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RAPID COMMUNICATION

Cocaine: On-Line Analysis of an Accumbens Amine Neural Basis for Psychomotor Behavior

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BRODERICK, P. A. *Cocaine: On-line analysis of an accumbens amine neural basis for psychomotor behavior.* PHARMACOL BIOCHEM BEHAV **40**(4) 959–968, 1991.—Dose-response studies on subcutaneous cocaine were done to ascertain its effects in nucleus accumbens in dopaminergic and serotonergic neuronal circuitry in the behaving rat with in vivo voltammetry. Simultaneously, and at each dose of cocaine, unconditioned psychomotor stimulant behavior induced by cocaine was studied in terms of multiple concurrent measures of spontaneous behavior and by activity pattern analysis, a study of spatial patterns of locomotion. Time course studies showed that the neurochemical effects of cocaine (10, 20, and 40 mg/kg SC) significantly ($p<0.0001$) increased accumbens synaptic concentrations of dopamine (DA) and concurrently and significantly ($p<0.0001$) decreased accumbens synaptic concentrations of serotonin (5-HT) in a dose response manner. Simultaneous behavioral time course studies showed that cocaine (10, 20, and 40 mg/kg SC) significantly ($p<0.0001$) increased ambulations (locomotor activity), fine movements (stereotypic movements of sniffing and grooming) and rearing behavior, while significantly decreasing agoraphobic behavior, as measured by a statistically significant increase in central ambulations ($p<0.0001$). The high dose of cocaine (40 mg/kg SC) significantly increased fine movements over those produced by the lower doses of cocaine ($p<0.0002$). One import of the findings is that the DA and 5-HT biogenic amine response occurs in a behavioral paradigm of psychomotor stimulation, which is a known measure of reinforcement. Another is that the biogenic amines DA and 5-HT are affected by cocaine in this reinforcement paradigm with exactly opposite directionality. Finally, acute cocaine administration is shown to produce a dose response inhibition of agoraphobia (fear), which is highly correlated ($\rho = .983$, $p<0.01$) with the opposing effects of cocaine on the accumbens biogenic amines, DA and 5-HT.

Cocaine Dopamine Serotonin Nucleus accumbens Freely moving rat
In vivo voltammetry (electrochemistry) Ambulations Central ambulations Rearing behavior Fine movements
Activity pattern analyses Psychomotor stimulant Reinforcement Agoraphobia

A current theory of addiction relates psychomotor stimulation and the process of positive reinforcement through homology, i.e., a derivation from common neurobiological mechanisms. Within this theoretical consideration, psychomotor stimulant behavior, i.e., approach behavior or locomotor behavior is a predictor and a measure of reinforcement (32). Within this context, cocaine is known as a distinctive psychomotor stimulant. Moreover, compelling evidence through various reinforcement paradigms shows that cocaine exerts its potent reinforcing properties through a dopaminergic molecular component, particularly in mesolimbic neuronal circuitry, and particularly at the dopamine transporter (6, 26, 27, 31). In tandem, the hyperactive locomotor activity produced by psychomotor stimulants has been shown to be highly correlated with increased DA levels in nucleus accumbens, postmortem (18). Thus the first purpose of this paper was to study a possible underlying commonality between a reinforcing dopaminergic mechanism and a reinforcing behavioral mechanism of cocaine, simultaneously, in vivo, on line, instantaneously and in real time, to further elucidate what appears to be the satisfying or compensating events of cocaine.

Furthermore, 5-HT mechanisms were studied because currently, the clinical literature is reporting both positive (13) and negative support (30) for the dopaminergic hypothesis of cocaine reinforcement. Extending the dopaminergic hypothesis to other neurotransmitters then is becoming crucial in terms of cocaine treatment modalities. A 5-HT mechanism is a good candidate for study because psychiatric and emotional disorders, including anxiety, have as their underlying neurobiological etiology, deficits in 5-HT functioning (16). Indeed, cocaine has been reported to cause such psychiatric disorders (15). A review of the literature shows (a) that cocaine is a potent reuptake inhibitor of 5-HT at the synapse (28), (b) that cocaine depressed 5-HT levels, postmortem (24), (c) that cocaine decreased 5-HT synthesis and turnover post mortem (11), (d) that impulse frequency in dorsal raphe 5-HT neurons was depressed by cocaine (5) and (e) that there may be a role for the reinforcing effects of cocaine through a 5-HT mediation (22). As is with DA mechanisms, 5-HT-cocaine interactions are associated with transporter mechanisms (25). Thus the second purpose of this paper was to study the effect of cocaine on the indoleamine, 5-HT, in nucleus accum-

