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Cocaine and Regional Brain Monoamines in Mice

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HADFIELD, M. G. AND C. MILIO. *Cocaine and regional brain monoamines in mice.* PHARMACOL BIOCHEM BEHAV **43**(2) 395–403, 1992. – Cocaine HCl (0, 10, or 50 mg/kg) was injected into adult male ICR mice IP. Thirty minutes later, brains were removed and nine regions were isolated: olfactory bulbs (OB), olfactory tubercles (OT), prefrontal cortex (PC), septum (SP), striatum (ST), amygdala (AMY), hypothalamus (HT), hippocampus (HC), and thalamus (TH). Using high-performance liquid chromatography, concentrations of norepinephrine (NE), dopamine (DA), serotonin (5-HT), and their major metabolites were determined. At 10 mg/kg cocaine, NE levels were increased in the AMY and its metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), was decreased in the PC, AMY, and HT. DA levels were also increased in the AMY, while its intracellular metabolite, dihydroxyphenylacetic acid (DOPAC), was decreased in the ST and its extracellular metabolite, homovanillic acid (HVA), was decreased in the PC. 3-Methoxytyramine (3-MT) levels were not altered in any tissue. 5-HT levels were increased in the AMY, HT, and TH, while its metabolite 5-hydroxyindoleacetic acid (5-HIAA) was decreased in the OB and ST. MHPG/NE ratios were decreased in the PC, AMY, and HT as were those for HVA/DA. DOPAC/DA ratios were decreased in the ST and AMY and increased in the SP while those for 3-MT/DA were decreased in the TH and increased in the PC. 5-HIAA/5-HT ratios were decreased in the AMY, HC and TH. At 50 mg/kg cocaine, there was an increase in DA in the TH. There was a decrease in DOPAC, HVA, and 3-MT, as well as the DOPAC/DA ratio in the ST. In the OT, there was a decrease in DOPAC, the DOPAC/DA ratio, 3-MT, and the 3-MT/DA ratio. HVA was increased in the TH. There was a decrease in 5-HIAA in the ST, HT, and TH. The 5-HIAA/5-HT ratio was decreased in the OT, PC, ST, AMY, HT, and TH.

Cocaine Monoamines Norepinephrine Dopamine Serotonin Metabolites Brain regions Mouse HPLC

COCAINE'S CNS effects are generally attributed to its action as a potent uptake inhibitor of norepinephrine (NE) (24), dopamine (DA) (14,15) and 5-hydroxytryptamine (5-HT) (23) at synaptic membranes. Cocaine also alters the concentration, release, synthesis, turnover, metabolism, and receptor sensitivity of monoamine neurotransmitters (1,3,6,8,9,11,15,17, 19,21). Yet, we know relatively little about cocaine's regional effects on brain monoamines. In the present study, we analyzed the concentration of NE, DA, 5-HT and their major metabolites in nine strategic mouse brain regions. The metabolite/neurotransmitter ratios were calculated as an indicator of neurotransmitter utilization.

METHOD

Adult male ICR mice (5–7 weeks of age) were used exclusively in these experiments (Dominion Laboratories, Dublin, VA). They were housed in an approved animal facility under the supervision of a doctor of veterinary medicine. Animals were kept under controlled conditions of temperature and humidity and received standard lab chow and water ad lib. Cocaine was administered IP at a dose of 10 mg/kg to 10 animals. Ten drug-free control animals received physiological saline IP. The experiment was repeated using a dose of 50 mg/kg cocaine. Thirty minutes later, brains were rapidly removed and frozen in liquid nitrogen (−320°C) to isolate the olfactory bulbs (OB) (10 mg/kg only), olfactory tubercles (OT), prefrontal cortex (PC), septum (SP), striatum (ST), amygdala (AMY), hypothalamus (HT), hippocampus (HC), and thalamus (TH). The amount of tissue obtainable from the nucleus accumbens (NA) was inadequate for analysis. The tissues were then weighed and homogenized in sodium acetate buffer that contained isoproterenol (IP) as an internal standard. The homogenate was filtered and centrifuged, and the monoamines were extracted in ascorbate oxidase before injection into our high-performance liquid chromatography (HPLC) system (12,13). The data were recorded as nanograms of monoamine/gram brain tissue for: NE, 3-methoxy-4-hy-

