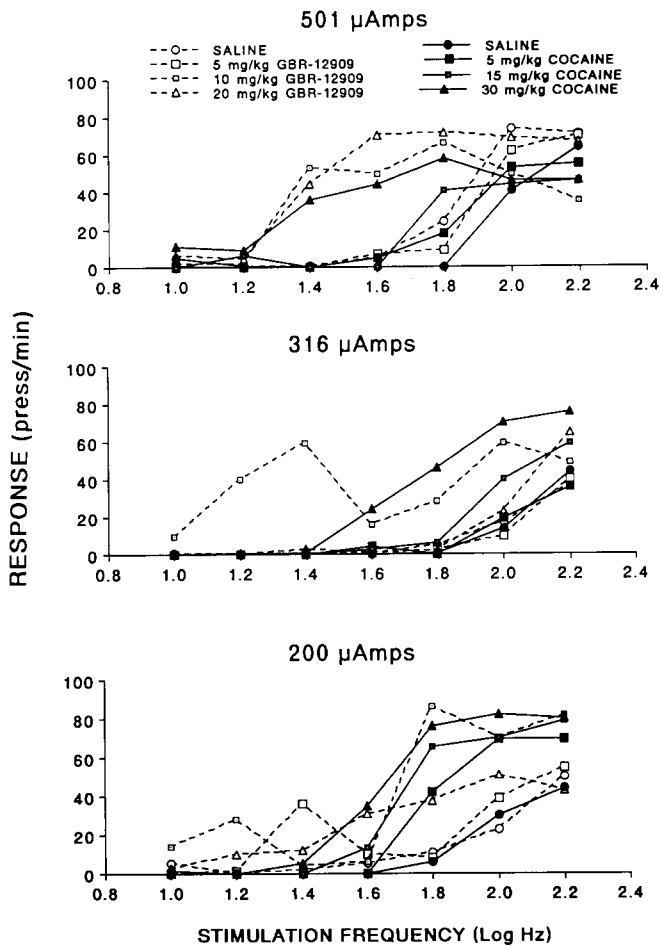

FIG. 4. Rate-frequency curves data at three stimulation currents (µAmps) of representative animals that were administered either GBR-12909 (open symbols and hatched lines) or cocaine (filled symbols and black lines) before ICSS testing.

considered the threshold of scientific interest (33). The worst case of a change in dynamic interval under drug conditions that could complicate LOR interpretation is the effect of the highest dose of cocaine at all ICSS currents in Fig. 3. Making the worst possible assumptions, LOR could miss-estimate the drug shift by 0.1 Log Hz or a bit less than half of the observed effect. Although the size of the potential error is considerable in this one case, the basic observation of psychostimulant-induced increases in ICSS reward is not threatened due to the consistency of other observations and the fact that these drugs can produce quite large LOR shifts with fairly little change in dynamic interval (e.g., the 10 mg/kg doses of GBR-12909 at all ICSS currents in Figs. 1 and 3). In the present study, we cannot strongly conclude that GBR-12909 was more potent than cocaine in affecting ICSS reward. Furthermore, our findings suggest that GBR-12909, when compared to the cocaine treatment, affected ICSS behavior, specifically dMAX and the dynamic interval scores, in a different manner. Previously, it has been shown that in vitro GBR-12909 is many times more potent than cocaine in blocking DA reuptake (2). However, another in vivo study using a different behavioral paradigm has shown that cocaine and GBR-12909 have similar potencies (3). The potency differences between in vitro and in vivo studies has been suggested to be due to the pharmokinetic properties of GBR-12909 (4), including its relatively poor penetration of the blood-brain barrier.

Taken together, the present results showed no evidence that the size of the ICSS reward effect produced by cocaine and GBR-12909 given acutely was dependent on the arbitrary choice of stimulation current over a range of 0.4 log μAmps. That is, these indirect DA agonists did not produce greater reward increases at lower or higher currents. The lack of apparent current dependency in this and another drug experiment (13) is important for neuropharmacological experiments in that a range of ICSS currents probably does not have to be tested to obtain an accurate estimate of the ICSS reward effects of dopaminergic drugs. However, higher doses of cocaine should be avoided, as they appear to significantly increase dynamic interval. At least dynamic interval should be measured in future studies. The overall finding with LOR scores makes the ICSS rate-frequency curve-shift test simpler and less cumbersome in psychostimulant drug studies.

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