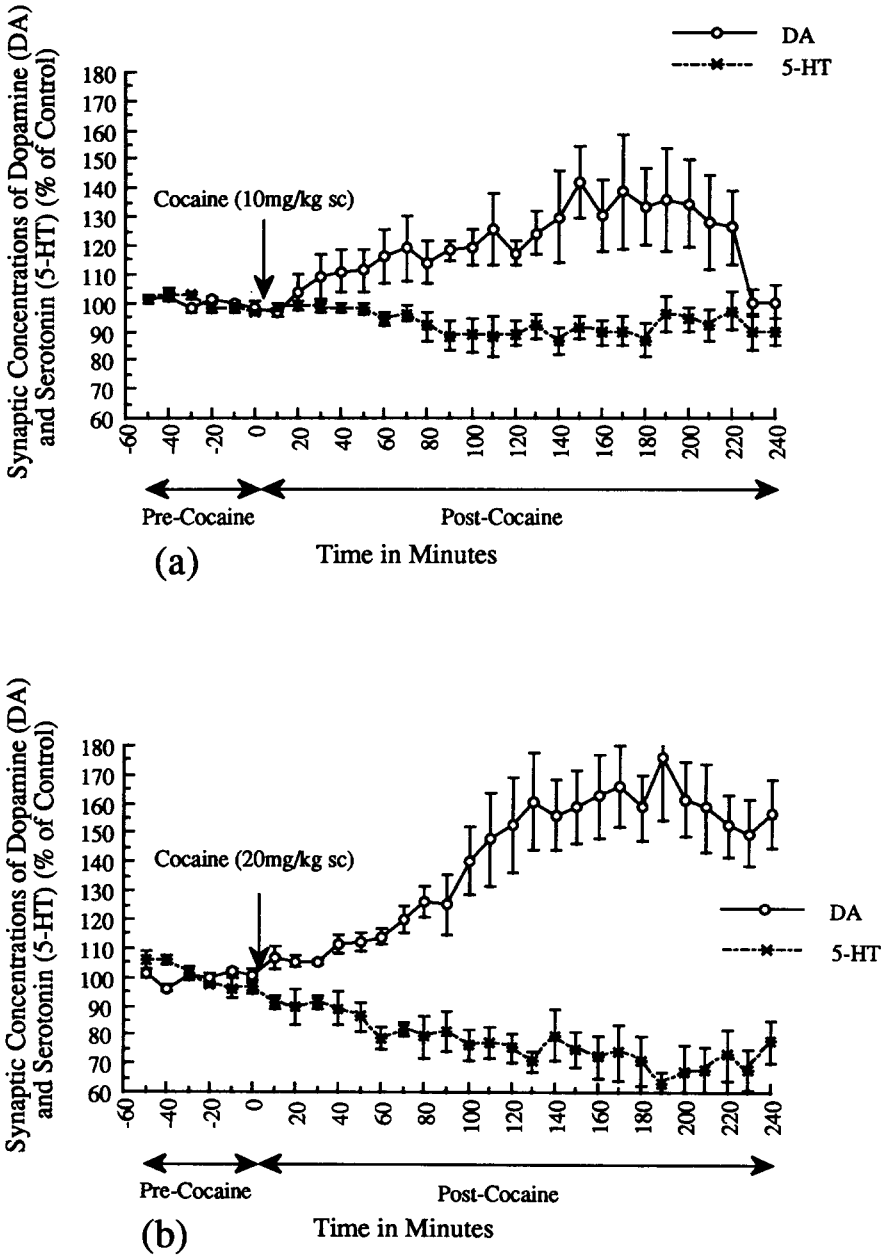

FIG. 1. (a) The effect of cocaine HCl (10 mg/kg SC) on synaptic concentrations of dopamine (DA) and serotonin (5-HT) in nucleus accumbens of behaving rats. Cocaine significantly increased synaptic DA [$p<0.05$, 95% confidence limits of the mean (CL)] between ten and twenty minutes after cocaine injection. Cocaine significantly decreased synaptic 5-HT ($p<0.05$, 95% CL) between forty and fifty minutes after cocaine injection (cf. the Results section for ANOVA statistics). (b) The effect of cocaine HCl (20 mg/kg SC) on synaptic concentrations of dopamine (DA) and serotonin (5-HT) in nucleus accumbens of behaving rats. Cocaine significantly increased synaptic DA ($p<0.05$, 95% CL) and significantly decreased synaptic 5-HT ($p<0.05$, 95% CL) between one and ten minutes after cocaine injection (cf. the Results section for ANOVA statistics).

bens of behaving rats. Serotonin was studied on line and concurrently with the study of DA and simultaneously with the psychomotor stimulant activity produced by cocaine.

METHOD

In Vivo Voltammetry

In the present studies, in vivo voltammetry was used. Specifically, semidifferential electroanalysis was used because this technique provides a clear separation of the biogenic amine neurotransmitters, DA and 5-HT. Dopamine and 5-HT were detected with a stearate working electrode (diameter: 175–200 μm) at oxidation potentials of $+0.14 \pm 0.015$ V and $+0.29 \pm 0.015$ V respectively. The microelectrode was fabricated by pulling the Teflon coat of a stainless steel wire (Medwire Corp., Mt. Ver-

non, NY) 500 μm over the edge of the stainless steel component of the wire to form a microcavity inside the teflon well. The microcavity was then packed with a graphite-nujol-stearate paste mixture. The electrode paste mixture consisted of USP ultrasuperior purity carbon (1.5 g) (Ultra-Carbon Corp., Bay City, MI), extra heavy Nujol (1.24 cc) (Plough Inc., Memphis, TN) and 99+% stearic acid (100 mg) (Sigma, St. Louis, MO). The detailed methodology for synthesizing this electrode paste mixture is published (2). After each electrode was fabricated, it was examined for homogeneity of paste distribution under a dissecting microscope at 30× magnification (Nikon, SMZ-1 with Nikon Transformer Illuminator XN, Garden City, NY). Then, a gas chromatographic and a combustion analysis method for the exact determination of electrode paste composition after paste synthesis can be performed. These methods are also published (3). A medium exchange technique was performed on each electrode in vitro before surgical insertion and implantation of the electrode in vivo. This procedure consisted of performing a selective preconcentration of the analytes, DA and 5-HT onto the electrode surface in phosphate buffer (0.01 M) pH 7.4, in a closed semidifferential circuit, scanning from −0.2 V to +0.4 V, at 2 nA/V, three separate times on three separate days. This method achieves optimum and stable preconcentration of analytes and improves the selectivity, the efficacy and the sensitivity of the electrode for analytes in electrolyte environments.

The in vivo electrochemical signal, both in vitro and in vivo, for DA was detected, without interference at the same oxidation potential, from 3,4-dihydroxyphenylacetic acid (DOPAC) or ascorbic acid. The electrochemical signal, both in vitro and in vivo, for 5-HT was detected, without interference at the same oxidation potential, from the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) or uric acid. Potentials were applied with a CV37 detector (BAS, West Lafayette, IN). The CV37 detector was electrically connected to a Minigard surge suppressor (Jefferson Electric Magnetek, NY) which was then connected to an electrical ground in isolation. Potentials were applied from −0.2 V to +0.4 V with respect to a Ag/AgCl (1 M NaCl) electrode, at a scan rate of 10 mV/s. One voltammetric scan was scanned in 60 seconds. Nonfaradaic charging current was eliminated in the first 25 seconds. The neurotransmitters, DA and 5-HT, were detected in approximately 13 and 12 seconds each respectively, in a sequential manner. The coulombic efficiency for the detection of serotonin was two- to three-fold greater than that for DA with a stearate electrode (1). The recording probes were stable in vivo throughout the studies without significant changes in their recording characteristics.

Working electrodes were precalibrated in vitro in a fresh deoxygenated phosphate buffer solution, pH 7.4 (0.01 M) containing μM and nM aliquot solutions of 10 μM DA (Sigma, St. Louis, MO) and 5-HT (99%, Aldrich, Milwaukee, WI). Working electrodes were also postcalibrated in vitro in a fresh deoxygenated phosphate buffer solution, pH 7.4 (0.01 M) made exactly as was the precalibration buffer, after each study was completed. Peak areas for DA and 5-HT were then measured and compared with in vitro measured precalibration peak areas for DA and 5-HT. Peak areas were calculated by multiplying the peak height (mm) of each electrochemical signal by the width (mm) of each electrochemical signal at ½ the peak height (mm). The detection limit for basal synaptic concentrations of DA in nucleus accumbens was 13 nM; the detection limit for basal synaptic concentrations of 5-HT in nucleus accumbens was 2 nM. 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.