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TABLE 1

EFFECTS OF COCAINE (10 AND 50 mg/kg) ON REGIONAL BRAIN LEVELS OF NE, DA, 5-HT, AND THEIR MAJOR METABOLITES

	OB		OT		PC		SP		ST	
	C	E	C	E	C	E	C	E	C	E
A 10 mg/kg										
NE	53 ± 7 2	51 ± 8 0	23 ± 2 3	24 ± 3 0	59 ± 4 4	58 ± 28	116 ± 12	120 ± 8		
MHPG	14 ± 1 9	11 ± 1 5	7 ± 0 6	10 ± 1 6	21 ± 1 4	16 ± 2.0*			41 ± 1 6	43 ± 2 6
MHPG/NE	0 22 ± 0 029	0.20 ± 0.030	0 33 ± 0.036	0.35 ± 0.048	0.42 ± 0.022	0 26 ± 0 022‡				
DA	116 ± 14	107 ± 14	1,399 ± 158	1,779 ± 207	26 ± 2 9	25 ± 2.1	51 ± 3 4	62 ± 14	2,998 ± 100	3,166 ± 233
DOPAC	16 ± 2	14 ± 2	48 ± 15	51 ± 15	4 8 ± 1	4 5 ± 0.6			211 ± 10	162 ± 15§
DOPAC/DA	0 14 ± 0 017	0 14 ± 0.022	0 037 ± 0 007	0.032 ± 0 006	0 26 ± 0 06	0.18 ± 0.027	35 ± 4 9	67 ± 8.9§	0.073 ± 0.002	0 048 ± 0 003‡
HVA	24 ± 5 4	27 ± 5 1	93 ± 15	108 ± 15	31 ± 3.3	13 ± 4.6†			547 ± 38	491 ± 27
HVA/DA	0.26 ± 0.054	0 29 ± 0.047	0 071 ± 0 008	0 058 ± 0 005	1 3 ± 0.17	0 65 ± 0.20*			0 175 ± 0 013	0 161 ± 0 008
3-MT	6 ± 1	10 ± 3			12 ± 4 7	17 ± 2.4			235 ± 8 3	251 ± 28
3-MT/DA	0 046 ± 0 006	0 081 ± 0.023			0 33 ± 0 072	0 67 ± 0.096*			0 078 ± 0 003	0.078 ± 0 003
SER	84 ± 9.8	76 ± 12			109 ± 9.3	116 ± 5.3	129 ± 28	139 ± 26	99 ± 10	94 ± 66
5-HIAA	40 ± 6	26 ± 2.8*	39 ± 5 3	48 ± 6 4	28 ± 2 1	27 ± 1.9			58 ± 4 8	43 ± 4 4*
5-HIAA/SER	0 45 ± 0 042	0 36 ± 0 038			0 27 ± 0.031	0 23 ± 0 015			0 6 ± 0 06	0 5 ± 0 04
B. 50 mg/kg										
NE			42 ± 5 5	40 ± 4 2	76 ± 11	110 ± 17	235 ± 20	189 ± 11		
MHPG			20 ± 3 3	19 ± 2 9	13 ± 0.7	17 ± 1 6*			53 ± 8 1	44 ± 6 2
MHPG/NE			0.48 ± 0.044	0 44 ± 0 050	0 20 ± 0.025	0.17 ± 0.03				
DA			1,244 ± 69	1,482 ± 99	21 ± 1 3	29 ± 3.7	66 ± 14	32 ± 3 9	7,119 ± 688	5,670 ± 509
DOPAC			101 ± 5 5	68 ± 5.3‡					209 ± 14	121 ± 15‡
DOPAC/DA			0.078 ± 0 003	0 047 ± 0 003‡					0.031 ± 0 001	0 022 ± 0 001‡
HVA			141 ± 17	123 ± 7 2			34 ± 6.7	39 ± 5 5	689 ± 71	483 ± 61*
HVA/DA			0 127 ± 0 026	0 081 ± 0 003					0.099 ± 0 011	0 083 ± 0.005
3-MT			106 ± 11	60 ± 5 9†					331 ± 42	219 ± 25*
3-MT/DA			0 085 ± 0 009	0 037 ± 0.004‡					0 046 ± 0 004	0 040 ± 0.004
SER			209 ± 14	252 ± 19	76 ± 5 4	96 ± 12	209 ± 19	198 ± 26	156 ± 12	139 ± 13
5-HIAA			112 ± 72	90 ± 11	26 ± 1 1	21 ± 2 4	32 ± 9.0	31 ± 6 7	132 ± 6 8	96 ± 6 7†
5-HIAA/SER			0.52 ± 0 017	0 37 ± 0 031†	0 36 ± 0 028	0 21 ± 0.023†			0 89 ± 0 049	0 69 ± 0 039†

continued

TABLE 1. Continued.

