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RAPID COMMUNICATION

Real Time Detection of Acute (IP) Cocaine-Enhanced Dopamine and Serotonin Release in Ventrolateral Nucleus Accumbens of the Behaving Norway Rat

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BRODERICK, P. A., E. P. KORNAK, JR., F. ENG AND R. T. WECHSLER. Real time detection of acute (IP) cocaine-enhanced dopamine and serotonin release in ventrolateral nucleus accumbens of the behaving Norway rat. PHARMA-COL BIOCHEM BEHAV 46(3) 715-722, 1993.—Cocaine (10 mg/kg), administered intraperitoneal (IP), was studied for its effects on dopamine (DA) and serotonin (5-HT) release in ventrolateral nucleus accumbens (vlNAcc) of conscious and behaving male, virus-free, Sprague-Dawley rats with in vivo electrochemistry (voltammetry). Miniature stearate probes detected DA and 5-HT release, on line and within a temporal resolution of seconds. Psychostimulant behaviors, in the form of four behavioral components (i.e., the classically DA-dependent behaviors of locomotor activity [ambulations], rearing, and stereotypy, and a 5-HT-ergic behavior, central ambulations) were studied concurrently with infrared photobeam detection. The results show that (IP) cocaine significantly increased vlNAcc DA release (p < 0.0001) and 5-HT release (p < 0.0012). Each of the four parameters of cocaine-induced psychostimulant behavior was concurrently and significantly increased as well (ambulations: p < 0.0001; rearing: p < 0.0008; stereotypy: p < 0.0004; central ambulations: p < 0.0082). Moreover, exactly coincident data points for DA and 5-HT release occurred 10 and 40 min after (IP) cocaine administration. Cocaine-induced DA and 5-HT release were highly and positively correlated during the first hour of study (p < 0.01). As expected, increased DA release in vlNAcc after cocaine administration was significantly and positively correlated with classically DA-dependent behaviors (first- and second-hour effects) (p < 0.01) and with the 5-HT-ergic behavior, central ambulations (p < 0.01). Also, cocaine-induced 5-HT release was significantly and positively correlated with 5-HT behavior (p < 0.01). However, not as expected, classically DA-dependent behaviors were positively correlated with cocaine-induced 5-HT release in vlNAcc throughout the two-hour period of study. Thus, the present findings show that 5-HT is a comediator with DA in the cocaine response in vlNAcc. Importantly, 5-HT may signal the known DA response to cocaine.

Cocaine
Psychostimulant behavior
In vivo electrochemistry (voltammetry)
Dopamine
Serotonin
Ventrolateral nucleus accumbens (vlNAcc)
Anxiety
Agoraphobia

THE relevance of A10 nucleus accumbens (NAcc) dopaminergic (DAergic) function to brain reward seems sufficiently explicit. Particularly, in paradigms of classical self-stimulation reinforcement phenomena two distinct models for the neuronal modus operandi of DA in the acute reinforcement process have been proposed. The first has been called "the two neuron" model, in which descending medial forebrain bundle (MFB) fibres synapse in A10 somatodendrites, ventral tegmental area (VTA), and subsequently give rise to ascending projections to NAcc. In this model, DA fibres may directly carry
Animals

Ronavirus, Toolan's H1 Virus, Micro Plasma Pulmonis Virus, Reo Virus Type 3, Sialodacryoadenitis Virus, Rat Co- and water ad lib and were group housed before surgery and behavioral studies). The animals were fed Purina Rat Chow free from the following viruses: Sendai Virus, Kilham Rat and throughout the experimental studies. The rats were tested individually housed after surgery. A 12-h dark/light cycle range 362-446 g at the time of the in vivo electrochemical and Sprague-Dawley rats (Charles River, Kingston, NY) (weight determination of its consequent acute behavioral (37) and neurochemical effects (9). Moreover, release mechanisms are primarily addressed. Previous studies have shown that cocaine's neurochemical effects are dependent on impulse flow (7, 12, 24). Cocaine utilizes release (41) as well as reuptake inhibitory processes (50) presynaptically.