Each Ag/AgCl reference electrode was fabricated by plating silver wire (Medwire Corp., Mt. Vernon, NY) with AgCl in a 1 M NaCl solution for 0.5 h with the setting on the voltmeter (Micronta®, Radio Shack, Franklin Square, NY) at a current of 2 mA per electrode. The silver wire was then inserted into a 5 mm part (0.5–2.0 μl) of a 0.5–200 μl pipette (Cole Parmer Instrument Company, Chicago, IL) and was covered with 5% agar in physiological saline. The opened end of the pipette was closed with absorbent cotton. An amphenol pin was soldered to the silver coated electrode at the opposite end. Each reference electrode is actually 3 mm in length and holds a 2 μl volume of 5% agar in physiological saline. The auxiliary electrode was stainless steel (200 μm) (Medwire, Mt. Vernon, NY).

Male, Sprague-Dawley rats were bred quarantined free from a number of viruses, which 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. The animals weight range was 330–410 g, (Charles River Laboratories, Kingston, NY). The animals were group housed (before surgery) and individually housed (after surgery) and were fed Purina Rat Chow and water ad lib. A twelve-hour dark-light cycle was maintained both in the housing of the animals and throughout the experimental studies. Each animal was anesthetized with pentobarbital Na (50 mg/kg IP) and was stereotaxically implanted (Kopf Stereotaxic, Tujunga, CA) with a stearate working electrode in nucleus accumbens (AP = −2.6, ML = +2.5, DV = −7.3) (20). An Ag/AgCl reference electrode, described above, was placed in contact with dura, 7 mm posteriorally and contralaterally to the working electrode. A stainless steel auxiliary electrode also described above, was placed in contact with dura. Body temperature was continuously monitored with a rectal probe and thermometer (Fisher Scientific, Fadem, NJ). Body temperature was maintained at 37.5±0.5°C with an aquamatic K module heating pad (American Hospital Supply, Edison, NJ). Booster injections of pentobarbital Na were administered once after the first two hours of surgery (0.10 cc) and once every subsequent hour (0.05 cc) to maintain an adequate level of anesthesia throughout surgery. The total time for surgery was three to four hours. The working, reference and auxiliary electrodes were held in place with dental acrylic (Kadon Cavity Liner, Caulk, Becker Parkin Dental Supply Co. Inc., NY). Animals recovered in an appropriately bedded Plexiglas cage (dimensions: 12″×12″×18″) after surgery and before the experimental studies began, with food and water ad lib. The animals were treated with physiological saline (0.5 cc) immediately and for two days after surgery. A great deal of care was taken to ensure the animals' well being throughout the studies.

In vivo voltammetric studies on conscious rats were begun seven to fourteen days after the aseptic surgical operations were performed. On each experimental day, animals were placed in a Plexiglas chamber within a faraday cage (dimensions: 24″× 18″×23.5″). The three-microelectrode assembly, enclosed within the animal's prosthetic acrylic cap, was connected to a CV37 detector 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 detector was electrically connected to a Minigard surge suppressor (Jefferson Electric, Magnetek, NY) which was then connected to an electrical ground in isolation. Stable electrochemical signals for DA and 5-HT were evident before cocaine administration. There were no movement or electrical artifacts. Cocaine (10–20–40 mg/kg SC) (Sigma, St. Louis, MO) was administered in separate studies to mimic studies which used similar doses and routes of administration as reinforcing (7). Voltammetric scans were repeated every ten minutes for a period of one hour before co-

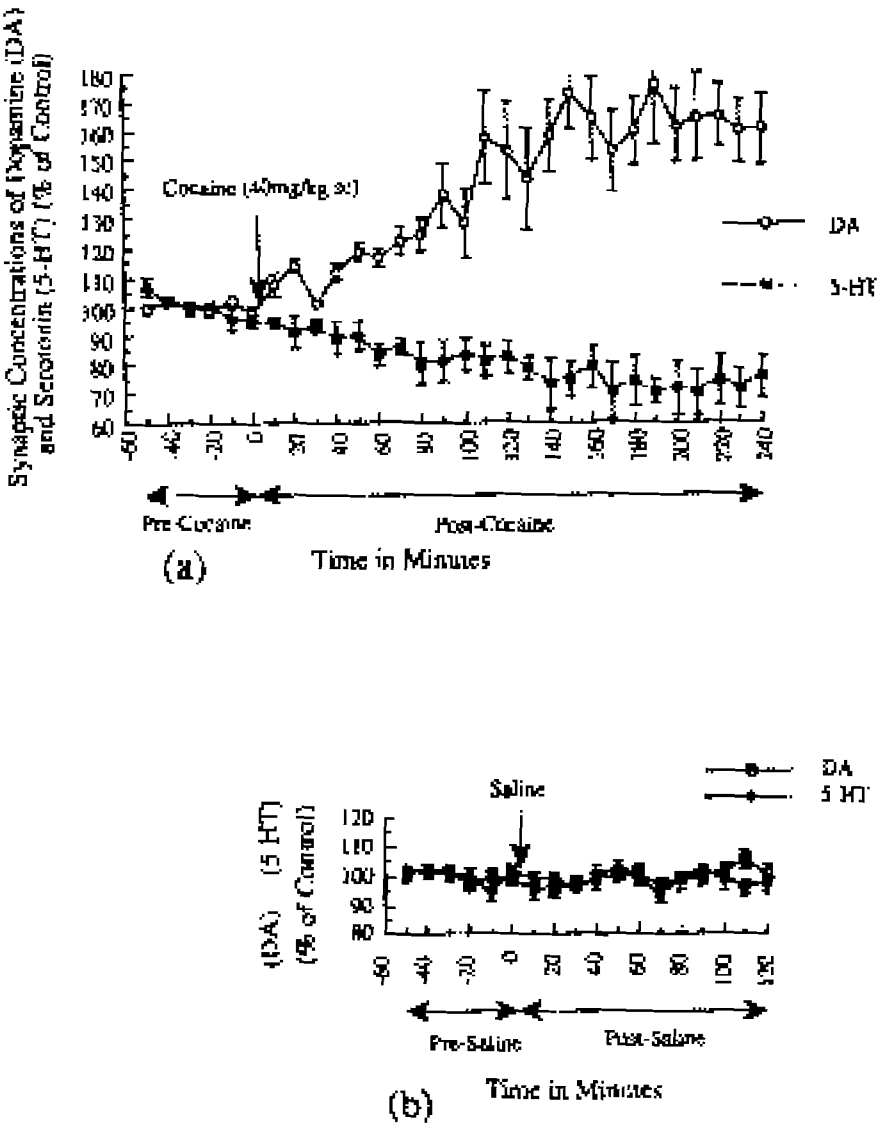

FIG. 2. (a) The effect of cocaine HCl (40 mg/kg SC) on synaptic concentrations of dopamine (DA) and serotonin (5-HT) in nucleus accumbens of behaving rats. Cocaine significantly increased DA ($p<0.05$, 95% C.I. between one and ten minutes) and significantly decreased 5-HT ($p<0.05$, 95% C.I. between ten and twenty minutes after cocaine injection (cf. the Results section for ANOVA statistics). (b) Graph showing that physiological saline (1 cc/kg IP) did not significantly affect synaptic concentrations of dopamine (DA) and serotonin (5-HT) in nucleus accumbens of behaving rats (cf. the Results section for ANOVA statistics).

caine administration and a period of four hours after cocaine administration. An initial one-hour period was allowed before the pre-cocaine baseline values were measured. This was to provide adequate time for the animal to complete exploratory activity in a novel environment.

