Pharmacology Biochemistry & Behavior, Vol. 40, pp. 969–975. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

RAPID COMMUNICATION

In Vivo Voltammetric Studies on Release Mechanisms for Cocaine With γ-Butyrolactone

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Received 28 August 1991

BRODERICK, P. A. *In vivo voltammetric studies on release mechanisms for cocaine with γ-butyrolactone.* PHARMACOL BIOCHEM BEHAV **40**(4) 969–975, 1991.—The effect of cocaine (20 mg/kg SC) on presynaptic mechanisms of release for dopamine (DA) and for serotonin (5-HT) was studied in nucleus accumbens of unrestrained rats (*Rattus norvegicus*). The studies were done by assaying synaptic concentrations of DA and 5-HT in the presence of the neuronal impulse flow inhibitor, γ-butyrolactone (γ-BL). The results were compared with cocaine effects on accumbens DA and 5-HT in the freely moving rat, without γ-BL treatment. A neurochemical time course profile showed that the cocaine-induced increase in accumbens synaptic concentrations of DA was significantly blocked ($p<0.0001$) after DA impulse flow was significantly inhibited ($p<0.0038$) by γ-BL (35.8%). The neurochemical time course profile concurrently showed that the cocaine-induced decrease in accumbens synaptic concentrations of 5-HT was significantly blocked ($p<0.0004$) after impulse flow was significantly inhibited ($p<0.025$) by γ-BL (50.6%). The findings show that cocaine's effects on synaptic concentrations for DA and for 5-HT in accumbens are dependent on neuronal impulse flow. The findings indicate that presynaptic releasing mechanisms, which may be different for DA vis-à-vis 5-HT, play a role in the mechanism of action of cocaine.

Cocaine Gamma-butyrolactone (γ-BL) Dopamine Serotonin Nucleus accumbens Freely moving rat
In vivo electrochemistry (voltammetry) Presynaptic release

THE complexity of the pharmacological effects of cocaine probably imply diverse actions. Nonetheless, a most compelling attribute for cocaine is its ability to induce reinforcement behavior. The potency of cocaine's reinforcing effects can readily lead to its self-administration and this is a phenomenon which has shown vulnerability across several species (1a, 13, 26, 28, 33). The hypothesis that a dopaminergic mesolimbic molecular component makes a significant contribution to the reinforcing properties of cocaine is generally well accepted (7, 12, 19, 24, 27, 28, 37). Moreover, evidence that cocaine increases mesolimbic synaptic concentrations of dopamine (DA) is abundant both from dialysis and in vivo voltammetric (electrochemical) studies (3, 7, 8, 10, 16, 18, 34). The most well known interpretation for these increased mesolimbic synaptic concentrations of DA is that cocaine is a DA reuptake inhibitor at the synapse. Importantly, it has been previously thought from in vitro studies that cocaine is either a weak but significant releaser of DA (31) or that cocaine simply does not release DA (15). However, because the process of reuptake inhibition is inherently interdependent on release mechanisms, this paper reexamined the possibility of a releasing mechanism of action for cocaine in vivo and on line in the unrestrained rat with in vivo voltammetry (electrochemistry). To do so, neuronal impulse flow was blocked by γ-butyrolactone (γ-BL), a compound known to inhibit neuronal impulse flow (35).

Interestingly, data are recently emerging to include a serotonergic manipulation by cocaine (11,17). Further data show that serotonin (5-HT) may mediate, at least in part, the reinforcing properties of cocaine and other psychomotor stimulants; the role of 5-HT however may exist in an inverse relationship to that of DA in reinforcement (7, 20, 25, 27). Thus a possible releasing mechanism for 5-HT was simultaneously studied in vivo and on-line with in vivo voltammetry using the γ-BL model.

METHOD

A series of studies, using the DA impulse blocker, γ-BL (750 mg/kg IP, corrected for density, 1.12 g/cc) were done to address the action of cocaine mechanistically. γ-BL is the lactone form of gamma-hydroxybutyrate (GHB), a naturally occurring CNS compound which has been shown to produce an anesthetic-like state, behavioral depression and EEG central excitation properties (38). γ-BL was used because it is quickly converted to GHB in plasma and liver and more uniformly distributed than is GHB (14). The effect of γ-BL is equivalent to axotomy (36).