MATERIALS AND METHODS

Animals

The studies were done in unrestrained freely moving male Sprague–Dawley rats (Charles River, Kingston, NY) (weight range 362–446 g at the time of the in vivo electrochemical and behavioral studies). The animals were fed Purina Rat Chow and water ad lib and were group housed before surgery and individually housed after surgery. A 12-h dark/light cycle was maintained both during the housing of the laboratory rats and throughout the experimental studies. The rats were tested free from the following viruses: 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 Encephalitoxozone Cuniculi Virus.

Surgery

Pentobarbital Na (50 mg/kg IP) was the general anesthetic employed to produce surgical anesthesia. A booster injection of pentobarbital Na (0.10 cc of the same solution) was administered once after the first two hours of surgery, and another booster (0.05 cc) was administered each of the two subsequent hours of surgery to maintain adequate anesthesia. Rats were tested for an absence of corneal, pinna, and leg flexion responses. Body temperature was continuously monitored with a rectal probe 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). Rats were stereotaxically implanted with stainless steel auxiliary microelectrodes and were placed in contact with cortex. The working (indicator), reference, and auxiliary microelectrodes were placed in plastic and in two days after surgery. Each animal was treated with care throughout the surgical procedures and the studies.

In Vivo Electrochemical (Voltammetric) Biotechnology

The methods for the manufacture of each of the three in vivo electrochemical microelectrodes have been published by this laboratory (4). The methodology previously described includes the conditioning or preconcentration steps for the working microelectrode and the specifications for the formulation and synthesis of the stearic acid carbon paste. A review of the historical and technical aspects of the field of in vivo electrochemistry is referenced (5). Electrocatalytic interactions between DA and ascorbic acid (AA) have been reported with a stearic acid macroelectrode in vitro (25), but more recent reports show that these interactions are insignificant in neuronal tissue in vivo when a stearic acid microelectrode is used (2). Precalibration and postcalibration procedures were done as previously described (6).

In vivo voltammetric (semiderivative) studies on conscious rats were begun approximately 9 to 14 days after the aseptic surgical procedures were performed. On each experimental day, an animal was placed in a faradic, Plexiglas chamber (24° × 18° × 23.5°). The three-microelectrode 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 cocaine (10 mg/kg IP) was administered. Cocaine (Sigma, St. Louis) was dissolved in doubly distilled water, and solutions were made fresh on the day of each study.

Behavior

On each day of the cocaine study, each animal was placed in the faradic copper-enclosed Plexiglas chamber described above. The behavioral chamber was novel to each animal, although each animal was habituated (i.e., had essentially completed exploratory behavior) before cocaine injection. Moreover, the behavioral chamber was equipped with side by
side double doors (W 15.75" × H 16") to enable a facile injection procedure. A series of infrared photobeams was encased in aluminum frames around the chamber's perimeter. When activated with an IBM computerized circuit, these infrared photobeams detected the animal's position in the behavioral chamber on an X–Y axes positional basis. Thus, multiple concurrent measures of the animal's activity were simultaneously assessed. The specific activities of each animal assayed were the "classically DA-dependent" behaviors—that is, 1) ambulations (locomotor activity or running ("running") is forward locomotion interacting with the maintenance of a horizontal position of the head, without lateral turning (61)), 2) rearing behavior (maximal upward vertical movement of the head involving recruitment of the body, without any forward or lateral movement (61)), 3) fine movements (combined stereotypic movements of head bob, sniffing, and grooming)—in addition to a 5-HT-ergic behavior, and 4) central ambulations (locomotor activity into the central part of the chamber). [Central ambulatory behavior is called agoraphobic (thigmotactic) inhibition and indicates reduced fear on the part of the animal (26)]. The status of the infrared photobeams was sampled every 100 ms. The system is a modified version of an Activity Pattern Monitor (San Diego Instruments, San Diego). Data were collected as measures of concurrent and separate activities for 10-min time periods.

Confirmation of Microelectrode Placement

Following the completion of the study, the prosthetic acrylic cap was removed from the skull while the animal was under Na pentobarbital anesthesia. Placement of working microelectrodes in vlNAcc was confirmed by the potassium ferrocyanide in 10% formalin blue dot method with transcardial perfusion (80 ml saline). The precise electrical specifications for deposition of the blue dot in vlNAcc was 50 μA current in a 30-s time period. Virtually no damage to brain tissue occurred. The working microelectrode was postcalibrated for in vitro electrochemical detection of DA and 5-HT.

