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Effects of cocaine on dopamine in subregions of the rat prefrontal cortex and their efferents to subterritories of the nucleus accumbens

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Abstract

The present study sought to investigate the contributions of the ventral prelimbic/infralimbic cortices and shell subterritory of the nucleus accumbens as well as the dorsal prelimbic/anterior cingulate cortices and core subregion of the nucleus accumbens to the acute systemic effects of cocaine (20 mg/kg i.p.) on both locomotor activity and simultaneous dialysate dopamine levels using a dual-probe microdialysis design. Basal dopamine levels were significantly higher in the ventral medial prefrontal cortex compared with the dorsal medial prefrontal cortex and higher concentrations of dopamine were also observed in the core of the nucleus accumbens compared with its shell counterpart. Cocaine produced a significant decrease in dopamine levels in both the ventral and dorsal medial prefrontal cortices. In contrast, cocaine significantly increased dialysate dopamine in the shell of the nucleus accumbens, whereas only a slight increase in dopamine was observed in the core subregion of the nucleus accumbens. A significant negative relationship between dopamine levels in the ventral and dorsal medial prefrontal cortices and dialysate dopamine concentrations in the shell and core of the nucleus accumbens was observed. Finally, in both the ventral and dorsal medial prefrontal cortices, the magnitude of the locomotor response to cocaine was inversely related to dialysate dopamine levels. In contrast, the magnitude of the locomotor response to cocaine became progressively larger as dopamine levels increased in the shell of the nucleus accumbens. These results show a dissociation in the pattern of dopamine release in subterritories of both the medial prefrontal cortex and nucleus accumbens in response to the acute systemic administration of cocaine.

Keywords: Cocaine; Dopamine; Cortex, medial prefrontal; Nucleus accumbens; Locomotor activity

1. Introduction

Recent evidence demonstrates that the two main subdivisions of the nucleus accumbens, the dorsolateral core and the ventromedial shell, can be differentiated by a distinct connectivity pattern originating from the medial prefrontal cortex, the basolateral amygdala, the subiculum of the hippocampal formation, and the entorhinal cortex (Zaborszky et al., 1985; Zahm and Heimer, 1990; Heimer et al., 1991, 1997; Berendse et al., 1992; Totterdell and Meredith, 1997). More specifically, the core of the nucleus accumbens receives major projections from the anterior cingulate and dorsocaudal prelimbic cortices, which are referred to as the dorsal prefrontal cortex (Zahm and Brog, 1992; Gorelova and Yang, 1997). In contrast to the core, the shell of the nucleus accumbens receives main afferents from the ventral prelimbic and rostral infralimbic cortices, which are termed the ventral prefrontal cortex (Zahm and Brog, 1992; Gorelova and Yang, 1997). Recent studies have clearly demonstrated that many drugs of abuse (Di Chiara, 1995), atypical neuroleptics (Graybiel et al., 1990; Deutch and Cameron, 1992; Merchant and Dorsa, 1993; Marcus et al., 1996), restraint or pharmacological stress (Deutch and Cameron, 1992; Kalivas and Duffy, 1995; Horger et al., 1995; Holahan et al., 1997; King et al., 1997), and novelty (Rebec et al., 1997; Rebec, 1998) affect dopamine neurotransmission mainly in the shell compartment of the nucleus accumbens. We have also recently shown that amphetamine preferentially increases dopamine and serotonin in the rostral portion and caudal subregion of the medial shell of the nucleus accumbens, respectively (Heidbreder and Feldon, 1998; Heidbreder et al., 1999a). Although most drugs of abuse are readily self-administered into the nucleus accumbens, cocaine is not (Carlezon et al., 1995). However, cocaine is self-administered directly into the medial prefrontal cortex (Goeders and Smith, 1983)