	AMY		HT		HC		TH	
	C	E	C	E	C	E	C	E
A. 10 mg/kg								
NE	82 ± 5.2	96 ± 3.7*	299 ± 16	292 ± 16	86 ± 3.7	91 ± 2.9	128 ± 7.5	127 ± 6.3
MHPG	21 ± 2 1	12 ± 1.3†	56 ± 2.8	43 ± 1.9†	9.8 ± 0.8	7.6 ± 0.8	26 ± 2.4	25 ± 3.2
MHPG/NE	0.27 ± 0.038	0.15 ± 0.019§	0.18 ± 0.012	0 14 ± 0.010§	0.11 ± 0.008	0.083 ± 0 009	0 21 ± 0.021	0.20 ± 0.028
DA	251 ± 48	454 ± 71*	64 ± 5	70 ± 0 4	44 ± 5	38 ± 4.8	19 ± 1 2	19 ± 1.4
DOPAC	36 ± 6.3	38 ± 4.9	29 ± 2.7	25 ± 3 4				
DOPAC/DA	0.11 ± 0.014	0.077 ± 0.005§	0.44 ± 0.04	0.35 ± 0.031				
HVA	336 ± 69	200 ± 42	67 ± 2.9	64 ± 4.1	9 ± 1.5	8 ± 0 9	20 ± 4	26 ± 10
HVA/DA	1.22 ± 0.304	0.46 ± 0 078*	1.14 ± 0.063	0.90 ± 0.060§	0.23 ± 0.048	0.32 ± 0.12	1 1 ± 0.16	1.2 ± 0.38
3-MT	33 ± 6.9	29 ± 3.8	60 ± 9	60 ± 5.6			17 ± 1.9	13 ± 2.0
3-MT/DA	0.103 ± 0.027	0.070 ± 0.013	0.92 ± 0.14	0.89 ± 0.093			1.1 ± 0.19	0.63 ± 0.060*
SER	209 ± 9.5	243 ± 12*	276 ± 16	319 ± 11*	89 ± 11	114 ± 7.4	181 ± 17	233 ± 16*
5-HIAA	63 ± 3	61 ± 4	122 ± 10	96 ± 8.2	53 ± 7.6	49 ± 4.6	96 ± 7.2	78 ± 6.0
5-HIAA/SER	0.29 ± 0.012	0.24 ± 0.010†	0.44 ± 0.028	0.30 ± 0.020†	0.62 ± 0.067	0 43 ± 0.042	54 ± 0 052	0.35 ± 0.023†
B. 50 mg/kg								
NE	83 ± 5.6	91 ± 7.1	316 ± 29	308 ± 17	45 ± 5.9	54 ± 7.8	97 ± 7 0	104 ± 8.6
MHPG	22 ± 2.3	16 ± 3.2	40 ± 3.6	35 ± 4.2	13 ± 2.7	6 ± 1.1	39 ± 2.2	40 ± 2 0
MPHG/NE	0.29 ± 0.038	0 18 ± 0.047	0.120 ± 0.004	0 110 ± 0.017			0 41 ± 0.023	0 39 ± 0 027
DA	317 ± 43	398 ± 76	49 ± 6.7	34 ± 6.7			35 ± 5 4	72 ± 13§
DOPAC	16 ± 2.7	13 ± 2.7	12 ± 2.3	10 ± 1 8			19 ± 6 8	20 ± 3.4
DOPAC/DA	0.052 ± 0.009	0 039 ± 0.006	0.30 ± 0.080	0.30 ± 0.10			0.37 ± 0.061	0.33 ± 0.076
HVA	38 ± 10	112 ± 39	24 ± 8.4	19 ± 2.9			22 ± 3.7	36 ± 3.0§
HVA/DA	0.133 ± 0.030	0.183 ± 0.044					0 59 ± 0.055	0.58 ± 0.089
3-MT	23 ± 3.8	16 ± 3.8						
3-MT/DA	0.079 ± 0.018	0.048 ± 0.011						
SER	190 ± 20	261 ± 37	208 ± 23	208 ± 15	75 ± 15	67 ± 12	165 ± 15	202 ± 12
5-HIAA	19 ± 3 2	14 ± 3.2	116 ± 6.0	76 ± 7.8†	41 ± 11	26 ± 4 1	97 ± 8.1	73 ± 3.5§
5-HIAA/SER	0.114 ± 0.016	0 043 ± 0.009†	0.611 ± 0.059	0.354 ± 0 045†	0.53 ± 0.061	0.53 ± 0.23	0.61 ± 0.066	0.35 ± 0.030†

*$p < 0.005$.
§$p < 0.02$.
†$p < 0.01$.
‡$p < 0.001$.

droxyphenylglycol (MHPG), DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT), 5-HT and 5-hydroxyindole-3-acetic acid (5-HIAA). Metabolite/neurotransmitter ratios were calculated from the monoamine levels as an indicator of transmitter utilization. All values were subjected to analysis of variance (ANOVA) and, subsequently, Dunnett posthoc tests to determine individual differences. The metabolite/neurotransmitter ratios were converted to percent change of drug values over control values to facilitate evaluation.

