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Effects of repeated GBR 12909 administration on brain stimulation reward

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Abstract

Male rats were trained at three separate currents to bar press for intracranial self-stimulation. On days 1 and 15, all subjects were given 1-(2-*bis*(4-fluorophenyl)-methoxy)-ethyl-4-(3-phenylpropyl) piperazine, also known as GBR 12909 (10 mg/kg, i.p.), prior to test session. Between these days, the paired Chronic-before group was injected (every other day) with GBR 12909 prior to intracranial self-stimulation, while unpaired, Chronic-after group was given the drug just after the end of the session. A third group (Control) received saline injections (i.p.) 20 min following the session. Although GBR 12909 was found to be reward enhancing, neither sensitization nor tolerance developed to the rewarding and performance/motor effects regardless of the injection regimen. In addition, the rewarding effects of intracranial self-stimulation were found to be independent of both current and environment-specific pairing. The present data obtained for GBR 12909 agree with previous observations of the effects of repeated administration of drugs of abuse on intracranial self-stimulation.

Keywords: Conditioning; GBR 12909; Reward; Self-stimulation

1. Introduction

1-(2-*bis*(4-Fluorophenyl)-methoxy)-ethyl-4-(3-phenylpropyl) piperazine (GBR 12909), has been proposed to constitute a putative "anti-cocaine" agent (e.g., Rothman and Glowa, 1995). Like cocaine, it binds to the dopamine transporter (DAT) at the terminal fields of the mesocorticolimbic pathway, where it inhibits the reuptake of dopamine leading to an increase in the extracellular concentration of dopamine (Baldo and Kelley, 1991; Phillips et al., 1989; Rothman et al., 1989, 1991; Westerink et al., 1987) and hence dopaminergic neurotransmission (Andersen, 1989; Carroll et al., 1992; Galloway, 1988; Heikkila and Manzino, 1984; Izenwasser et al., 1990; Kuhar et al., 1991; Lacey et al., 1990; Nissbrandt et al., 1991; Ritz et al., 1987; Rothman, 1990; Rothman et al., 1992). Thus, GBR 12909, akin to cocaine, produce reward-enhancing and locomotor-stimulating effects. Interestingly, a greater occupancy at the DAT, and thus a more potent inhibition of dopamine reuptake by GBR 12909 (IC_{50} = 4.3 nM), is needed to produce behavioral effects in comparison to those produced by cocaine (IC_{50} = 89 nM) at lower DAT occupancy (Hanson et al., 1997; Heikkila and Manzino, 1984; Rothman et al., 1992). Thus, a compound, such as GBR 12909 that is able to substantially occupy the DAT could reduce the reinforcing effects of cocaine and thus serve as a cocaine antagonist (e.g., Carroll et al., 1992; Rothman, 1990; Rothman and Glowa, 1995).

Behavioral studies showed that GBR 12909 and cocaine generalize to each other when rats are trained to discriminate either compound from saline (Cunningham and Callahan, 1991; Melia and Spealman, 1991; Ukai et al., 1993; Witkin et al., 1991; however, see also Tella et al., 1996). Short-term substitution of GBR 12909 for cocaine self-administration was found to occur in rats and monkeys (Bergman et al., 1989; Howell and Byrd, 1991; Roberts, 1993). Further, the reinforcing effects of both drugs were determined to be comparable, as demonstrated by a decrease in reward thresholds in intracranial self-stimulation paradigm (Maldonado-Irizarry et al., 1994).