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and 6-hydroxydopamine lesions of dopamine terminals in the medial prefrontal cortex result in a supersensitivity to the reinforcing effects of cocaine (Schenk et al., 1991). Whether cocaine-induced changes in dopamine neurotransmission in the medial prefrontal cortex leads to changes in dopamine within the nucleus accumbens that also mediate the behavioral expression of the cocaine effects is unclear. Bilateral ibotenic acid lesions of the dorsal prefrontal cortex, but not lesions of either the ventral prefrontal cortex, fimbria-fornix, amygdala or periventricular thalamus, block the *expression* of behavioral sensitization to cocaine (Pierce et al., 1998). These results suggest that the dorsal prefrontal cortex, which provides glutamatergic afferents specifically to the core of the nucleus accumbens, enhances the expression of behavioral sensitization to cocaine by increasing glutamate transmission in this subterritory of the nucleus accumbens. Interestingly, quinolinic acid lesions of the prelimbic area of the prefrontal cortex have been reported to affect the *development* of sensitization to the locomotor activating effects of cocaine (Tzschentke and Schmidt, 1998) thus corroborating the idea of a frontal midline area characterized by its own internal functional heterogeneity. The question of whether increased dopamine levels in the shell of the nucleus accumbens as an index of psychostimulant-induced effects is also controlled by subterritories of the prefrontal cortex is unresolved.

The observation that corticostriatal neurons from different laminae of the prefrontal cortex terminate in different subregions of the striatum suggests that this pattern of innervation may provide a functional segregation for cortical control of striatal functions (Gerfen, 1989). If this speculation has credence, it also suggests that neurons originating from deep layers of the prelimbic cortex control a very different aspect of striatal function compared with corticostriatal neurons from the superficial layers of the anterior cingulate cortex. This hypothesis is further supported by the recent discovery that the dopamine transporter, which is a protein that removes dopamine from the extracellular space after its release, is densely distributed in the dorsal anterior cingulate cortex and distributed only sparsely to the deep layers of the prelimbic cortex (Sesack et al., 1998). Moreover, these observations are consistent with the lower immunoreactivity and mRNA signal for the dopamine transporter in the ventral tegmental area as compared with the substantia nigra (Shimada et al., 1992; Ciliax et al., 1995). Thus, the density of the dopamine transporter in terminal regions would reflect differences in the dopamine cells of origin, because the superficial layers of the anterior cingulate cortex are innervated primarily by the A_9 cells dorsal to the substantia nigra pars compacta, the A_8 dopamine cells of the retrorubral area, and to a lesser extent from the A_{10} parabrachial pigmented nucleus and linear nuclei whereas the input to the deep layers of the prelimbic and infralimbic cortices derives from both the parabrachial pigmented nucleus and midline linear nuclei of the ventral tegmental area (Williams and Goldman-Rakic, 1998).

Despite the multiregional character of the medial prefrontal cortex (medial precentral, medial orbital, anterior cingulate, prelimbic, and infralimbic cortices), most recent studies have considered the frontal midline area as a whole entity (Tanda et al., 1997; Wilkinson et al., 1998; You et al., 1998). However, the available literature points to the relevance of conducting a functional analysis of prefrontal subregions to better understand the role of the prefrontal cortex in the regulation of subterritories of the ventral striatum (Mogensen and Holm, 1994; Morgan and LeDoux, 1995; Seamans et al., 1995; Jinks and McGregor, 1997; Ragozzino et al., 1998). Accordingly, the present study sought to study the contributions of the ventral prelimbic/infralimbic cortices and shell subterritory of the nucleus accumbens as well as the dorsal prelimbic/anterior cingulate cortices and core subregion of the nucleus accumbens to the acute effects of cocaine on both locomotor activity and simultaneous dialysate dopamine levels using a dual-probe microdialysis design.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Institute of Toxicology, Schwerzenbach, Switzerland) weighing 300 g were housed in a temperature- and humidity-controlled environment. They had free access to food pellets and water and were kept on a reverse 12 h light/dark cycle. Daily care provided to the animals included changing and cleaning soiled cages, providing food and water, and monitoring the general health of all animals. All the procedures used in this study were approved by the Swiss Federal Veterinary Office.