Behavior

Activity pattern analysis can simultaneously monitor several different responses both as they occur spatially and temporally. Activity pattern analysis measures multiple concurrent measures of ambulations (*locomotor activity*), *central ambulations*, *rearing* behavior and fine movements (sniffing and grooming). An outer exterior layer of the cage consisted of copper which provides a faradaic environment for the monitoring of the electrochemical signals in vivo. Each animal's movements were detected by a 16 × 16 array of infrared photobeams held in place by an aluminum frame. The aluminum frame was placed 3/4 inch above the Plexiglas floor of the behavioral cage (24" × 16" × 13.5"). The infrared photobeams were sampled by an IBM computer to define the x-y position of the animal within a 1.5 inch resolution. When an x-y position is calculated, it is used to define an animal's position in one of sixteen equally sized sectors and one of nine unequally sized regions. These regions are particularly important because they are used for many descriptive measures of *entries spent in the center of the cage*. This is a reliable measure of thigmotaxia, i.e., the agoraphobic response which is equivalent to fear (54). Rearing, wherein both forepaws of the animal

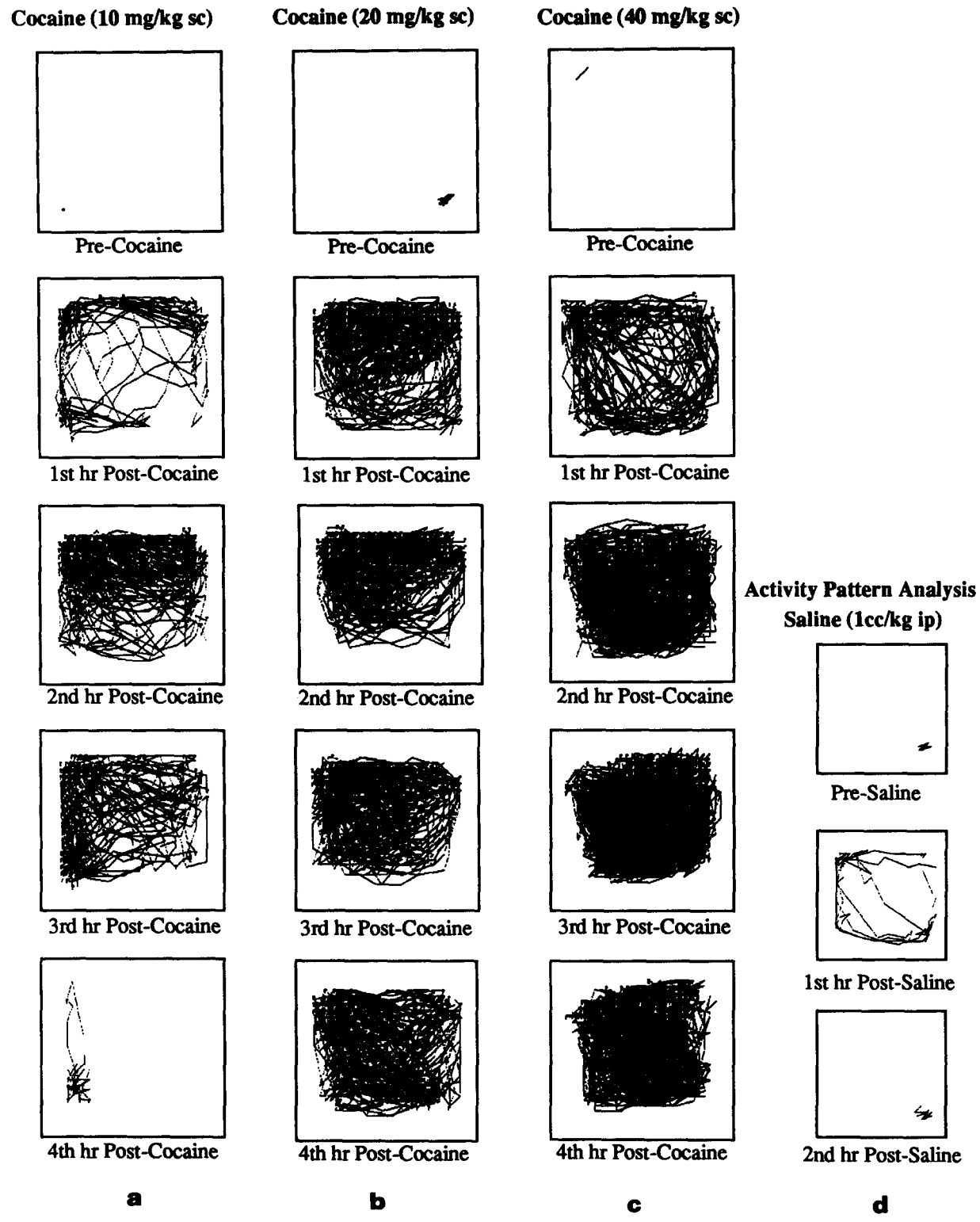

FIG. 3. (a–c) Representative activity pattern analysis plots showing the effect of cocaine (10, 20 and 40 mg/kg SC) on the spatial and temporal movement patterns of animals. Each dose of cocaine produced a statistically significant ($p<0.0001$) increase in psychomotor stimulant activity (cf. the Results section and Tables 1 through 3 for ANOVA and 95% confidence limits statistics). Part (d) shows activity pattern analysis after injection of physiological saline (1 cc/kg IP) (cf. the Results section and Table 4 for ANOVA and 95% Confidence Limits statistics).