The studies were done in unrestrained, freely moving male, Sprague-Dawley rats (390–440 g, Charles River, Kingston, NY). The animals were group housed and were fed Purina Rat Chow and water ad lib before surgery and individually housed (after surgery). A twelve-hour dark-light cycle was maintained both

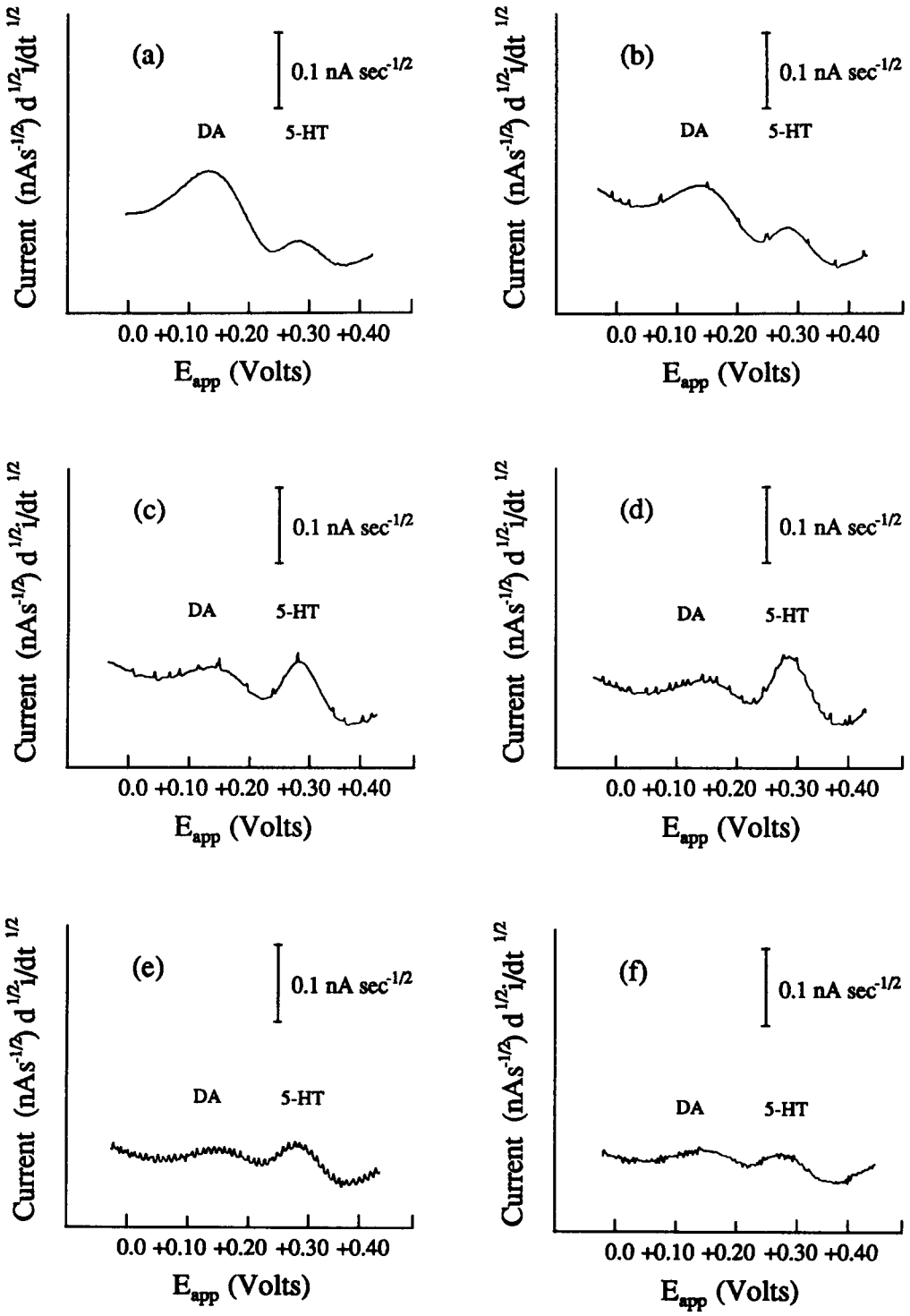

FIG. 1. Semidifferential voltammograms recorded in vivo, in nucleus accumbens in the unrestrained, male, virus free, Sprague-Dawley rat. The in vivo electrochemical signals for dopamine (DA) and for serotonin (5-HT) are representative of the group of animals studied (N = 5). Each voltammogram (same animal control) is depicted directly from raw data, by standard computer scanning techniques: (a) Basal DA and 5-HT signals in the behaving rat. (b) DA and 5-HT signals after γ-BL impulse flow block. (c) DA and 5-HT signals, one hour after cocaine administration (in the presence of the γ-BL impulse flow block). (d) DA and 5-HT signals, two hours after cocaine administration (in the presence of the γ-BL impulse flow block). (e) DA and 5-HT signals, three hours after cocaine administration (in the presence of the γ-BL impulse flow block). (f) DA and 5-HT signals, four hours after cocaine administration (in the presence of the γ-BL impulse flow block).