The animals were anaesthetized with sodium pentobarbital (60 mg/kg i.p.). Each rat was mounted on a stereotaxic apparatus (David Kopf, Topanga, CA) with the upper incisor bar set 3.5 mm below the interaural line. The skull was exposed and a hole drilled for unilateral placement of intracerebral cannula guides into (1) the core of the nucleus accumbens and the ipsilateral dorsal subregion of the medial prefrontal cortex, and (2) the shell of the nucleus accumbens and the ipsilateral ventral subregion of the medial prefrontal cortex. The coordinates, with respect to bregma were as follows (Paxinos and Watson, 1986): for the *shell of the nucleus accumbens*: +1.2 mm anterior (A) to bregma; 0.8 mm lateral (L) to the midsagittal sinus; 5.8 mm ventral (V) to the dura surface; for the *core of the nucleus accumbens*: A = +1.2 mm, L = 2.0 mm, V = 5.8 mm); for the *dorsal part of the medial prefrontal cortex*: A = 2.7 mm, L = 0.5 mm; V = 4.0 mm); for the *ventral part of the medial prefrontal cortex*: A = 3.2 mm, L = 0.5 mm, V = 6.0 mm. Following surgery, the animals were housed individually in Plexiglas cages (50 × 25 × 20 cm)

with free access to food and water. Rats were then allowed to recover for one week before the dialysis experiment started.

2.2. Measurement of locomotor activity

Each microdialysis cage was equipped with one infrared-sensitive miniaturized camera with an 8 mm lens and an infrared light source. The video signal from each camera was forwarded to separate video monitors (Sony, SSM-930CE), which were connected to a video cassette recorder (Sony, SVT-1000P), a digital field switcher (Panasonic, WJ-FS20) and a Sony Trinitron monitor. The digital field switcher allowed the connection of four cameras, and permitted either single or quad output pictures for monitoring of behavior and behavioral analysis. In addition to this on-line observational system, an infrared sensor unit (Coulbourn Instruments, Model E24-61) was positioned on a stand with an angle of 15° at 40 cm above the bottom of the cage. The movement units detected by the sensor were transmitted through an infrared motion interface (Coulbourn Instruments, Model E91-12-421) to an infrared motion activity monitor controller (Habitest Universal Link, Coulbourn Instruments). Data recording was controlled by an IBM-PC clone. Each experimental group (nucleus accumbens shell–ventral medial prefrontal cortex vs. nucleus accumbens core–dorsal medial prefrontal cortex) contained 6 rats, and assignment of these rats to the activity cages was counterbalanced across all groups.

2.3. Brain microdialysis procedure

Four hours before the beginning of the experiment, the animals were briefly anaesthetised with methoxyflurane (Pitman-Moore, Mundelein, IL) to facilitate manual insertion of the microdialysis probes (CMA/7, 2 mm active membrane length) into the guide cannulae. The animals were then placed into circular polycarbonate test chambers (ø 30 cm; *H*: 35 cm). Both inlet and outlet tubings of the probes were connected to a dual quartz lined two-channel swivel (Instech Lab., Plymouth Meeting, PA) located on a low mass spring counterbalanced arm to allow free movement of the rat within the experimental chamber. The liquid swivel was connected to a gas-tight syringe on a microinfusion pump (Instech 2000, Instech Lab., Plymouth Meeting, PA). The microdialysis probes were flushed at 1.0 μl/min with artificial cerebrospinal fluid containing 145 mM NACl, 2.7 mM KCl, 1.0 mM $MgCl_2 \cdot 6H_2O$, 1.2 mM $CaCl_2 \cdot 2H_2O$, and 2.0 mM Na_2HPO_4, adjusted to pH 7.4 with 85% H_3PO_4 (high pressure liquid chromatography grade). The physiological perfusate was filtered through a 0.22 μm filter (Millipore, Bedford, MA). When the experiment started, dialysate samples were collected every 10 min at 2.2 μl/min in polyethylene microcentrifuge vials. Once dopamine levels in the perfusates had stabilized (100 min), six consecutive samples were collected every 10 min for the determination of basal levels in both the nucleus accumbens and prefrontal cortex. Stable baseline measurements were determined before introducing an independent variable for within animal reliability. Animals were first administered with cocaine (20 mg/kg i.p.) and dopamine levels in both the medial prefrontal cortex and nucleus accumbens were measured for 120 min. All the animals were then challenged with saline (1.0 ml/kg i.p.) and dialysate dopamine levels in both regions were measured for an additional period of 60 min.