TABLE 1

THE EFFECT OF COCAINE (10 mg/kg SC) ON BEHAVIORAL PARAMETERS: TIME COURSE

	Ambulations	Central Ambulations	Rearing Behavior	Fine Movements
Pre - cocaine	254.50 ± 93.33	0.10 ± 0.00	1.73 ± 1.03	6.53 ± 3.67
	217.83 ± 127.63	0.10 ± 0.00	4.92 ± 4.82	13.55 ± 8.62
	264.00 ± 124.72	0.10 ± 0.00	1.92 ± 1.82	7.40 ± 7.12
	110.68 ± 25.63	0.10 ± 0.00	0.25 ± 0.15	3.88 ± 2.30
	106.33 ± 25.36	0.10 ± 0.00	0.10 ± 0.00	2.90 ± 1.78
	90.33 ± 14.78	0.10 ± 0.00	0.10 ± 0.00	7.02 ± 3.18
	173.95 ± 52.65	**0.10 ± 0.00**	**1.50 ± 0.76**	**6.85 ± 2.78**
Post - cocaine	*1137.33 ± 102.38	*3.38 ± 2.04	*28.50 ± 6.56	*43.17 ± 8.83
1st Hour	*998.33 ± 116.11	*2.07 ± 1.47	*7.67 ± 2.44	*24.85 ± 7.23
	*625.17 ± 80.21	*1.07 ± 0.66	*3.70 ± 1.18	*16.00 ± 5.74
	*798.83 ± 153.45	*1.90 ± 1.20	*10.83 ± 5.19	*21.50 ± 5.77
	*703.67 ± 99.33	*1.53 ± 0.60	*14.00 ± 1.61	*27.00 ± 5.03
	*728.67 ± 154.65	*3.03 ± 1.25	*17.67 ± 5.52	*29.67 ± 9.00
	832.00 ± 30.41	**2.16 ± 0.53**	**13.73 ± 2.28**	**27.03 ± 1.69**
Post - cocaine	*738.50 ± 124.22	*2.55 ± 1.44	*30.33 ± 12.93	*45.00 ± 16.18
2nd Hour	*883.00 ± 171.36	*6.03 ± 3.74	*33.17 ± 11.94	*44.50 ± 14.78
	*1155.00 ± 204.06	*19.68 ± 6.87	*46.50 ± 12.63	*71.83 ± 15.29
	*1180.83 ± 226.04	*18.68 ± 7.58	*43.50 ± 12.24	*62.83 ± 14.54
	*1352.50 ± 171.73	*25.17 ± 7.80	*37.83 ± 8.89	*67.00 ± 8.30
	*1276.50 ± 228.06	*26.33 ± 9.62	*40.33 ± 9.24	*61.83 ± 10.35
	1097.72 ± 39.79	**16.41 ± 3.01**	**38.61 ± 1.78**	**58.83 ± 3.15**
Post - cocaine	*1368.83 ± 271.92	*28.67 ± 10.79	*42.50 ± 6.05	*67.67 ± 11.61
3rd Hour	*1363.00 ± 286.65	*27.17 ± 9.92	*38.50 ± 11.93	*68.50 ± 18.25
	*1261.00 ± 222.28	*21.17 ± 8.36	*34.67 ± 12.97	*58.17 ± 15.74
	*1136.33 ± 165.15	*21.02 ± 11.8	*20.83 ± 6.70	*37.33 ± 10.07
	*1206.33 ± 255.58	*19.17 ± 7.13	*30.17 ± 11.10	*47.50 ± 14.15
	*1180.00 ± 224.44	*17.85 ± 11.59	*33.00 ± 12.47	*58.00 ± 19.11
	1252.58 ± 43.73	**22.51 ± 1.86**	**33.28 ± 3.03**	**56.19 ± 3.59**
Post - cocaine	*991.67 ± 229.98	*11.18 ± 5.85	*19.17 ± 8.07	*31.83 ± 12.26
4th Hour	*857.67 ± 140.32	*12.72 ± 7.54	*18.67 ± 9.07	*34.83 ± 15.31
	*805.00 ± 231.96	*12.55 ± 8.5	*12.70 ± 6.63	*26.17 ± 10.10
	*756.50 ± 228.50	*20.55 ± 14.19	*17.02 ± 9.06	*40.00 ± 22.46
	*1171.50 ± 264.82	*22.28 ± 11.89	*23.28 ± 13.43	*47.25 ± 21.75
	*820.25 ± 222.30	*18.28 ± 10.81	*24.28 ± 12.54	*43.28 ± 20.77
	900.43 ± 36.78	**16.26 ± 2.82**	**19.18 ± 1.54**	**37.23 ± 4.35**

*$p<0.05$, 95% confidence limits of the mean (cf. text for ANOVA statistics). Bold: Hourly mean ± SE (N = 6) from each accumulated 10 min mean ± SE (N = 6).

are away from the floor for a period of at least 1 s, is measured by a series of infrared photobeams about 6 inches from the floor of the plexiglass cage. The computer samples the status of all the beams and the circuits in the cage every 100 ms. The system is a modified version of an Activity Pattern Monitor (San Diego Instruments, San Diego, CA).

Statistical differences between DA and 5-HT effects with and without cocaine treatment were determined by standard repeated measures analysis of variance (ANOVA). ANOVAs were followed by the post hoc test, Fisher PLSD, (least square difference) (Statview, BrainPower Inc., Calabasas, CA) to determine statistically significant differences in neurotransmitter changes which occurred hourly after drug administration. Ninety-five percent confidence limits measures were also performed on each point of the time course data following the administration of drug. Behavioral (frequency) data were treated the same. Changes in DA and 5-HT values after drug treatment are presented as percent change of measurements (peak area) from unstimulated baseline values (peak area) to minimize normal between animal variations. Neurochemical and behavioral correlations were statistically analyzed by the Spearman Rank Coefficient of Correlation (ρ).

RESULTS

Figure 1a and b show the effects of cocaine (10 and 20 mg/kg SC respectively) on the in vivo synaptic concentrations of DA and 5-HT in nucleus accumbens of behaving rats. Cocaine (10 mg/kg SC) significantly increased DA [ANOVA: $F(4,20) = 10.897$, $p<0.0001$, $N = 5$] above basal (endogenous) same animal control values and significantly decreased 5-HT [ANOVA: $F(4,20) = 30.67$, $p<0.0001$, $N = 5$] below basal same animal control values. The DA signal reached a maximum value (to 142% of control, $p<0.05$) (controls = 100% throughout) during the 3rd hour and returned to control values during the 4th hour of study. Synaptic concentrations of 5-HT reached a maximum decrease to 86.53% of control ($p<0.05$) during the 3rd hour and