Statistics

Each component of the psychostimulant behavior monitored, in addition to DA and 5-HT release assayed, was tested for statistically significant differences between pre- and post-cocaine (10 mg/kg IP) (same animal control) by standard repeated-measures analysis of variance (ANOVA) (Statview, Brain Power Inc., Calabasas, CA). ANOVAs were followed by post hoc tests, Fisher PLSDs (least square differences), and the Scheffe F test (Statview, Brain Power Inc.) to determine hourly statistically significant differences. Statistically significant differences were also calculated on the individual time course data points by 95% confidence limits (95% CL), setting the p value at p < 0.05. Changes in DA and 5-HT values after (IP) cocaine treatment vis à vis untreated (same animal) controls are presented as percent change, whereas behavioral data are presented as frequency or number of behavioral events. Control is represented as 100%.

Since the actual detection time for DA is 10–15 s, the percent change in synaptic concentrations of DA at each data point post-cocaine represents a current measurement within the same discrete synaptic environment as that for DA, within vlNAcc within a 10–13-s time period.

Finally, cocaine-induced DA and 5-HT release in vlNAcc and consequent psychostimulant behavior were studied for statistically significant correlative value by the Pearson product–moment coefficient of correlation (r), simple and polynomial regression (Statview, Brain Power Inc.); corresponding z values were derived from the table of z for values of r from 0.0 to 1.0.

RESULTS

Figure 1 shows the effect of cocaine (10 mg/kg IP) on synaptic concentrations of DA and 5-HT in the vlNAcc. Cocaine (10 mg/kg IP) significantly increased the in vivo electrochemical signal for DA, F(2, 10) = 96.604, p < 0.0001, N = 6. Post hoc analysis further shows that there were statistically significant differences from baseline in each hour of the two hours tested (Fisher PLSD = 4.852, Scheffe F = 33.062 and 95.616, first and second hours respectively). Dopamine release was significantly increased 110% (p < 0.05, 95% CL) over baseline within 10 min and was maximally increased 136% (p < 0.05, 95% CL) over baseline within 90 min after cocaine administration (baseline = 100%).

Also in Fig. 1, cocaine (10 mg/kg IP) simultaneously and significantly increased the in vivo electrochemical signal for 5-HT, F(2, 10) = 14.135, p < 0.0012, N = 6. Post hoc analysis further shows that there were statistically significant differences from baseline in the first hour of study (Fisher PLSD = 6.048, Scheffe F = 13.125 and 0.886, first and second hours respectively). 5-HT was significantly increased to 108% (p < 0.05, 95% CL) over baseline (100%) within 10 min and was maximally increased to 123% (p < 0.05, 95% CL) over baseline within 40 min after cocaine administration.

Moreover, cocaine's colocalized effects on DA and 5-HT release in vlNAcc were significantly and positively correlated in the first hour of study (Pearson product: rₚᵅ = 0.833, z = 1.1881, p < 0.01). Interestingly, exactly coincident points occurred at the 10-min and 40-min marks of the time course study after (IP) cocaine administration.

Figure 2 shows the concurrent effect of cocaine (10 mg/kg IP) on the frequency (number) of ambulations (locomotor activity) in the same group of animals in which neurochemistry was assayed. Cocaine (10 mg/kg IP) significantly increased the frequency of ambulations, F(2, 10) = 27.502, p < 0.0001, N = 6. Post hoc analysis further shows that there were statistically significant differences from baseline in the first hour of the two hours tested (Fisher PLSD = 193.583, Scheffe F = 26.852 and 5.851, first and second hours respectively). Thus, cocaine's effects on hyperactive behavior progressively declined in the second hour of study with the exception of the 90-min mark of the time course, at which time ambulatory behavior abruptly rose and then fell. Frequency of ambulations was significantly increased to 943 ± 130 photobeam interruptions (p < 0.05, 95% CL) from a baseline of 187 ± 35 within 10 min, and maximally increased to 1070 ± 124 photobeam interruptions (p < 0.05, 95% CL) within 20 min after cocaine administration.