2.4. Chromatographic analysis of brain microdialysates

A chromatography workstation (Millenium, Millipore, Bedford, MA) was used in conjunction with a solvent delivery pump (Rheos 4000, Flux Instruments, Switzerland) and an electrochemical amperometric detector (Antec-Decade, Leyden, The Netherlands) with a working electrode set at +750 mV versus Ag/AgCl for the detection of dopamine. A six-port rotary valve (Model 7125, Rheodyne, Berkeley, CA, USA) was used for sample injection. Chromatographic separations were performed using a Chrompack glass column (100 (*L*) × 3 (i.d.) × 9 (o.d.) mm) packed on microparticulate (5 μm) silica gel. The mobile phase consisted of 37.5 mM citric acid, 58.5 mM sodium acetate, 0.72 mM disodium ethylenediamine tetraacetate (Na_2EDTA), and 0.23 mM 1-Octanesulfonic acid sodium salt. To this solution, 0.1% diethylamine and 7% methanol (v/v) were added and thoroughly mixed. The pH of the final solution was adjusted to 4.1 with phosphoric acid (85%). The mobile phase was filtered through a 0.22 μm filter (Millipore, Bedford, MA, USA), degassed under vacuum, and delivered at a flow rate of 1.0 ml/min. The position and height of the peaks of the endogenous components were compared with 22 μl samples of an external calibrating standard solution containing 100, 10, and 1 nM dopamine. The detection limit for dopamine was 0.1 fmol. For in vitro recovery, the same dialysis probes previously used in vivo were placed in a solution of artificial cerebrospinal fluid containing 0, 1, 5, 10, 50, and 100 nM. The probes were perfused with artificial cerebrospinal fluid solutions and the resulting curves were used to calculate their in vitro recoveries. The peak height of the dialysate divided by the peak height of the standard solution gave the relative recovery of the probes. The mean (±S.E.M.) in vitro recovery for dopamine at room temperature (21°C) and 2.2 μl/min for the same probes used in vivo was 13.1 ± 0.4%. The data reported here were not corrected for these recoveries.

2.5. Drugs

Citric acid, sodium acetate, Na_2EDTA, 1-Octanesulfonic acid sodium salt, methanol, diethylamine, and phosphoric acid were analytical grade and were obtained from Sigma (St. Louis, MO, USA) and Fluka BioChemica

(Ronkonkoma, NY, USA). Cocaine hydrochloride was also obtained from Sigma and dissolved in 0.9% saline at 20 mg/ml.

2.6. Histology

After the final dialysis samples were collected, the rat was sacrificed and histological verification of probe placement was made via frozen coronal sections (20 μm thick) using a freezing microtome. The final analysis included 12 animals, with the following number of rats in each group: ventral medial prefrontal cortex-shell ($n = 6$), dorsal medial prefrontal cortex-core ($n = 6$).

2.7. Data analysis

The locomotor activity data were analyzed using a within-subjects analysis of variance with five sequences (basal, cocaine 1, cocaine 2, saline 1, and saline 2) of 6 blocks of 10 min each. After confirmation of main effects or interactions by the overall analysis of variance, contrasts were defined to compare the means of selected levels of the sequences. Statistical significance was set at a probability level of $P < 0.05$ for all tests. The average level of dopamine in three samples immediately preceding the administration of cocaine was defined as the baseline control (100%). Basal dopamine levels were analyzed by an analysis of variance with a main factor of subterritory (ventral medial prefrontal cortex vs. dorsal medial prefrontal cortex, nucleus accumbens shell vs. nucleus accumbens core) and a repeated measurements factor of 3 blocks of 10 min each. Cocaine-induced changes in dopamine were expressed as a percentage of baseline control. An overall analysis of variance with a main factor of subregion (ventral vs. dorsal medial prefrontal cortex, nucleus accumbens shell vs. nucleus accumbens core) and a repeated measurements factor of 18 blocks of 10 min each was applied to the neurochemical raw data. The differences between individual means were assessed with the post-hoc Fischer's Protected test. Statistical significance was set at a probability level of 0.05 for all tests. The relationship between neurochemical data and spontaneous locomotor activity was analysed using regression analyses. The determination rates of the regression model, as well as the partial adjusted regression coefficients, their tests of significance and *P*-values for every variable were calculated.