TABLE 2

THE EFFECT OF COCAINE (20 mg/kg SC) ON BEHAVIORAL PARAMETERS: TIME COURSE

	Ambulations	Central Ambulations	Rearing Behavior	Fine Movements
Pre - cocaine	268.25 ± 74.33	1.08 ± 0.98	2.58 ± 2.48	6.55 ± 4.46
	471.25 ± 235.01	4.55 ± 3.28	7.30 ± 5.16	17.28 ± 8.83
	62.00 ± 28.14	0.10 ± 0.00	0.10 ± 0.00	3.53 ± 1.42
	225.75 ± 167.30	2.33 ± 2.23	4.08 ± 3.98	7.58 ± 7.48
	316.25 ± 207.83	1.83 ± 1.73	7.58 ± 7.48	14.05 ± 9.03
	175.50 ± 59.36	0.10 ± 0.00	2.05 ± 1.20	4.03 ± 1.39
	253.17 ± 56.30	**1.66 ± 0.68**	**3.95 ± 1.22**	**8.83 ± 2.28**
Post - cocaine	*707.25 ± 218.86	*3.53 ± 2.20	*16.03 ± 7.15	*27.28 ± 11.00
1st Hour	*1178.50 ± 208.92	*7.75 ± 2.17	*15.75 ± 2.98	*38.25 ± 12.74
	*1035.25 ± 274.87	*16.53 ± 14.19	*20.25 ± 8.59	*53.50 ± 9.47
	*1247.00 ± 364.09	*25.00 ± 13.52	*31.75 ± 9.47	*70.75 ± 16.76
	*1213.25 ± 354.68	*34.25 ± 16.60	*29.25 ± 13.07	*53.25 ± 10.88
	*1178.25 ± 312.65	*39.53 ± 18.51	*28.53 ± 15.98	*50.25 ± 13.42
	1093.25 ± 82.64	**21.10 ± 5.88**	**23.59 ± 2.90**	**48.88 ± 6.06**
Post - cocaine	*1266.25 ± 291.84	*45.00 ± 14.48	*34.75 ± 19.17	*64.75 ± 25.24
2nd Hour	*1300.00 ± 215.85	*34.75 ± 9.59	*42.50 ± 17.75	*68.75 ± 20.54
	*995.50 ± 126.38	*27.25 ± 9.75	*42.50 ± 11.86	*57.50 ± 12.18
	*1426.00 ± 259.11	*35.75 ± 8.73	*48.75 ± 4.99	*74.50 ± 7.64
	*1168.75 ± 198.53	*27.50 ± 4.50	*42.75 ± 5.45	*65.70 ± 7.78
	*1502.50 ± 280.13	*41.50 ± 13.21	*33.50 ± 8.54	*62.25 ± 10.33
	1276.50 ± 74.08	**35.29 ± 2.94**	**40.79 ± 2.33**	**65.58 ± 2.36**
Post - cocaine	*1079.75 ± 211.58	*30.75 ± 9.23	*35.00 ± 8.90	*56.50 ± 8.82
3rd Hour	*1292.50 ± 288.39	*42.75 ± 9.12	*31.50 ± 4.57	*59.50 ± 11.64
	*1216.00 ± 299.36	*35.50 ± 9.06	*28.75 ± 6.30	*52.50 ± 15.71
	*1380.25 ± 220.70	*39.00 ± 11.16	*26.75 ± 6.36	*53.00 ± 10.50
	*1440.50 ± 300.80	*48.00 ± 12.56	*27.50 ± 5.01	*59.50 ± 14.01
	*1240.00 ± 260.05	*37.75 ± 8.14	*26.25 ± 3.33	*47.00 ± 7.15
	1274.83 ± 52.15	**38.96 ± 2.43**	**29.29 ± 1.37**	**54.67 ± 1.97**
Post - cocaine	*1406.75 ± 299.77	*46.00 ± 10.27	*22.25 ± 3.12	*48.75 ± 8.28
4th Hour	*1424.75 ± 287.27	*49.75 ± 13.58	*18.00 ± 5.00	*51.50 ± 13.13
	*1570.75 ± 184.25	*46.75 ± 6.91	*17.50 ± 2.40	*42.25 ± 9.12
	*1578.00 ± 141.27	*51.50 ± 4.29	*19.00 ± 3.67	*43.00 ± 3.03
	*1372.50 ± 190.83	*36.75 ± 9.28	*20.50 ± 7.47	*38.75 ± 7.45
	*1506.00 ± 103.11	*46.00 ± 9.04	*12.25 ± 3.12	*32.25 ± 6.50
	1476.46 ± 35.78	**46.13 ± 2.08**	**18.25 ± 1.39**	**42.75 ± 2.82**

*$p<0.05$, 95% confidence limits of the mean (cf. text for ANOVA statistics). Bold: Hourly mean ± SE (N = 4) from each accumulated 10 min mean ± SE (N = 4).

returned to baseline in the 4th hour. 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 same animal control values. 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 showed a trend toward a return to baseline values in the 4th hour.

Figure 2a shows the effects of cocaine (40 mg/kg SC) on the in vivo synaptic concentrations of DA and 5-HT in nucleus accumbens of behaving rats. Cocaine (40 mg/kg SC) significantly increased DA [ANOVA: $F(4,20) = 53.723$, $p<0.0001$, N = 5] above basal same animal control values and significantly decreased 5-HT below basal same animal control values [ANOVA: $F(4,20) = 93.232$, $p<0.0001$, N = 5]. Synaptic concentrations of DA maximally increased earlier on, 150 minutes after cocaine injection to 172.92% of ($p<0.05$). The electrochemical DA signal stabilized in the 4th hour. Synaptic concentrations of 5-HT reached its maximum decrease (to 70.1% of control values, $p<0.05$) at 210 minutes after cocaine injection and then also stabilized in the 4th hour. Figure 2b shows that saline did not significantly affect DA [ANOVA: $F(2,10) = 1.561$, $p<0.257$, N = 5] nor did saline significantly affect 5-HT [ANOVA: $F(2,10) = 1.04$, $p<0.3887$, N = 4]. The effects of cocaine on DA and 5-HT were highly correlated ($\rho = 1.0$, $p<0.01$).