Figure 3 shows the concurrent effect of cocaine (10 mg/kg IP) on the frequency (number) of rearings. Cocaine (10 mg/kg IP) significantly increased the rearing frequency, F(2, 10) = 15.749, p < 0.0008, N = 6. Furthermore, post hoc analysis shows that there were statistically significant differences
FIG. 1. The effects of cocaine (10 mg/kg IP) on concurrent DA and 5-HT release in vlNAcc in male, virus-free, Sprague-Dawley rats (N = 6) (cf. text for analysis of variation statistics). Detection limits for synaptic concentrations of DA and 5-HT as low as 5 nmol and 1 nmol, respectively, are currently possible with this biotechnology. *p < 0.05 (95% confidence limits).

from baseline in the first hour of the two hours tested (Fisher PLSD = 9.056, Scheffe F = 15.592 and 2.661, first and second hours respectively). Cocaine’s effects on rearing were dissipated in the second hour except at the 90-min mark of the time course, at which time behavior abruptly increased and subsequently decreased. Rearing frequency was significantly increased to 28 ± 5 photobeam interruptions (p < 0.05, 95% CL) from a baseline of 3 ± 0.8 within 10 min and maximally increased to 31 ± 3 (p < 0.05, 95% CL) within 50 min after cocaine administration.

FIG. 2. The effect of cocaine (10 mg/kg IP) on the frequency of ambulations (locomotor activity or running behavior) in the same group of Norway rats (cf. text for analysis of variation statistics). Baseline photobeam interruptions were 187 ± 35 (representing habituated behavior). *p < 0.05 (95% confidence limits).
Figure 3 also shows the concurrent effect of cocaine (10 mg/kg IP) on the frequency (number) of fine movements. Cocaine (10 mg/kg IP) significantly increased the frequency of fine movements, \( F(2, 10) = 18.833, p < 0.0004, N = 6 \). Post hoc analysis further shows that there were statistically significant differences from baseline in the first hour of the two hours tested (Fisher PLSD = 10.532, Scheffe \( F = 18.402 \) and 2.486, first and second hours respectively). Cocaine's effects on stereotypy dissipated in the second hour of study with the exception of the behavior seen at the 90-min mark which abruptly rose and momentarily fell. Frequency of fine movements was significantly increased to 38 ± 4 photobeam interruptions \( p < 0.05, 95\% \) CL) from a baseline of 5 ± 2 within 10 min and was maximally increased to 39 ± 6 \( p < 0.05, 95\% \) CL) within 50 min after cocaine administration.

Figure 4 shows the concurrent effect of cocaine (10 mg/kg IP) on the frequency (number) of central ambulations. Cocaine (10 mg/kg IP) significantly increased the frequency of central ambulations, \( F(2, 10) = 8.074, p < 0.0082, N = 6 \). Post hoc analysis further shows that there were statistically significant differences from baseline in the first hour of the two hours tested (Fisher PLSD = 2.751, Scheffe \( F = 7.949 \) and 1.216, first and second hours respectively). Cocaine's effects on central ambulations were completed during the second hour. However, at the 90-min point of the time course, central ambulatory behavior underwent a transient rise and fall, not unlike its previous pattern but very similar to the pattern of the ambulatory, rearing, and stereotypic fine movement behavior seen in Figs. 2 and 3. Frequency of central ambulations was significantly increased to 3 ± 1 photobeam interruptions \( p < 0.05, 95\% \) CL) from a baseline of 0 ± 0.04 within 10 min and maximally increased to 9 ± 5 \( p < 0.05, 95\% \) CL) within 50 min after cocaine administration.

Increased DA release in vlNAcc after cocaine administration was significantly and positively correlated with classically DA-dependent behaviors (first- and second-hour effects) (Pearson product: \( r_{(0)} > 0.651, z_t > 0.7753, p < 0.01 \)) and with the 5-HT-ergic behavior, central ambulations (Pearson product: \( r_{(0)} = 0.606, z_t < 0.7089, p < 0.01 \)). Cocaine-induced 5-HT release was significantly and positively correlated with the 5-HT behavior (Pearson product: \( r_{(0)} = 0.595, z_t < 0.6931, p < 0.01 \)). However, classically DA-dependent behaviors were significantly and more positively correlated with cocaine-induced 5-HT release in vlNAcc than with DA release throughout the two-hour period of study (Pearson product: \( r_{(0)} > 0.732, z_t > 0.9287, p < 0.01 \)).