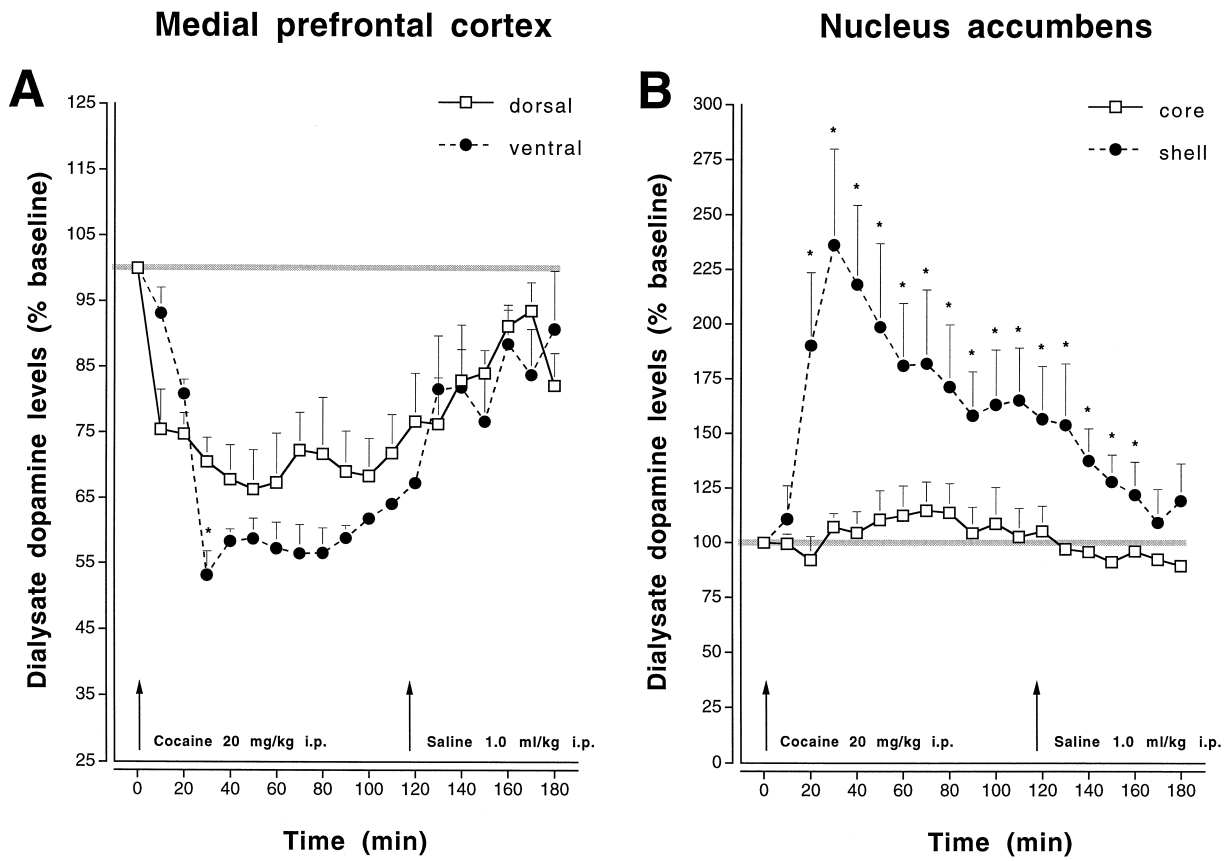

Fig. 1. Medial prefrontal and nucleus accumbens dopamine responses to the acute administration of cocaine. The figure represents the time course of dialysate dopamine levels in subregions of the medial prefrontal cortex (panel A) and nucleus accumbens (panel B) in response to the acute systemic administration of cocaine (20 mg/kg i.p.). The data are expressed as mean (±S.E.M.) percent baseline dopamine and every data point represents a 10 min dialysate sampling period. $^{*}P < 0.05$ as compared with the corresponding sample in the other curve (unpaired *t*-test).