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Since most drugs are administered chronically, it is pertinent to assess whether repeated administration of a given compound leads to long-term behavioral changes. These changes are often reflected in tolerance or sensitization, that is either a decrease or an increase, respectively, in the effectiveness (physiological or behavioral) of a given drug after chronic administration (Stewart and Badiani, 1993). Although sensitization to cocaine's reward-enhancing and locomotor-stimulating effects was reported following repeated treatment (Henry and White, 1991; Hooks et al., 1993; Kalivas and Duffy, 1990; Koff et al., 1994; Post and Rose, 1976), long-term effects of GBR 12909 have only been evaluated in relation to changes in locomotion. GBR 12909 has been generally found to be less potent than cocaine in enhancing locomotion (Rothman et al., 1992). For example, in comparison to vehicle-treated rats, an increase in locomotor activity (measured by photocell interruptions) was observed following the administration of a subthreshold dose of GBR 12909 (6 mg/kg, i.p.) on an every-other-day regimen with 20 mg/kg (i.p.) of GBR 12909 for 14 days (Baldo and Kelley, 1991; Kelley and Lang, 1989). Further, mixed evidence exists for cross-sensitization between GBR 12909 and cocaine (Baldo and Kelley, 1991; Steketee, 1998). A low dose of cocaine significantly increased locomotion, an index of sensitization, with prior GBR 12909 exposure (20 mg/kg, i.p. given every other day for 14 days) (Baldo and Kelley, 1991). However, sensitization that developed to a single injection of 40 mg/kg (i.p.) of cocaine did not generalize to GBR 12909-induced locomotion (Elmer et al., 1996).

Chronic effects of GBR 12909 on reward have not yet been assessed, but it was reported that GBR 12909 administered acutely at several doses decreases intracranial self-stimulation reward thresholds independently of performance variables (Kling-Petersen et al., 1994; Maldonado-Irizarry et al., 1994; Rompre and Bauco, 1990). This may not be surprising in light of the observation that GBR 12909 has generally been found to be less potent than cocaine in motor stimulating activity (Rothman et al., 1992).

The present study was therefore designed to examine the effects of repeated GBR 12909 administration on reward thresholds, by using a comparable dose and the same regimen that had previously produced locomotor sensitization (Baldo and Kelley, 1991; Kelley and Lang, 1989). The intracranial self-stimulation rate–frequency method was utilized (Campbell et al., 1985; Kling-Petersen and Svensson, 1993; Miliaressis et al., 1986; Stellar and Stellar, 1985; Wise and Rompre, 1989), which yields two measures: a maximum response rate, reflecting performance capacity, and a reward threshold, called locus of rise. The latter corresponds to the frequency at half-maximal rate of responding and is analogous to ED_{50} in behavioral pharmacology (Stellar and Stellar, 1985). Drug-induced changes were evaluated at multiple current intensities, because tolerance and/or sensitization may go undetected at only one current (Stellar et al., 1990; Wauquier and Niemegeers, 1974). Also, if the reward-enhancing effect of GBR 12909 is homologous to the locomotor activating effect of this drug, then repeated intracranial self-stimulation testing under GBR 12909 influence would result in further increases in measured reward (i.e., development of sensitization). In addition, it has previously been shown that behavioral effects of drugs are not only controlled by specific pharmacological properties, but also by the environmental conditions in which they are administered. For example, behavioral effects of either cocaine or amphetamine are enhanced when either drug is given in association with environmental novelty (e.g., Badiani et al., 1995a,b). For that reason, the potential effects of conditioning, either paired or unpaired, with the intracranial self-stimulation session, were also investigated.

2. Materials and methods

2.1. Animals

Adult male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA), weighing between 300 and 500 g, were housed individually in standard clear plastic home cages ($23 \times 41 \times 21$ cm) with food (Purina lab chow) and water available ad lib. The colony was set at a 12-h dark/12-h light reverse cycle (lights on at 1900 h). Thirty-nine rats were stereotaxically implanted under Sodium pentobarbital (60 mg/kg, i.p.) anesthesia with flat-cut monopolar, stainless steel electrodes (Plastics One). The stimulating electrode was aimed at the lateral hypothalamus at the following coordinates: AP -3.0 from bregma, ML -1.7 from midsaggital sinus and DV -7.5 from cortex (flat skull). A wire attached to the skull screws served as a ground connection for the electrode. Dental acrylic applied to both the electrode and skull screws secured the assembly to the skull. Antibiotic was topically applied to each rat daily for at least 2 weeks following surgery.