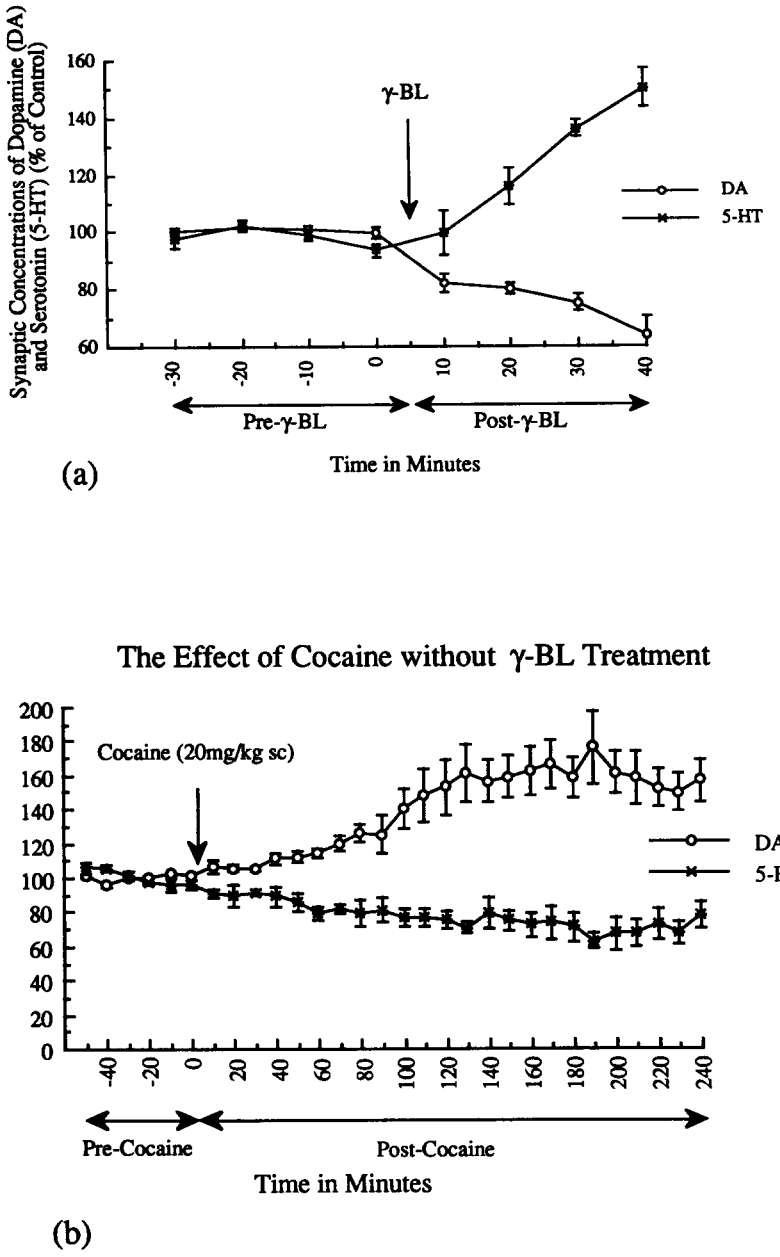

FIG. 2. (a) The effect of gamma-butyrolactone (γ-BL) (750 mg/kg IP, corrected for density: 1.12 g/cc) on basal (endogenous) synaptic concentrations of dopamine (DA) and serotonin (5-HT) in nucleus accumbens of unrestrained, male, virus-free, Sprague-Dawley rats. γ-BL significantly decreased synaptic concentrations of DA [ANOVA: $F(1,4)=36.326$, $p<0.0038$, $N=5$]. γ-BL significantly increased synaptic concentrations of 5-HT [ANOVA, $F(1,4)=12.229$, $p<0.025$, $N=5$]. (b) The effect of cocaine (20 mg/kg SC) on basal (endogenous) synaptic concentrations of DA and 5-HT in nucleus accumbens of unrestrained, male, virus-free, Sprague-Dawley rats ($N=6$, 4 respectively). Cocaine significantly increased synaptic DA concentrations [ANOVA: $F(4,20)=73.047$, $p<0.0001$, $N=6$] and significantly decreased synaptic 5-HT concentrations [ANOVA: $F(4,20)=50.044$, $p<0.0001$, $N=4$].