RESULTS

Cocaine (10 or 50 mg/kg, IP) selectively altered the concentration of NE, DA, 5-HT, and their major metabolites in mouse brain depending upon the region studied. The metabolite/neurotransmitter ratios calculated from these values were more dramatically affected. The specific values are shown in Tables 1A and B. The ANOVA value for the data as a whole was $p < 0.0005$. For individual values, significant changes and their probability level are indicated by symbols. To appreciate the degree of change visually, these values are converted to percent of control values in bar graphs (Figs. 1-3).

At the 10-mg/kg dose of cocaine, NE levels were increased in the AMY and its metabolite, MHPG, was decreased in the PC, AMY, and HT. DA levels were also increased in the AMY while its intracellular metabolite, DOPAC, was decreased in the ST and its extracellular metabolite, HVA, was decreased in the PC. 3-MT levels were not significantly altered in any tissue. 5-HT levels were increased in the AMY, HT, and TH while its metabolite 5-HIAA was decreased in the OB and ST. MHPG/NE ratios were decreased in the PC, AMY, and HT, as were those for HVA/DA. DOPAC/DA ratios were decreased in the ST and AMY and increased in the SP, while those for 3-MT/DA were decreased in the TH and increased in the PC. 5-HIAA/5-HT ratios were decreased in the AMY, HT, and TH. At the 50-mg/kg dose of cocaine, there was an increase in DA in the TH. There was a decrease in DOPAC, HVA, and 3-MT, as well as the DOPAC/DA ratio in the ST. In the OT, there was a decrease in DOPAC, the DOPAC/DA ratio, 3-MT, and the 3-MT/DA ratio. HVA was increased in the TH. There was a decrease in 5-HIAA in the ST, HT, and TH. Finally, the 5-HIAA/5-HT ratio was decreased in the OT, PC, ST, AMY, HT, and TH.

DISCUSSION

In the present study, cocaine produced a global effect on the serotonergic system. This was demonstrated by a decline in 5-HIAA/5-HT ratios, following the 50-mg/kg dose, in almost every brain region studied. According to George (10), cocaine has the highest affinity for the 5-HT transport site, causing greater inhibition and disruption of 5-HT neurons. Furthermore, only 5-HT neurotoxins decrease the high-affinity binding of cocaine (4). NE and DA neurotoxins do not exhibit this effect. At 10 mg/kg cocaine, 5-HT levels were elevated in the AMY, HT, and TH. At 50 mg/kg cocaine, the 5-HT values were not significantly different from control levels though trends toward an increase were observed in the OT, PC, AMY, TH. Other studies have shown a dose-dependent inhibition of 5-HT cell firing with increasing concentrations of cocaine (4).

There is great variation in the literature on the effect of cocaine on 5-HT biosynthesis (9). Some have shown an inhibition of a high-affinity tryptophan uptake pump (11), whereas others report increases (18) or decreases (25) in tryptophan hydroxylase. Galloway (9) measured in vivo and in vitro 5-HT and DA accumulation after inhibition of aromatic acid decarboxylase with NSD-1015. Cocaine inhibited both 5-HT and DA synthesis in a dose- and time-dependent manner. Friedman et al. (8) reported a decrease in 5-HT turnover. Broderick (2,3) demonstrated differential effects of cocaine on mesolimbic DA and 5-HT release in freely moving animals.

The most consistent effect of cocaine on the dopaminergic system in the present study occurred in the ST. There was a dose-dependent decline in the major DA metabolites, DOPAC, and HVA. DA itself was only significantly increased in the AMY at 10 mg/kg and in the TH at 50 mg/kg. Decreases in DA metabolites have been reported in the NA, ST, and A10 DA region following acute administration of cocaine. However, chronic treatment with cocaine eliminated the decrease in the A10 DA region (20).

Several dialysis experiments in the ST of rats measured an increase in the extracellular DA levels. Rats pretreated with cocaine for 1 week responded to a challenge dose with an increase in DA and a decrease in DOPAC, as well as with behavioral augmentation (1). Similar studies in the NA showed that increased DA levels and decreased DA metabolite values were positively correlated with enhanced motor activity (17,19). Hurd found that IV cocaine produced a dose- and time-dependent effect on extracellular DA in the ST (16). The DA concentrations increased within 10 min and returned to control values after 30 min. When the experiment was performed in a calcium-deficient environment, this pattern was not seen.