2.2. Apparatus

Based on published methods (Maldonado-Irizarry et al., 1994), subjects were placed in a standard one-lever operant box with a houselight mounted in the ceiling and a reinforcement light on the wall. Rats were connected to stimulation leads (Plastics One) and a commutator (Mercotac) which allowed free movement within the chamber. A Stimtek stimulator/microcontroller networked to an IBM PC-controlled the lights of the chamber, time of trials, parameters of stimulation and data collection.

2.3. Self-stimulation training

Approximately 2 days after electrode implantation, animals were trained to lever press on a continuous reinforce-

ment schedule set throughout the experiment at a 1.0-s burst of 0.1-ms square wave monophasic cathodal constant current pulses. Using a pulse frequency of either 100 or 158 Hz, stimulation current was adjusted to maximize the rate of responding while minimizing secondary effects of stimulation (i.e., vocalization, motor effect, retreat, freezing, etc.). After mastery of the continuous reinforcement schedule was achieved, rats were switched to a variable interval one (VI-1) schedule and gradually progressed to a final VI-3 schedule. Testing consisted of a series of 90-s trials. The stimulation frequency varied across trials. The first 30 s of each trial, serving as a period of adjustment, was discarded. A 10-s blackout of the chamber house light signaled the start of a new trial. The illumination of the reinforcement light marked the duration of brain stimulation delivery. Animals on the VI-3 s schedule were trained in a descending pattern of stimulation frequencies ranging from 2.4 to 1.0 log Hz (251–10 Hz) in 0.2 log Hz steps at the selected optimum current (that is the current that produced the most vigorous and consistent responding).

2.4. Procedure

Baseline rate–frequency curves were collected for three stimulation currents [low (200–316 μA), medium (316–501 μA) and high (501–794 μA)] delivered in 0.2 log μA steps. Within each group, order of the three currents was ascending for one-half of the subjects and descending for the other half. Each rate–frequency curve yielded two data points: the asymptotic maximal response rate and the locus of rise. Once stability was achieved (defined as less than 0.1 log Hz differences for locus of rise and less than 20% daily changes in maximal response rate for at least 7 days) the subjects were judged to be ready to receive 10 mg/kg GBR 12909, i.p. (Novo Nordisk, Denmark). The baseline frequency thresholds ranged between 1.90 and 2.05 log Hz (81–112 Hz) for "low" currents, 1.77–1.94 log HZ (59–87 Hz) for "medium" currents and 1.61–1.77 log Hz (41–59 Hz) for "high" currents. The drug was dissolved in heated distilled water and tartaric acid (five parts drug to one part acid). This specific dose was chosen, because it was previously found to induce a reliable leftward shift in locus of rise, that is a decrease in reward (Maldonado-Irizarry et al., 1994), without producing stereotypies that are often observed at higher doses (Baldo and Kelley, 1991).

Animals were randomly assigned to three groups: paired, Chronic-before ($n = 6$), unpaired, Chronic-after ($n = 5$) or Control ($n = 6$). All groups received 10 mg/kg of GBR 12909, administered systemically 20 min prior to intracranial self-stimulation on days 1 and 15. On days 3, 5, 7, 9, 11, and 13 the Chronic-before group continued to receive the same dose prior to testing. Animals in the Chronic-after and Control groups were injected with 10 mg/kg of GBR 12909 (i.p.), or saline (2 ml/kg, i.p.), respectively, 20 min after the termination of behavioral testing.

2.5. Data analysis

Locus of rise and maximum response rate data were gathered from at least 5 days of baseline (non-drug condition) and averaged for each rat at each current. All subsequent locus of rise data were defined as a difference from averaged baseline data (dLOR) and was calculated by subtracting baseline locus of rise value from the value obtained during the test day separately for each of the three experimental conditions. Difference in maximum response rate for each test day was defined as the percentage of the baseline data. Difference in locus of rise and maximum response rate were analyzed separately by performing experimental group (Chronic-before, Chronic-after, Control) by current (low, medium, high) by test day (1 through 15) repeated measures analysis of variance (ANOVA). Significant differences among relevant groups for both difference in locus of rise and difference in maximum response rates were further examined by performing Tukey's Protected t comparisons test (May et al., 1990).