during the housing of the rats and throughout the experimental studies. The rats were virus-free; the specific viral tests, which the animals underwent, included: Sendai Virus, Kilham Rat Virus, Reo Virus Type 3, Sialodacryoadenitis Virus, Rat Corona Virus, Toolan's H1 Virus, Micro Plasma Pulmonis Virus, Lymphocytic Choriomeningitis Virus, Hantaan Virus and Encephalitozoon Cuniculi Virus.

Rats were anesthetized with pentobarbital Na (50 mg/kg IP). Booster injections of pentobarbital Na were administered once after the first two hours of surgery (0.10 cc) and once every

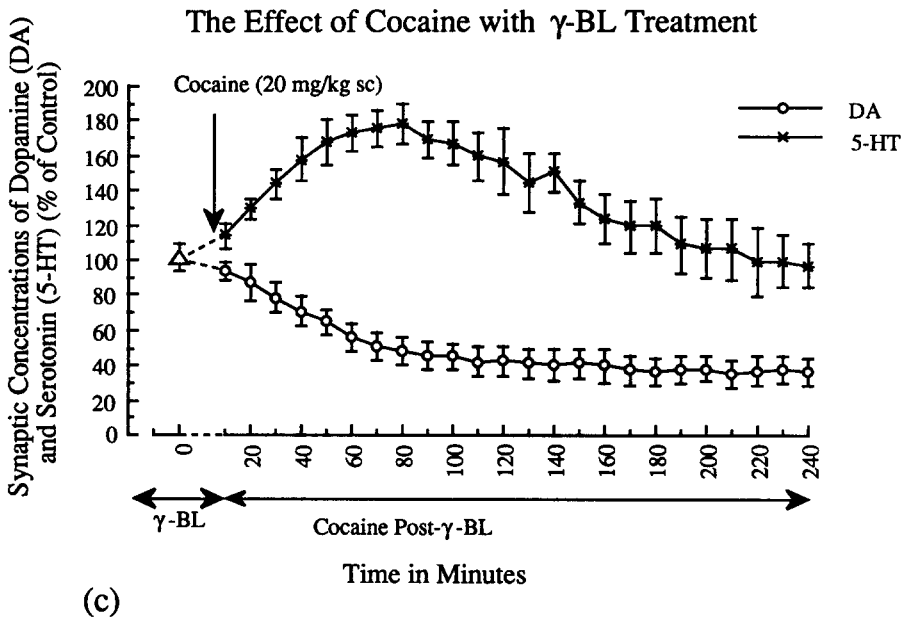

FIG. 2. (c) The effect of cocaine (20 mg/kg SC) on synaptic concentrations of DA and 5-HT in nucleus accumbens of unrestrained, male, virus-free, Sprague-Dawley rats (N=5), when neuronal impulse flow was significantly inhibited by γ-BL. Synaptic concentrations of accumbens DA significantly decreased [ANOVA: $F(4,20)=121.502$, $p<0.0001$, N=5] and synaptic concentrations of accumbens 5-HT significantly increased [ANOVA: $F(4,20)=25.451$, $p<0.0001$, N=5] in γ-BL-treated rats.