Figure 3a–d shows specific activity patterns induced by cocaine (10, 20, and 40 mg/kg SC) and by saline respectively. It is evident that cocaine induces longer acting psychomotor stimulant effects with a dose response relationship. The most dramatic

TABLE 3

THE EFFECT OF COCAINE (40 mg/kg SC) ON BEHAVIORAL PARAMETERS: TIME COURSE

	Ambulations	Central Ambulations	Rearing Behavior	Fine Movements
Pre - cocaine	358.40 ± 237.65	1.48 ± 1.38	4.30 ± 3.91	7.80 ± 5.57
	173.20 ± 74.34	0.10 ± 0.00	1.55 ± 0.93	2.86 ± 2.11
	526.00 ± 258.66	2.46 ± 1.73	14.53 ± 7.18	18.62 ± 9.53
	254.80 ± 84.59	0.28 ± 0.18	4.33 ± 4.23	7.64 ± 5.05
	220.80 ± 91.25	0.28 ± 0.18	4.30 ± 2.63	7.42 ± 3.97
	425.60 ± 176.45	0.66 ± 0.38	14.30 ± 8.20	20.62 ± 9.69
	326.47 ± 54.91	**0.88 ± 0.38**	**7.22 ± 2.32**	**10.83 ± 2.89**
Post - cocaine	*1064.20 ± 194.28	*6.84 ± 3.63	*33.75 ± 11.76	*43.40 ± 14.82
1st Hour	*1420.20 ± 518.00	*18.04 ± 10.72	*35.75 ± 10.28	*61.62 ± 24.34
	*1488.40 ± 590.97	*32.42 ± 25.15	*29.50 ± 8.02	*54.60 ± 21.47
	*1294.20 ± 450.33	*26.42 ± 18.18	*37.25 ± 15.04	*61.20 ± 16.38
	*1059.60 ± 341.47	*23.04 ± 11.86	*27.25 ± 11.90	*45.40 ± 11.67
	*1387.60 ± 348.15	*33.42 ± 15.93	*40.75 ± 15.98	*67.62 ± 17.85
	1285.70 ± 75.29	**23.36 ± 4.06**	**34.04 ± 2.04**	**55.64 ± 3.94**
Post - cocaine	*1797.80 ± 281.14	*39.20 ± 10.23	*30.00 ± 12.12	*68.80 ± 12.35
2nd Hour	*1643.80 ± 427.30	*45.80 ± 19.19	*27.25 ± 3.97	*63.80 ± 20.56
	*1572.80 ± 411.13	*43.40 ± 19.74	*31.50 ± 11.03	*62.60 ± 15.98
	*1632.20 ± 414.07	*52.80 ± 24.22	*37.00 ± 8.81	*80.00 ± 24.45
	*1765.40 ± 626.93	*55.00 ± 30.25	*24.50 ± 12.40	*56.60 ± 20.91
	*1811.20 ± 617.11	*49.82 ± 33.07	*29.50 ± 6.75	*68.62 ± 19.87
	1703.87 ± 40.85	**47.67 ± 2.44**	**29.96 ± 1.73**	**66.74 ± 3.23**
Post - cocaine	*1832.80 ± 620.76	*53.42 ± 36.37	*36.00 ± 10.70	*66.60 ± 22.43
3rd Hour	*1805.40 ± 629.41	*59.22 ± 41.30	*44.25 ± 15.46	*82.80 ± 28.00
	*2298.00 ± 660.43	*72.60 ± 46.99	*53.00 ± 14.55	*95.80 ± 30.72
	*1864.00 ± 647.79	*59.82 ± 40.32	*63.50 ± 30.93	*89.62 ± 28.63
	*1691.80 ± 417.79	*42.42 ± 24.60	*49.25 ± 25.06	*77.20 ± 24.14
	*1695.00 ± 519.46	*51.82 ± 32.88	*21.25 ± 7.22	*52.20 ± 19.08
	1864.5 ± 91.47	**56.55 ± 4.11**	**44.54 ± 5.97**	**77.37 ± 6.50**
Post - cocaine	*1502.80 ± 534.87	*50.42 ± 36.90	*37.50 ± 17.82	*84.20 ± 23.85
4th Hour	*1563.80 ± 592.87	*54.04 ± 36.66	*31.00 ± 14.52	*73.62 ± 26.08
	*1476.80 ± 561.78	*57.44 ± 36.38	*44.00 ± 26.76	*83.60 ± 21.77
	*1301.60 ± 464.05	*48.02 ± 27.18	*24.00 ± 7.91	*52.82 ± 17.25
	*1227.60 ± 535.71	*44.62 ± 28.98	*49.00 ± 26.11	*66.22 ± 25.27
	*1680.80 ± 320.78	*69.20 ± 25.90	*43.75 ± 20.48	*71.80 ± 22.43
	1458.90 ± 68.49	**53.96 ± 3.56**	**38.21 ± 3.81**	**72.04 ± 4.79**

*$p<0.05$, 95% confidence limits of the mean (cf. text for ANOVA statistics). Bold: Hourly mean ± SE (N = 5) from each accumulated 10 min mean ± SE (N = 5).

inhibition of the agoraphobic response at the highest dose of cocaine is notable.

Table 1 shows a time course effect of cocaine (10 mg/kg SC) on the psychomotor stimulant behavior: ambulations, rearings, fine movement and agoraphobic behavior, as measured by the central ambulation parameter. Cocaine (10 mg/kg SC) significantly (ANOVA: $p<0.0001$, N = 6, $df = 4,20$) increased ambulations (F = 42.589), rearing (F = 47.095), fine movements (F = 42.864) and central ambulations (F = 18.052) above basal same animal control values. Concurrent DA and 5-HT changes were highly correlated with ambulation behavior ($\rho = .9$, $p<0.01$). The reduction in agoraphobic behavior is significant ($p<0.0001$) and occurs immediately after cocaine injection. Moreover, DA and 5-HT changes were highly correlated with the reduction in agoraphobic behavior ($\rho = 1.0$, $p<0.01$).

Table 2 shows a time course effect of cocaine (20 mg/kg SC) on psychomotor stimulant behavior. In a dose response fashion, cocaine (20 mg/kg SC) significantly increased all psychomotor stimulant behaviors (ANOVA: $p<0.0001$, N = 4, $df = 4,20$): ambulations (F = 73.525), rearing (F = 48.836), fine movements (F = 40.967) and central ambulations (F = 27.034) above basal same animal control values. All of the psychomotor stimulant behaviors, induced by cocaine, returned to baseline values in the fifth hour (data not shown). DA and 5-HT changes were highly correlated ($\rho = .9$, $p<0.01$) with ambulation behavior. Agoraphobic inhibition began to occur immediately and significantly ($p<0.0001$) after cocaine injection. The inhibition of agoraphobia was also highly correlated with simultaneous DA and 5-HT changes induced by cocaine ($\rho = 1.0$, $p<0.01$).