Provocatively, the noted abrupt rise and fall in each of the cocaine-induced psychostimulant behaviors occurred when 5-HT release underwent a divergence in direction from concurrent DA release. Interestingly, the Pearson product-moment coefficient of correlation tests show that DA and 5-HT release were highly and positively correlated with classically DA-dependent behaviors up to the 90-min mark, \( r_{(0)} > 0.697, z_t > 0.8673, p < 0.01 \).

Preliminary results from studies of the immediate aftereffects of acute (IP) cocaine show that 5-HT release continues to increase after the two-hour period of study at a time during which DA release begins to decrease and cocaine-induced psychostimulant behaviors have begun to reach completion.

**DISCUSSION**

These data demonstrate that acute (IP) cocaine increases both DA and 5-HT release in vlNAcc concurrently and in vivo in the freely moving and behaving animal. The DAergic elements of the cocaine effect seen here are consistent with the body of evidence already presented. Moreover, new findings show that (IP) cocaine increased 5-HT release in vlNAcc. Thus, these data show that the effects of cocaine on DA neu-
The present results demonstrate, consistent with others (37), that the route of administration for cocaine administered acutely is a crucial factor in its consequent effects. Also, the data demonstrate that anesthesia does not significantly influence the 5-HT-ergic response to cocaine (9).

Real time detection of DA and 5-HT release in vlNAcc in the conscious animal provides an excellent tool for studying the nature of the "classically DA-dependent" and 5-HT-ergic psychostimulant behaviors induced by cocaine. Psychostimulant behaviors have been termed dysfunctional, nonadaptive, composite aggregates of subsystems which mediate movement along independent spatial dimensions (61). In this view, psychostimulant behaviors occur as a result of the initial activation and then deactivation of DAergic systems. However, in another view, the neurotransmitter DA functions in mesolimbic and nigrostriatal neuronal circuitry differentially; locomotor activity is primarily controlled by NAcc (ventral striatum) and stereotypic fine movements are primarily controlled by dorsal striatum (51). Placing the present findings within the latter framework, cocaine induced an increase in DA release in vlNAcc that was correlated as expected with cocaine-induced increased locomotor activity. Correspondingly, cocaine-induced maladaptive rearing behavior and stereotypic fine movement behavior were correlated with increased DA release as well. This response too was expected (i.e., based on the postulated partial mediation of these behaviors by NAcc).

Notably, the present results are different from the effects of (SC) cocaine on 5-HT release in vlNAcc, in the same paradigm (6), and are similar to the effect of (IV) cocaine on 5-HT-ergic release in vlNAcc, in the chloral hydrate-anesthetized rat paradigm (9). Thus, the present data demonstrate, consistent with others (37), that the route of administration for cocaine administered acutely is a crucial factor in its consequent effects. Also, the data demonstrate that anesthesia does not significantly influence the 5-HT-ergic response to cocaine (9).

FIG. 4. The effect of cocaine (10 mg/kg IP) on frequency of central ambulation behavior (agoraphobic inhibition) in the same group of Norway rats (cf. text for analysis of variation statistics). Baseline photobeam interruptions were 0 ± 0.04 (representing habituated behavior). *p < 0.05 (95% confidence limits).
Nonetheless, the present data show that the ebb and flow of each of the cocaine-induced classically DA-dependent behaviors were also dramatically correlated with the neurotransmitter 5-HT. Therefore, the present behavioral data further support a contributory role for 5-HT in the underlying mechanism of action of cocaine. That cocaine has the capability of showing anti-agoraphobic inhibitory characteristics in the "central ambulations" paradigm is also consistent with its 5-HTergic effects.

In conclusion, the present studies show that 5-HT may signal or precede the DAergic events associated with the well-known acute cocaine-induced DAergic dysfunction in A10 neuronal circuits. Interpretation of these results appears to parallel the "modulatory model" of brain reward. More importantly though, the data may bear relevance to aspects of chronic cocaine abuse such as those described in the Opponent Process Theory (35,36,57). Perhaps 5-HT may serve as a putative regulator during addictive and withdrawal processes.

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