subsequent hour (0.05 cc) to maintain an adequate level of anesthesia throughout surgery, i.e., to maintain, e.g., an absence of corneal and pinnal reflexes. Rats were stereotaxically implanted with stearate working electrodes in nucleus accumbens (AP = −2.6, ML = +2.5, DV = −7.3) (23). Stereotaxic equipment was purchased from Kopf Stereotaxic, Tujunga, CA. Working electrodes were inserted at a rate of 0.5 mm, every five minutes. Body temperature was continuously monitored with a rectal probe and thermometer (Fisher Scientific, Fadem, NJ) and was maintained at 37±0.5°C with an aquamatic K module heating pad (American Hospital Supply, Edison, NJ). Ag/AgCl reference electrodes and stainless steel auxiliary electrodes were placed in contact with cortex. The total time for the surgical procedure was three to four hours. The working, reference and auxiliary microelectrodes were held in place with dental acrylic (Kadon Cavity Liner, Caulk, Becker Parkin Dental Supply Co. Inc., NY). The fabrication of each type of electrode in the in vivo electrochemical (voltammetric) three-electrode assembly is taught in previous publications (5,7). Preconcentration steps (conditioning) of the working electrode is also taught in a previous publication (5) and methods to determine the composition of the electrode paste mixture is also taught and previously published (6). The coulombic efficiency for the detection of DA vis-à-vis 5-HT with a stearate working electrode is previously described (4). Precalibration and postcalibration procedures were also done as previously described (7). Animals recovered in an appropriately bedded Plexiglas cage (dimensions: 12″×12″×18″) after surgery and before the experimental studies began. Animals were treated with physiological saline (0.5 cc) immediately and for two days after surgery. Each animal was treated with care throughout the surgical procedure and throughout the studies.

In vivo voltammetric (semidifferential) studies on conscious rats were begun approximately nine to fourteen days after the aseptic surgical procedures were performed. On each experimental day, an animal was placed in a Plexiglas chamber within a faraday cage (dimensions: 24″×18″×23.5″). The three electrode assembly, enclosed within the animal's prosthetic acrylic cap, was connected to a CV37 detector (BAS, West Lafayette, IN) by means of a mercury commutator (Brain Research Instruments, Princeton, NJ), a flexible cable and a mating connector (BJM Electronics, Staten Island, NY). The CV37 was electrically connected to a Minigard surge suppressor (Jefferson Electric, Magnetek, NY) which was then connected to an isolated electrical ground. Stable in vivo electrochemical signals for DA and 5-HT were evident before either γ-BL [750 mg/kg IP, corrected for density (1.12 g/cc)] or cocaine (20 mg/kg SC) were administered. γ-BL was purchased in liquid form from Sigma, St. Louis, MO. Cocaine (Sigma, St. Louis, MO) was dissolved in deionized (resistance 5 MΩ) organic free water. Solutions were made fresh on the day of each study. The effect of γ-BL on DA and 5-HT neurotransmission without cocaine administration was studied for forty minutes in keeping with its reported maximal effect (36). The effect of γ-BL on the action of cocaine on DA and 5-HT was studied for 4 hours after cocaine injection, also in keeping with a previous report (7).

Statistically significant changes after γ-BL on DA and 5-HT synaptic concentrations in nucleus accumbens were determined by standard repeated measures, analysis of variance (ANOVA) (Statview, Brain Power Inc., Calabasas, CA). Statistically significant differences between the effects of cocaine on DA and on 5-HT, without impulse flow inhibition by γ-BL, and those after impulse flow inhibition, were also determined by ANOVA. Confidence Limits (95%) measures were also performed on each point of the time course data following administration of drug. Results are expressed as % of control to minimize between animal variations. Each animal was studied as its own control. Basal DA detection limits, as low as 13 nM and basal 5-HT detection limits, as low as 2 nM are currently possible.

Histological placements of working electrodes in nucleus accumbens were confirmed by the potassium ferrocyanide blue dot

method (specifications: current 50 μA, time in seconds, 30). Virtually no damage to brain tissue occurred.