It seems that cocaine exerts its effect primarily by releasing DA from its granular stores. This is supported by those employing techniques of extracellular single-cell recording and microontophoresis. Cocaine caused a dose-dependent partial inhibition of the firing rate of the mesoaccumbens A10 DA neurons in the ventral tegmental area (7). When the vesicular stores of DA were depleted by reserpine, the ability of the IV cocaine to suppress A10 neuronal activity was diminished.

DA is responsible for behavioral effects of cocaine such as euphoria, locomotor stimulation, and craving (5,10,22,26). The reinforcing properties of cocaine appear to be due to elevated DA levels in the limbic system (17). Of the above major DA pathways, the mesocortical is less responsive to the effects of cocaine. This is true for our current study where few changes were seen in the PC. Previously, we demonstrated that DA uptake was inhibited more significantly in the ST than in the PC by cocaine (14).

The noradrenergic system was more affected at 10 than at 50 mg/kg cocaine. At 10 mg/kg cocaine, there was an increase in NE in the AMY and a decrease in MHPG and the MHPG/NE ratios in the PC, AMY, and HT. The only change at 50 mg/kg was an increase in MHPG in the PC. No dose-dependent relationships were observed. Pradhan et al. (21) showed a biphasic effect of cocaine on NE at various time intervals. Acute cocaine increased NE levels 10 min following administration whereas a time interval of 20 min decreased values to normal or below normal levels. Gold reported that cocaine activates presynaptic α_2-receptors on NE neurons, which may diminish NE release as the dose of cocaine increases (11). The correlation between the noradrenergic system and behavioral manifestations is unclear. According to deWit and Wise (5), there is no NE involvement in cocaine reinforcement.

In conclusion, it can be seen that cocaine produces selective effects on various serotonergic, dopaminergic, and noradren-