2.6. Histology

Subjects were sacrificed with an overdose of Sodium pentobarbital (100 mg/ml) and perfused transcardially with isotonic saline followed by 10% formalin. Brains were sectioned at 40 μm, placed on gelatin-coated slides and stained with Cresyl violet for cell bodies, in order to determine the placement of electrodes.

3. Results

Electrode tips of all self-stimulating subjects included in the analyses were verified to be in the lateral hypothala-

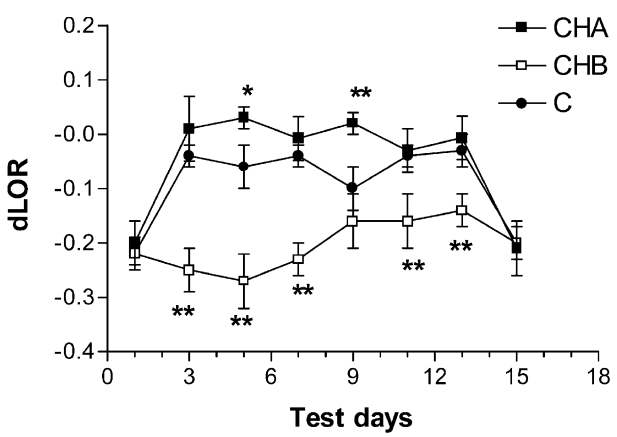

Fig. 1. Comparison of mean (±S.E.M.) difference in locus of rise for each experimental group, across all treatment days: Chronic-after (CHA), Chronic-before (CHB), saline Control (C). Same symbols indicate relevant group differences revealed by post-hoc analyses; $^{**}P < 0.01$, $^{*}P < 0.05$, different from all other groups on a specific test day.

mus and were located within the range of the following coordinates: −3.14 to −2.56 mm (AP), 1.5 to 2.0 mm (ML) and 7.5 to 8.5 mm (DV).