RESULTS

An in vivo semidifferential voltammogram showing the detection of the electroactive species for DA and for 5-HT in nucleus accumbens in the unrestrained animal is shown in Fig. 1a. The neurochemical profile consists of the concurrent and separate detection of DA at 0.14 ± 0.015 V and 5-HT at 0.29 ± 0.015 V. The percent baseline values for DA and 5-HT did not vary more than 10% around the mean. The in vivo electrochemical signals for DA and 5-HT were distinct. The dopamine metabolites, 3–4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) and the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) were not detected at the same oxidation potentials as those for either DA or 5-HT. The same tenet holds for the possible interfering chemicals, ascorbic acid and uric acid. Figure 1b shows the representative effect of γ-BL on synaptic concentrations of DA and 5-HT in nucleus accumbens of the same animal, at the time at which DA impulse flow was significantly inhibited ($p<0.05$) by 35.8% and 5-HT impulse flow was significantly inhibited ($p<0.05$) by 50.6%. A distinctive electroencephalographic (EEG) spike discharge pattern occurred in each of the DA and 5-HT in vivo electrochemical signals.Very interestingly, the EEG pattern, induced by synaptic currents, exhibited a reproducible rate constancy, both within same animal studies, in addition to between animal studies, after γ-BL. Figure 1c–f show the effect of cocaine on γ-BL induced signals for DA and 5-HT in nucleus accumbens. EEG patterns are evident; the frequency of the spike discharges has changed. The action of cocaine on the in vivo electrochemical signal for both DA and 5-HT is concurrently blocked by the administration of the impulse flow inhibitor, γ-BL.

Figure 2a is a line graph showing the effect of γ-BL on synaptic concentrations of DA and 5-HT in nucleus accumbens. γ-BL significantly decreased [ANOVA: $F(1,4)=36.326$, $p<0.0038$, $N=5$] synaptic concentrations of DA by 35.8%. The effect began to occur significantly (18.0%, $p<0.05$) between one and ten minutes. Synaptic concentrations of 5-HT significantly increased [ANOVA: $F(1,4)=12.229$, $p<0.025$, $N=5$] by 50.6% after γ-BL administration. The effect began to occur significantly (15.8%, $p<0.05$) between ten and twenty minutes after γ-BL injection.

Figure 2b shows the effects of cocaine on synaptic concentrations of DA and 5-HT without γ-BL treatment. Cocaine (20 mg/kg SC) significantly increased DA [ANOVA: $F(4,20)=73.047$, $p<0.0001$, $N=6$] above basal same animal control values and significantly decreased 5-HT [ANOVA: $F(4,20)=50.044$, $p<0.0001$, $N=4$] below basal values (same animal control). Synaptic concentrations of DA increased maximally to 176.25% of control ($p<0.05$) and this occurred 190 minutes after injection of cocaine. Analysis of the electrochemical signal showed a trend towards baseline in the 4th hour (approximately 50% of the animals had a DA signal returning to baseline). At the 20 mg/kg SC dose of cocaine, those DA synaptic concentrations that did not return in the fourth hour to baseline, did so during the fifth hour (data not shown). Synaptic concentrations of 5-HT reached a maximum decrease to 62.81% of control ($p<0.05$) at 190 minutes and returned to baseline values (100%) in the 4th hour.

Figure 2c shows the effect of synaptic concentrations of DA and 5-HT when DA impulse flow has been significantly blocked ($p<0.0038$) and 5-HT impulse flow has been significantly blocked ($p<0.025$) by γ-BL. Cocaine (20 mg/kg SC) after γ-BL treatment, significantly decreased DA [ANOVA: $F(4,20)=121.502$, $p<0.0001$, $N=5$] below basal same animal control values and significantly increased 5-HT [ANOVA: $F(4,20)=25.451$, $p<0.0001$, $N=5$] above basal same animal control values. Synaptic concentrations of DA decreased to 36.7% of control ($p<0.05$) and this occurred 180 minutes after injection of cocaine. Synaptic concentrations of 5-HT reached a maximum increase to 178.0% of control ($p<0.05$) at 80 minutes and returned to baseline values (100%) in the 4th hour.