Table 3 shows a time course effect of cocaine (40 mg/kg SC) on psychomotor stimulant behavior. Cocaine (40 mg/kg SC) significantly increased each of the psychomotor stimulant behaviors (ANOVA, $p<0.0001$, N = 5, $df = 4,20$): ambulations (F = 94.242), rearing (F = 14.262), fine movements (F = 33.737) and central

TABLE 4

THE EFFECT OF SALINE ON BEHAVIORAL PARAMETERS: TIME COURSE

	Ambulations	Central Ambulations	Rearing Behavior	Fine Movements
Pre - saline	642.60 ± 206.80	1.06 ± 0.61	14.62 ± 8.94	20.42 ± 11.05
	189.00 ± 77.97	0.10 ± 0.00	0.28 ± 0.18	1.46 ± 0.96
	119.60 ± 23.41	0.10 ± 0.00	0.10 ± 0.00	1.86 ± 1.34
	103.60 ± 32.01	0.10 ± 0.00	0.88 ± 0.78	1.08 ± 0.98
	273.00 ± 110.71	0.10 ± 0.00	2.46 ± 1.92	5.84 ± 4.38
	184.40 ± 72.98	0.48 ± 0.38	4.08 ± 3.98	4.46 ± 3.90
	252.03 ± 81.87	**0.32 ± 0.16**	**3.74 ± 2.26**	**5.85 ± 3.01**
Post - saline	*821.00 ± 215.46	*2.04 ± 0.81	*24.42 ± 9.13	*32.20 ± 11.40
1st Hour	302.2 ± 82.28	0.28 ± 0.18	5.71 ± 2.73	9.51 ± 2.95
	234.3 ± 77.41	0.53 ± 0.38	6.82 ± 2.30	7.11 ± 2.65
	85.80 ± 26.47	0.10 ± 0.00	0.10 ± 0.00	0.28 ± 0.18
	154.40 ± 68.39	0.10 ± 0.00	1.46 ± 0.96	2.46 ± 2.14
	222.20 ± 178.58	0.48 ± 0.38	2.88 ± 2.78	10.86 ± 10.54
	303.32 ± 107.83	**0.59 ± 0.30**	**6.9 ± 3.65**	**10.40 ± 4.66**
Post - saline	229.80 ± 117.46	0.10 ± 0.00	0.10 ± 0.00	2.24 ± 1.48
2nd Hour	211.80 ± 59.78	0.10 ± 0.00	0.28 ± 0.18	1.22 ± 0.36
	98.00 ± 40.94	0.10 ± 0.00	0.10 ± 0.00	1.48 ± 1.38
	198.80 ± 67.55	0.10 ± 0.00	0.10 ± 0.00	0.48 ± 0.38
	111.20 ± 41.50	0.10 ± 0.00	0.10 ± 0.00	1.68 ± 1.58
	89.60 ± 53.39	0.10 ± 0.00	0.10 ± 0.00	2.48 ± 2.38
	156.53 ± 25.93	**0.10 ± 0.00**	**0.13 ± 0.03**	**1.60 ± 0.20**

*$p<0.05$, 95% confidence limits of the mean (cf. text for ANOVA statistics). Bold: Hourly mean ± SE (N = 5) from each accumulated 10 min mean ± SE (N = 5).

ambulations ($F = 63.961$) above basal same animal control values. Inhibitory agoraphobic behavior occurred immediately and significantly ($p<0.0001$) after cocaine injection. Reduction in agoraphobia was highly correlated with cocaine-induced alterations in the biogenic amines, DA and 5-HT ($\rho = .95$, $p<0.01$). DA and 5-HT changes were highly correlated with ambulations behavior ($\rho = .85$, $p<0.05$), rearing behavior ($\rho = .8$, $p<0.05$) and fine movements ($\rho = .95$, $p<0.01$). Fine movements were significantly ($p<0.0002$) increased over those which were induced by cocaine (20 mg/kg SC).

Table 4 shows that saline did not significantly increase any psychomotor stimulant behavior: ambulations [ANOVA: $F(2,10) = 3.517$, $p<0.0697$, $N = 5$], rearing [ANOVA: $F(2,10) = 3.657$, $p<0.0643$, $N = 5$], central ambulations [ANOVA: $F(2,10) = 3.171$, $p<0.0858$, $N = 5$] and fine movements [ANOVA: $F(2,10) = 4.85$, $p<0.0789$, $N = 5$] over basal control values. Behavior resulting from transient arousal were apparent ten minutes after saline injection. These effects do not, however, correlate with the concurrent neurochemical measures.

DISCUSSION

The data show that synaptic concentrations of DA in nucleus accumbens in freely moving rats are significantly increased by cocaine. These data are consistent with others (7, 17, 21), and lend support to the generally accepted hypothesis that the continuous changes in synaptic DA induced by cocaine are due to an indirect agonist action (12), which occurs by either a DA reuptake inhibition (4), increased DA release (3a,29) or both. The data support the reported action of an acute decreased response of somatodendritic DA neurons to a cocaine-induced terminal accumbens activated DA increase (9). The strong correlation between the cocaine-induced increase in DA synaptic concentrations and the cocaine-induced psychomotor stimulant behavior supports the hypothesis that the neurochemically reinforcing and the behaviorally reinforcing properties of cocaine are coincident in homology (32). The long-lasting effect of cocaine, when it is given by the subcutaneous route, is consistent with the pharmacokinetics of subcutaneous cocaine (19). The significantly increased stereotypic grooming and sniffing behaviors (fine movements) after cocaine are most dramatic at the highest dose of cocaine. This is a finding consistent with previous behavioral data (23).

That cocaine decreased synaptic concentrations of 5-HT, in vivo, is a new finding. The opposing directionalities of the serotonergic and the dopaminergic action of cocaine show a high correlation to cocaine-induced measures of psychomotor stimulant activity. The relevant outcome of this finding is that decreased synaptic concentrations of 5-HT are highly correlated with the reinforcement capabilities of cocaine. Also important about the present findings is that the depressed serotonergic neurochemistry, underlying the action of cocaine on presynaptic mesolimbic circuitry, is consistent with a direct coupling to a cocaine-induced depressed somatodenditic dorsal raphe impulse frequency, previously shown by others (5). The previous paper (5) attributed the silenced 5-HT neurons in dorsal raphe after cocaine to a consequence of somatodendritic autoinhibition. It was postulated that 5-HT neuronal depression may be due to a compensatory neuronal feedback from cocaine-induced enhanced 5-HT-reuptake inhibition at neuronal terminals. The present data, however, indicate a direct autoreceptor-type agonistic action for cocaine on 5-HT. The discovery that cocaine acts peripherally at the 5-HT_3 receptor (10), although as a weak antagonist, supports this hypothesis. Since the CNS serotonergic properties of cocaine are just emerging, it is not unlikely that cocaine exerts

a 5-HT agonist action centrally and a 5-HT antagonist action peripherally, similarly to the action of the psychostimulant lysergic acid diethylamide (LSD) (8). Future provocative strategies for cocaine treatment modalities, then, can be based on the simultaneous and opposing modulatory roles for DA and 5-HT in reinforcement.

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