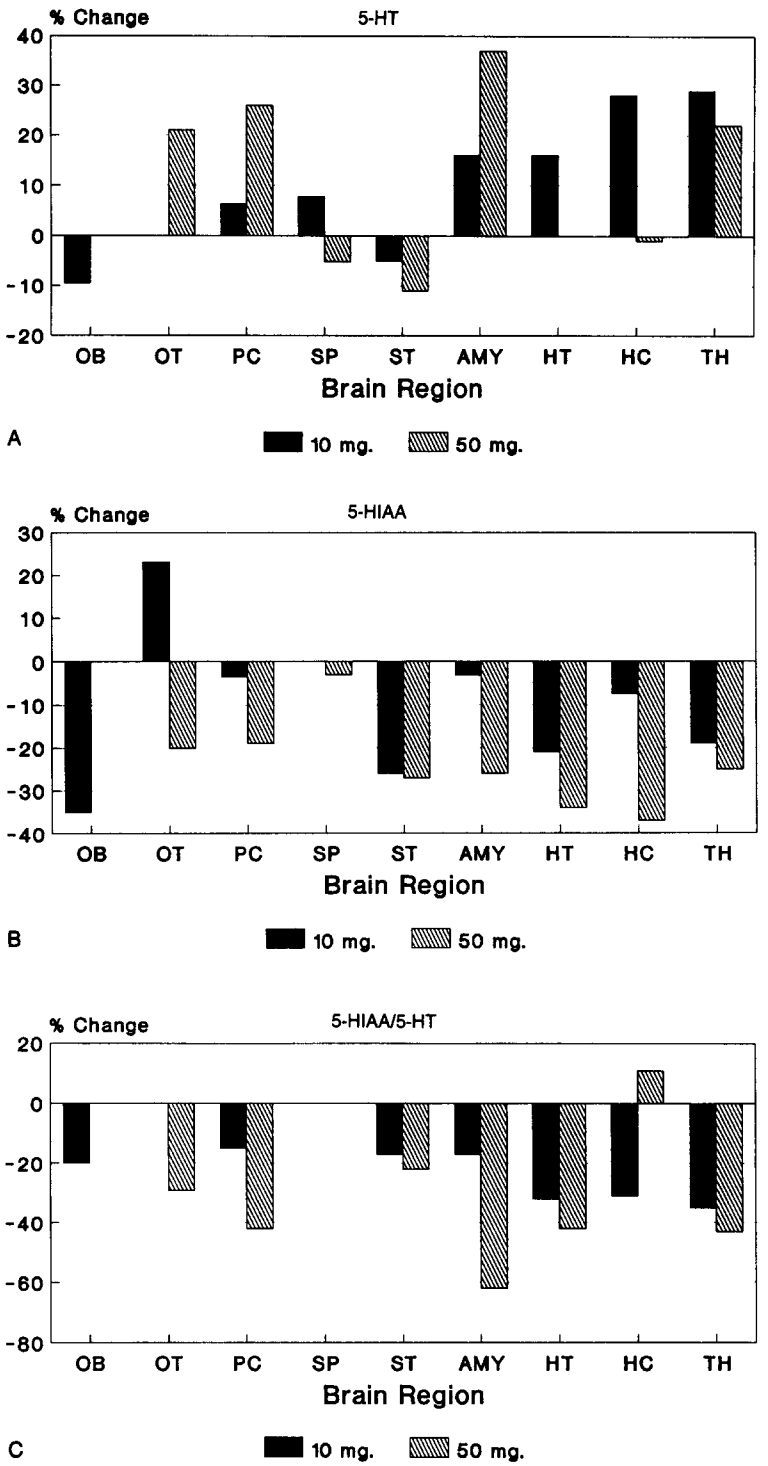
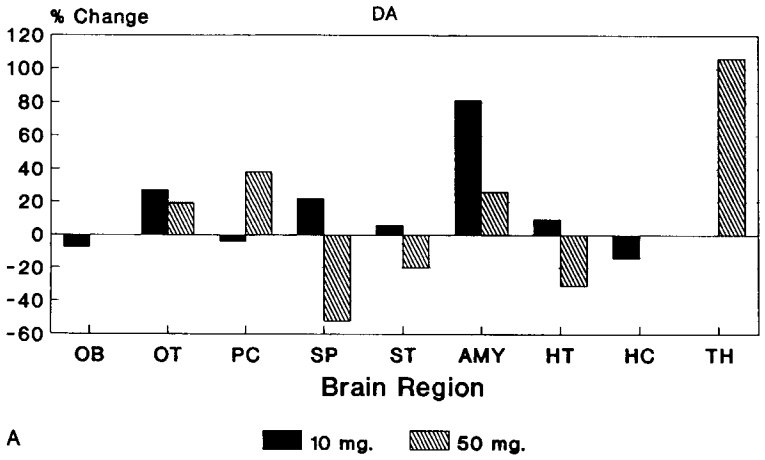
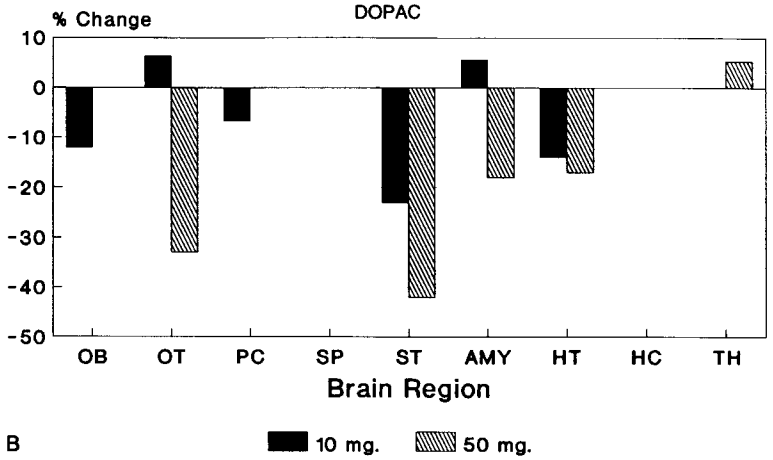


FIG. 1. Serotonergic systems (A) 5-HT; (B) 5-HIAA; (C) 5-HIAA/5-HT. Percent change in regional levels of mouse brain monoamines produced by 10 and 50 mg cocaine HCl (delivered 30 min before intraperitoneally). The baseline, drug-free control values (with which the drug values are compared) are set at 0%. All values are derived from Tables 1A and 1B, which should be consulted for SEs and probability values. Abbreviations used were previously defined in the text. See Table 1 for *p* values.