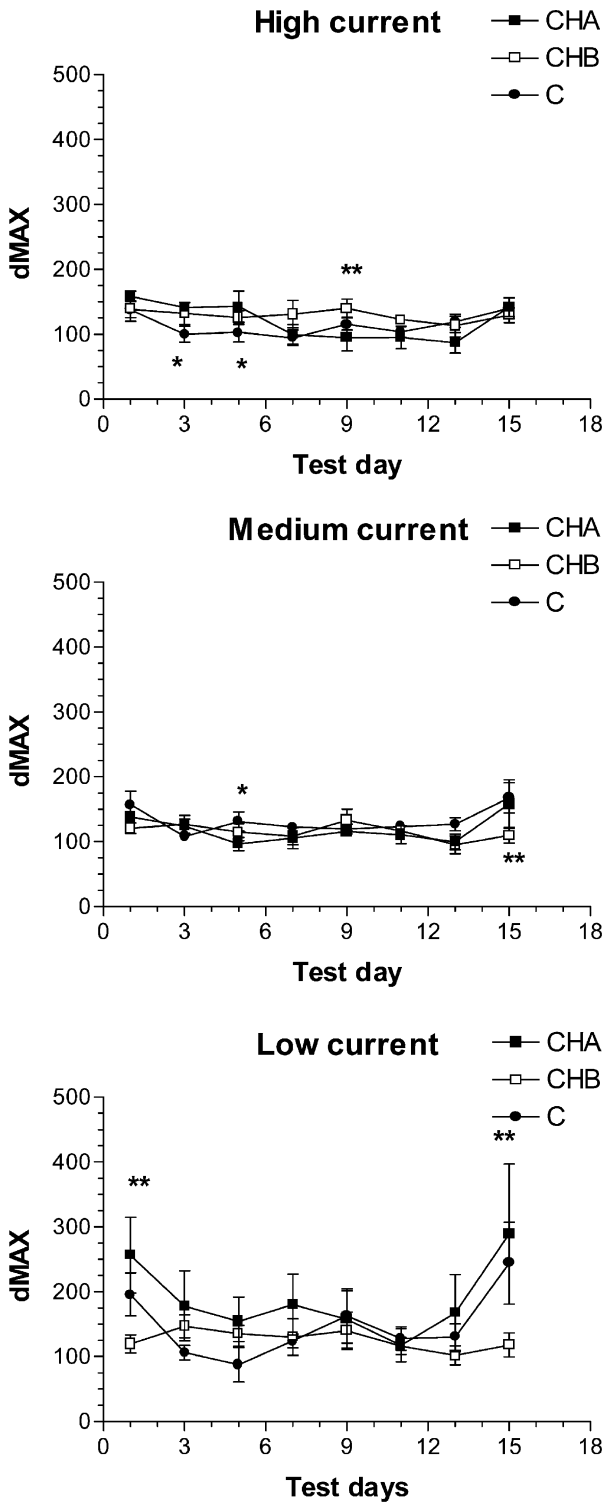

Fig. 2. Comparison of mean (±S.E.M.) difference in maximum response rate for each experimental group, across three currents; for legend refer to Fig. 1; $^{**}P < 0.01$; $^{*}P < 0.05$, different from all other groups on a specific test day.

3.1. Locus of rise

There was no effect of current and thus the data were collapsed across this variable. A main effect of group [$F(2,51) = 18.64$, $P < 0.0001$], test day [$F(7,357) = 11.68$, $P < 0.0001$], as well as an interaction between group and test day [$F(14,357) = 4.02$, $P < 0.0001$] were revealed. Post-hoc analyses (Fig. 1) revealed that in comparison to Control or Chronic-after groups, the Chronic-before group showed a significant decrease in the difference in locus of rise (increase in reward) on all, except 1, 9 and 15, test days. In addition, difference in locus of rise for the Control group was significantly greater than for the Chronic-after group on test days 5 and 9.

3.2. Maximum response rate

A significant main effect of current [$F(2,30) = 4.67$, $P < 0.05$] and test day [$F(7,105) = 6.26$, $P < 0.0001$] was found for difference in maximum response rates. In addition, there was a significant group by test day [$F(14,105) = 2.25$, $P < 0.05$], as well as current by test day interaction [$F(14,210) = 2.22$, $P < 0.01$]. Post-hoc analyses (Fig. 2) revealed that these interactions were due to the Control groups showing smaller difference in maximum response rates than the Chronic-after group on days 2 and 5 and Chronic-after than Chronic-before group on day 9 at high current. At medium current Control group showed higher difference in maximum response rates than Chronic-after on day 5 and the Chronic-after group larger than Chronic-before one on day 15. Finally, at low current Chronic-after group demonstrated higher difference in maximum response rates than Chronic-before on both days 1 and 15, when the injections were all given prior to a test session. There was no difference, however, between days 1 and 15 difference in maximum response rates data at any of the three currents.

In summary, for both the locus of rise and maximum rate of responding measures, the results indicate that even though occasional differences were observed among groups on days 3–13, no sensitization or tolerance was noted, as indicated by a comparison of days 1 and 15 data.

4. Discussion

Although repeated treatment with 10 mg/kg (i.p.) GBR 12909 enhanced reward (lowered locus of rise), there were no reliable differences from test days 1–15 on both the difference in locus of rise and difference in maximum response rates measures for the three groups, suggesting that neither sensitization nor tolerance had developed. These results are consistent with previous data, which demonstrated that in the intracranial self-stimulation paradigm there is no evidence of sensitization (or toler-

ance) following repeated treatment with cocaine (Frank et al., 1988; Bauco and Wise, 1997) and other drugs of abuse (Wise, 1996). There may hence not necessarily be a homology between sensitization of the locomotor activating effects of GBR 12909 and the rewarding effects of this compound (e.g., Robinson and Berridge, 1993). This hypothesis is based on the observation that no alterations in reward-enhancing effects of cocaine (as measured by intracranial self-stimulation) following repeated treatment were found (Bauco and Wise, 1997; Frank et al., 1988), yet such changes were noted when locomotion was measured (Henry and White, 1991; Hooks et al., 1993; Kalivas and Duffy, 1990; Koff et al., 1994; Post and Rose, 1976). This and our finding do not appear to support the psychomotor stimulant theory of addiction that would predict similar alteration in both the locomotor activating and intracranial self-stimulation reward-enhancing effects following repeated psychomotor stimulant treatment reflective of common biological substrates (Wise and Bozarth, 1987). Presumably, the mesolimbic dopamine system would be common to both effects. However, it is conceivable that exposure to intracranial self-stimulation leads to adaptations that may prevent further changes in the rewarding strength of drugs (Carlezon et al., 2000).