3. Results

3.1. Basal dopamine levels in subregions of both the medial prefrontal cortex and nucleus accumbens

Basal dopamine levels were significantly higher in the ventral medial prefrontal cortex (0.97 ± 0.1 pg/μl sample) compared with the dorsal medial prefrontal cortex (0.18 ± 0.01 pg/μl sample) and higher concentrations of dopamine were also observed in the core of the nucleus accumbens (2.02 ± 0.2 pg/μl sample) compared with its shell counterpart (0.28 ± 0.03 pg/μl sample). An analysis of variance with a main factor of subterritory (ventral medial prefrontal cortex vs. dorsal medial prefrontal cortex) and a repeated measurements factor performed on the last three dialysate samples revealed a significant effect of subterritory ($F(1,10) = 10.1$; $P < 0.01$) but no significant effect of time ($F(2,20) = 2.1$; $P = 0.1$) and no significant subterritory × time interaction ($F(2,20) = 1.5$; $P = 0.2$). The analysis of variance applied to the basal dopamine values from subregions of the nucleus accumbens also revealed a significant effect of subterritory ($F(1,10) = 22.1$; $P < 0.001$) but no significant effect of time ($F(2,20) = 1.3$; $P = 0.3$) and no significant subterritory × time interaction ($F(2,20) = 3.4$; $P = 0.06$).

3.2. Effect of acute cocaine administration on dialysate dopamine levels in subregions of both the medial prefrontal cortex and nucleus accumbens

Cocaine (20 mg/kg i.p.) differentially affected dialysate dopamine levels in the medial prefrontal cortex and nucleus accumbens. Thus, cocaine produced a significant decrease in dopamine levels in both the ventral and dorsal medial prefrontal cortices (Fig. 1A). In contrast, cocaine significantly increased dialysate dopamine in the shell of the nucleus accumbens, whereas only a slight increase in dopamine was observed in the core subregion of the nucleus accumbens (Fig. 1B). Separate analyses of variance with a main factor of subterritory (ventral vs. dorsal medial prefrontal cortex, nucleus accumbens shell vs. nucleus accumbens core) and a repeated measurements factor of time were applied to the data. In the medial prefrontal cortex, there was no significant main effect of subterritory