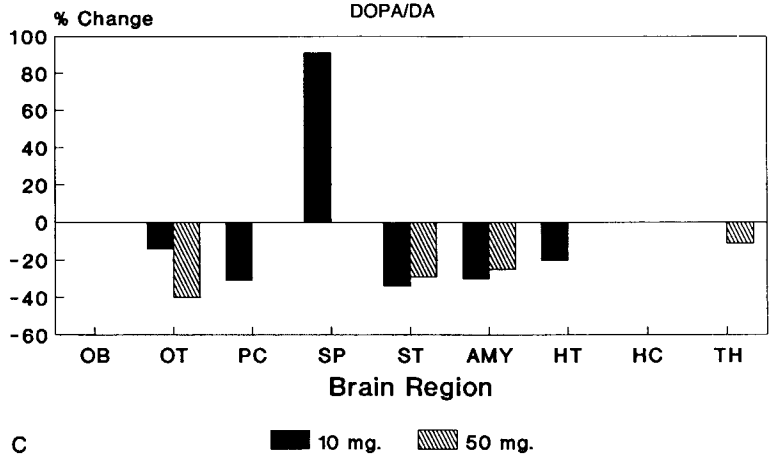
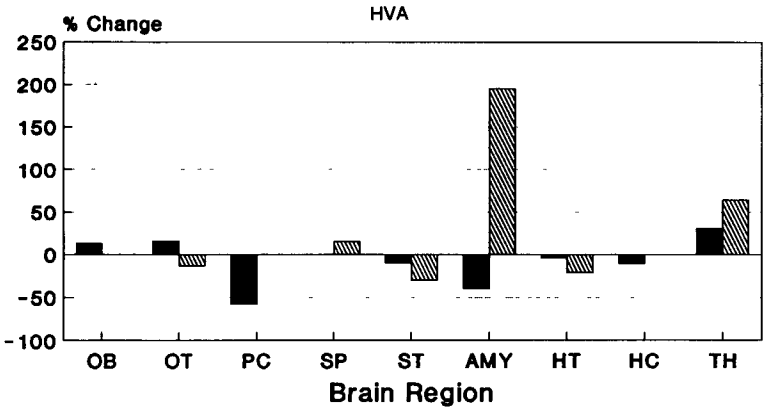


FIG. 2 Dopaminergic systems. (A) DA; (B) DOPAC; (C) DOPAC/DA; (D) HVA; (E) HVA/DA; (F) 3MT, (G) 3-MT/DA. See Table 1 for p values and Fig 1 for details
(continued)



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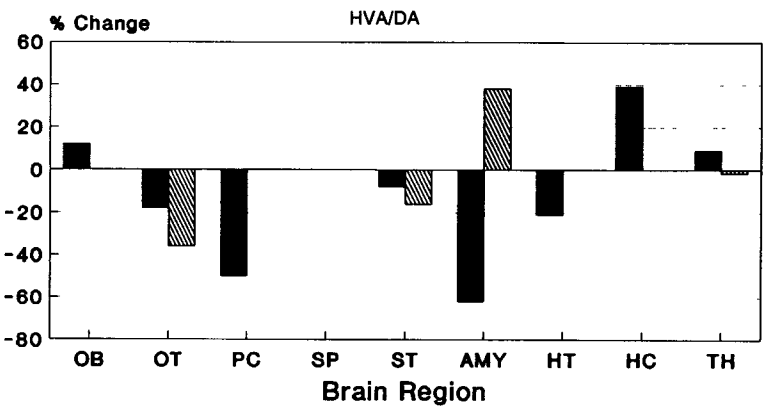

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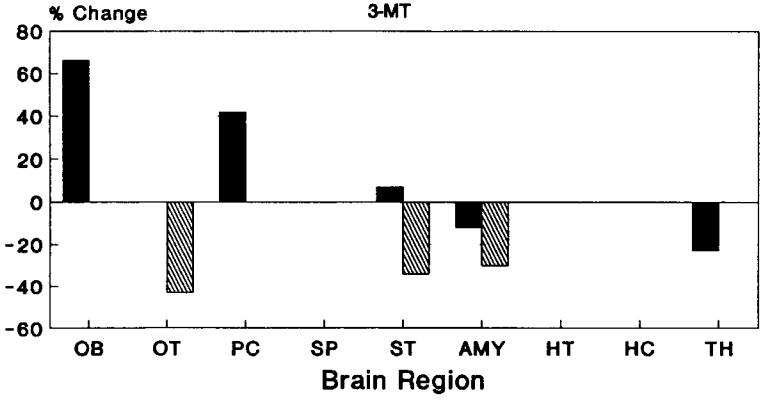

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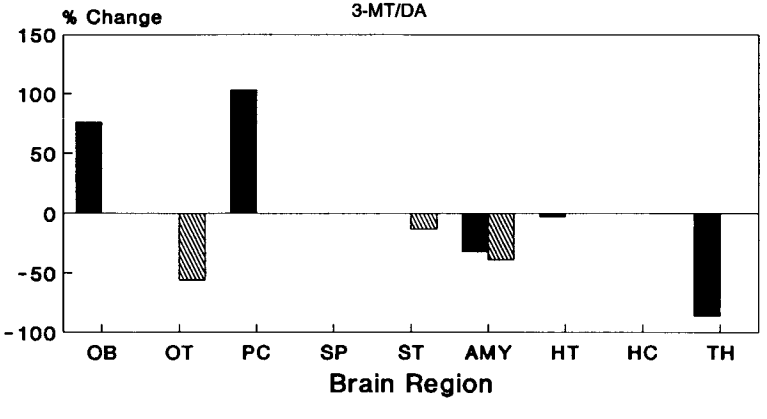

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FIG. 2. Continued.