It is also entirely possible that the dose and/or a schedule of injection and testing could have contributed to the outcome of the present study. A GBR 12909 dose of 20 mg/kg (i.p.) administered using a similar schedule led to a sensitized response (increased locomotion), as measured by photocell interruptions (Baldo and Kelley, 1991). The evaluation of this dose was not possible in the present intracranial self-stimulation paradigm because stereotypic lever-pressing behavior tended to occur leading to unreliable difference in locus of rise and difference in maximum response rates measures.

The results on the reward-enhancing effect of GBR 12909, independent of the current intensity, are consistent with previous work in our (Maldonado-Irizarry et al., 1994) and other laboratories (Kling-Petersen and Svensson, 1993; Rompre and Bauco, 1990). Interestingly, receiving GBR 12909 or saline after the test session (Chronic-after group) was hedonically neutral, although less so for the Control (saline) group on test days 5 and 9. It is possible that the Chronic-after group learned to anticipate reward from GBR 12909 and therefore did not work as hard during the session to acquire reinforcement.

Although current intensity did not have an effect on difference in locus of rise values, it did alter difference in maximum response rates on some test days. The differences between groups on specific test days and current suggest that overall, the Control group showed lesser difference in maximum response rates, than the Chronic-after or Chronic-before groups at high current. In contrast, at the medium current, Control group demonstrated greater difference in maximum response rates than Chronic-after or Chronic-before. At low current the only difference that was revealed was between Chronic-after and Chronic-before groups on days 1 and 15, when treatment was identical in all groups. The reason for these slight differences in maximum response rate may lie in the observation that higher currents recruit more reward-relevant neurons, which can mask performance effects of the stimulation.

Context-specific pairing of intracranial self-stimulation and GBR 12909 effects was also not a contributing factor in the present study. The environment-specific cues did not reliably contribute to locus of rise and maximum response rate measures. If conditioning were important, then we would expect only the Chronic-before (paired) group, in which the acute GBR 12909 effects and Intracranial self-stimulation were coincident, to develop sensitization (or tolerance) to GBR 12909-induced reward and/or behavioral performance. The present data are inconsistent with studies that showed the development of sensitization to cocaine-induced locomotion, following specific pairing of cocaine's acute effects and the testing chamber (Badiani et al., 1995b; Hinson and Poulos, 1981; Kiyatkin, 1992; Post et al., 1981, 1987, 1992a,b). In addition, these findings are counter to the hypothesis proposed by Robinson and Berridge (1993), which states that associative learning enhances the incentive salience attributed to drug-associated stimuli. It is possible that sensitization to GBR 12909 might have been counteracted by habituation to the drug injection prior to test session in the Chronic-before group, whereas habituation in the Chronic-after group occurred without such drug effects. It has been proposed, however, that the extent of sensitization to a psychostimulant (or lack of thereof) can be determined by the behavior elicited by it rather than by the environment in which it was administered (Willner et al., 1992). Specifically, cocaine may act to block the exteroceptive stimuli from gaining access to the appropriate brain mechanisms (Damianopoulos and Carey, 1992), which may also apply to GBR 12909.

In conclusion, the present data do not support the homology between the development of sensitization to the locomotor activating effects and the reward-enhancing effects of repeated GBR 12909. The repeated intermittent treatment with GBR 12909 resulted in stable increases in reward (decrease in difference in locus of rise), but neither sensitization nor tolerance was observed to develop under the present intracranial self-stimulation paradigm, which may serve as a measure of the rewarding effects of GBR 12909 regardless of previous exposure to the compound. In this respect, the effects of GBR 12909 on intracranial self-stimulation appear to be similar to repeated cocaine treatment.

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