DISCUSSION

γ-BL is a known impulse flow inhibitor; γ-BL effectively creates what is equivalent to a lesion or axotomy of DA neurons in neuronal terminals of nigrostriatal and mesolimbic neuroanatomical substrates (1, 35, 36). When γ-BL was shown to block neuronal impulse flow, both DA levels postmortem and DA synthesis were increased (14). Moreover, these γ-BL effects were accompanied by a protection from the expected disappearance of DA in the presence of the DA depletor, α-methylparatyrosine (αmpt) (29). Thus the prediction about the ability of an axotomized DA neuron, to cause decreased DA release, consequent to a DA presynaptic regulation, was hypothesized (36). The present findings are consistent with this hypothesis. The data presented here show a significantly decreased in vivo electrochemical signal for DA in nucleus accumbens in the unrestrained rat after intraperitoneal γ-BL administration. Release mechanisms are clear because the decreased in vivo electrochemical DA signal is inconsistent with known γ-BL-induced increased DA levels, postmortem (1, 14, 29). Moreover, release mechanisms are clear because the decreased in vivo electrochemical DA is inconsistent with known γ-BL-induced increased DA synthesis (36). The occurrence of EEG spike discharges in γ-BL voltammograms is consistent with the action of γ-BL in seizure activity (38). Finally, this paper presents new findings that γ-BL-induced EEG changes can be directly detected in vivo and voltammetrically, with a rate constancy.

Ample evidence exists to show that the psychomotor stimulant, cocaine, increases synaptic concentrations of DA in mesolimbic neuronal circuitry and that this cocaine-induced alteration in the DA pathway is correlated with the reinforcing capability of cocaine. The present paper shows, however, that when cocaine was administered in the presence of the impulse flow inhibitor, γ-BL, the in vivo electrochemical for DA was reversed. Since γ-BL per se caused a decreased DA release, the net result of impulse flow inhibition on the action of cocaine-induced DA changes, was essentially a complete block of the DA response to cocaine. Thus the action of cocaine is dependent on impulse flow, indicating that a release mechanism for DA is important. These data are in agreement with others (2,8). Taken together with other studies, which show that cocaine's action is inhibited by blocking sodium channels (21) and by blocking calcium channels (22), the hypothesis that cocaine's mechanism of action involves a releasing mechanism, becomes stronger. The significance of the data lies in the consideration that the action of cocaine on DA neurons inherently depends on the intact activity of DA neurons and on the amount of DA available at the synapse. Such a consideration may highlight the concept of using tight binding DA reuptake inhibitors for cocaine treatment strategies (30). Importantly, these findings that cocaine acts directly on a presynaptic terminal mechanism of release for cocaine [reportedly, vesicular (31)], support the view that vesicular

release of DA by cocaine provides protection from gross neuronal pathologies (32).

In the γ-BL model, as previously reported (35,36), the effects of γ-BL impulse flow inhibition on 5-HT levels postmortem and on 5-HT synthesis were markedly different from the reported DA effects, as seen both in the same predominantly DA neuronal circuitry (14) or in predominantly 5-HT circuitry (9). Neither of these 5-HT parameters was significantly affected by either γ-BL treatment or by lesioning. Whereas the γ-BL model predicted that axotomy would decrease DA release, any prediction for presynaptic 5-HT mechanisms had remained undelineated. This paper presents new findings which show that γ-BL significantly increased synaptic concentrations of 5-HT. The results are reconcilable with presynaptic release, if one possible explanation is an impulse independent release mechanism. Another explanation may be a resultant unmasking of 5-HT reuptake inhibition consequent to release inhibition. Alternatively, 5-HT storage mechanisms may be affected.

Cocaine was unable to exert its decreased modulation on 5-HT neurons in nucleus accumbens in the presence of γ-BL in the unrestrained rat. In the presence of γ-BL, the in vivo electrochemical signal for 5-HT was completely reversed. Since γ-BL per se increased 5-HT, the net result was essentially a blockade of cocaine action. Thus this paper presents evidence that cocaine's mechanism of action depends on an intact 5-HT neuronal circuitry. The significance of the data is conceptually similar to that for DA. The action of cocaine on 5-HT is dependent on the amount of 5-HT at the synapse. Therefore, the consequent implications for reuptake inhibitory processes, for genetic vulnerability, for neuronal autoregulation and for differences in gross neuropathology, apply as well. This opens enormous possibilities for tactical manipulation of the synapse in the treatment of cocaine dysfunction.

ACKNOWLEDGEMENTS

This research was supported by NIDA Award #R01-04755 and by PSC/CUNY Award No. 6-61188 to P. A. Broderick. Excellent research assistance was provided by Frankie Eng, Frank Phelan and Robert Wechsler.

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