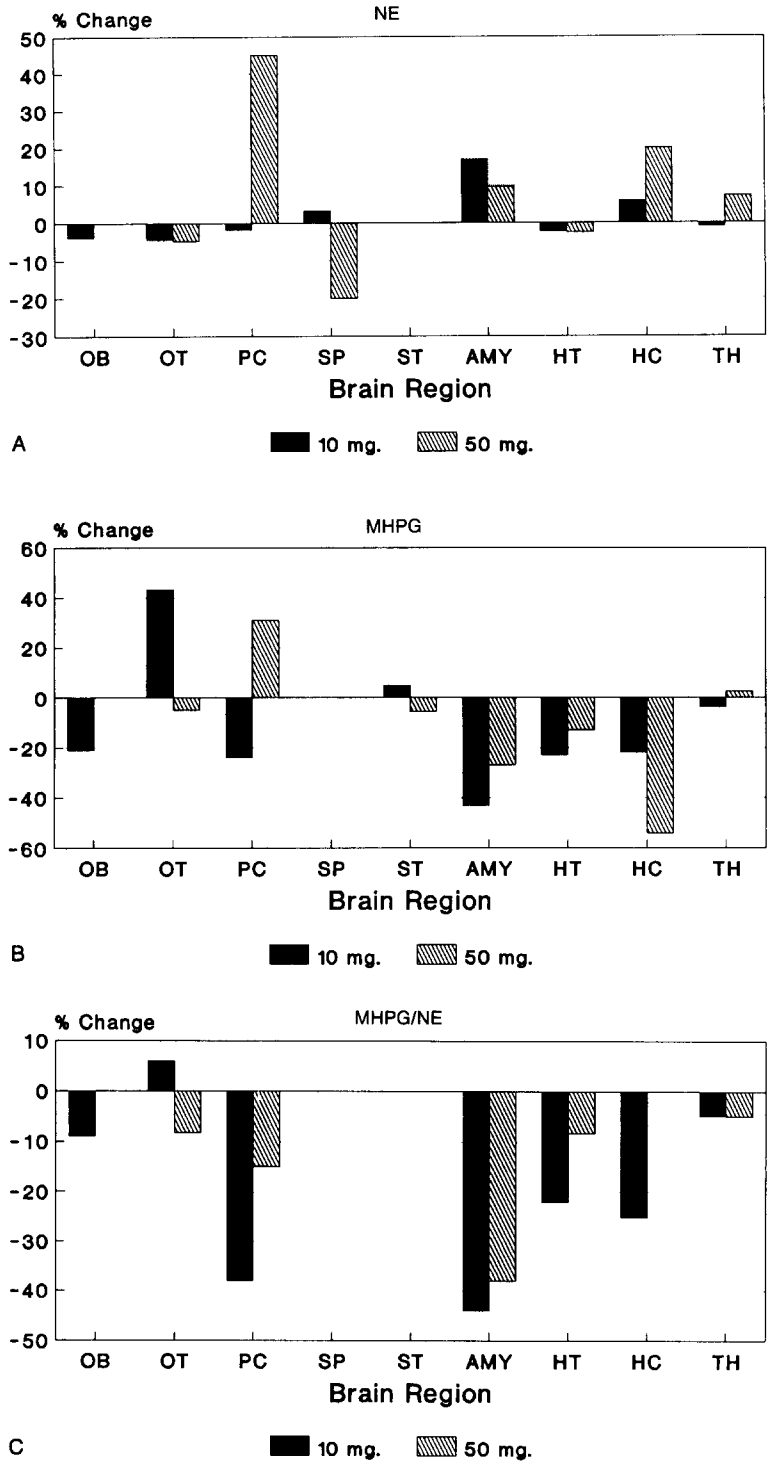

FIG. 3. Noradrenergic systems (A) NE; (B) MHPG; (C) MHPG/NE). See Table 1 for p values and Fig. 1 for details.

ergic systems in the mouse brain depending upon the specific brain region examined and the dose of drug given. These regional actions and the differences produced on the various monoamine systems may be explained in part by variations in the numbers and sensitivity of the native receptor subtypes and transport molecules to cocaine. The fact that cocaine alters certain monoamine systems dramatically, others to a lesser extent, and some not at all, depending upon the brain region studied, provides a unique CNS "signature" or "fingerprint" for this agent. This constellation of monoamine changes must be an important determinant on the behavioral effects that cocaine produces in mice.

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