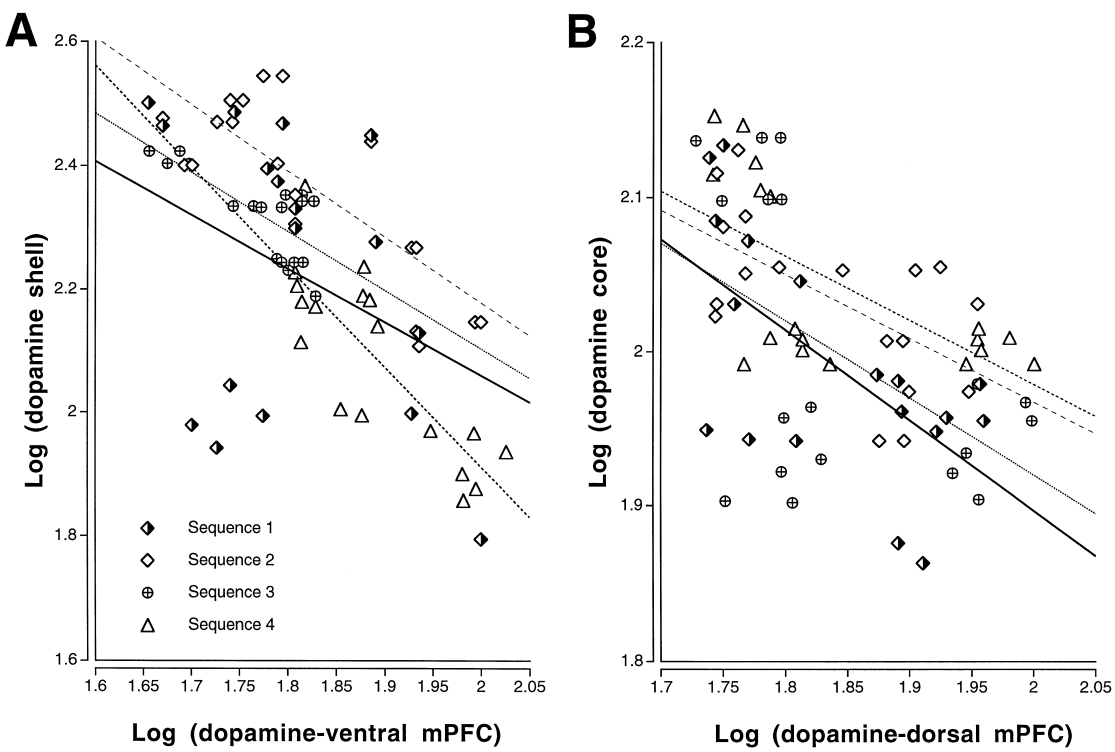

Fig. 2. Relationship between the dopamine response to cocaine into the medial prefrontal cortex and the dopamine response to cocaine into the nucleus accumbens. The figure illustrates that the magnitude of the extracellular dopamine response in both the shell (panel A) and core (panel B) of the nucleus accumbens becomes progressively smaller as dialysate dopamine levels increase in the ventral and dorsal medial prefrontal cortices, respectively. Linear regression analyses were applied to the 4 successive sequences of 30 min (i.e., 120 min) following cocaine administration (6 rats × 3 × 10 min samples each = 18 points per sequence). *Ventral medial prefrontal cortex vs. nucleus accumbens shell*: sequence 1 ($Y = 3.8 - 0.87x$, $r = 0.4$, $r^2 = 0.1$), sequence 2 ($Y = 4.3 - 1.07x$, $r = 0.8$, $r^2 = 0.6$), sequence 3 ($Y = 4.02 - 0.96x$, $r = 0.7$, $r^2 = 0.5$), sequence 4 ($Y = 5.6 - 1.6x$, $r = 0.8$, $r^2 = 0.7$). *Dorsal medial prefrontal cortex vs. nucleus accumbens core*: sequence 1 ($Y = 3.1 - 0.59x$, $r = 0.6$, $r^2 = 0.4$), sequence 2 ($Y = 2.8 - 0.41x$, $r = 0.6$, $r^2 = 0.4$), sequence 3 ($Y = 2.9 - 0.5x$, $r = 0.5$, $r^2 = 0.2$), sequence 4 ($Y = 2.8 - 0.42x$, $r = 0.6$, $r^2 = 0.4$).

($F(1,8) = 0.8$; $P = 0.4$), but there was a significant effect of time ($F(18,144) = 20.1$; $P < 0.0001$) and a significant subterritory × time interaction ($F(18,144) = 2.7$; $P < 0.0006$). In the nucleus accumbens, however, the analysis of variance revealed a significant main effect of subterritory ($F(1,8) = 7.03$; $P < 0.03$) as well as a significant effect of time ($F(18,126) = 10.7$; $P < 0.0001$) and a significant subterritory × time interaction ($F(18,126) = 5.9$; $P < 0.0001$).

3.3. Relationship between changes in dialysate dopamine in subregions of the medial prefrontal cortex and in subregions of the nucleus accumbens following the acute administration of cocaine

A regression analysis of the changes in dialysate dopamine levels in the medial prefrontal cortex over changes in dialysate dopamine levels in the nucleus accumbens following the acute administration of cocaine

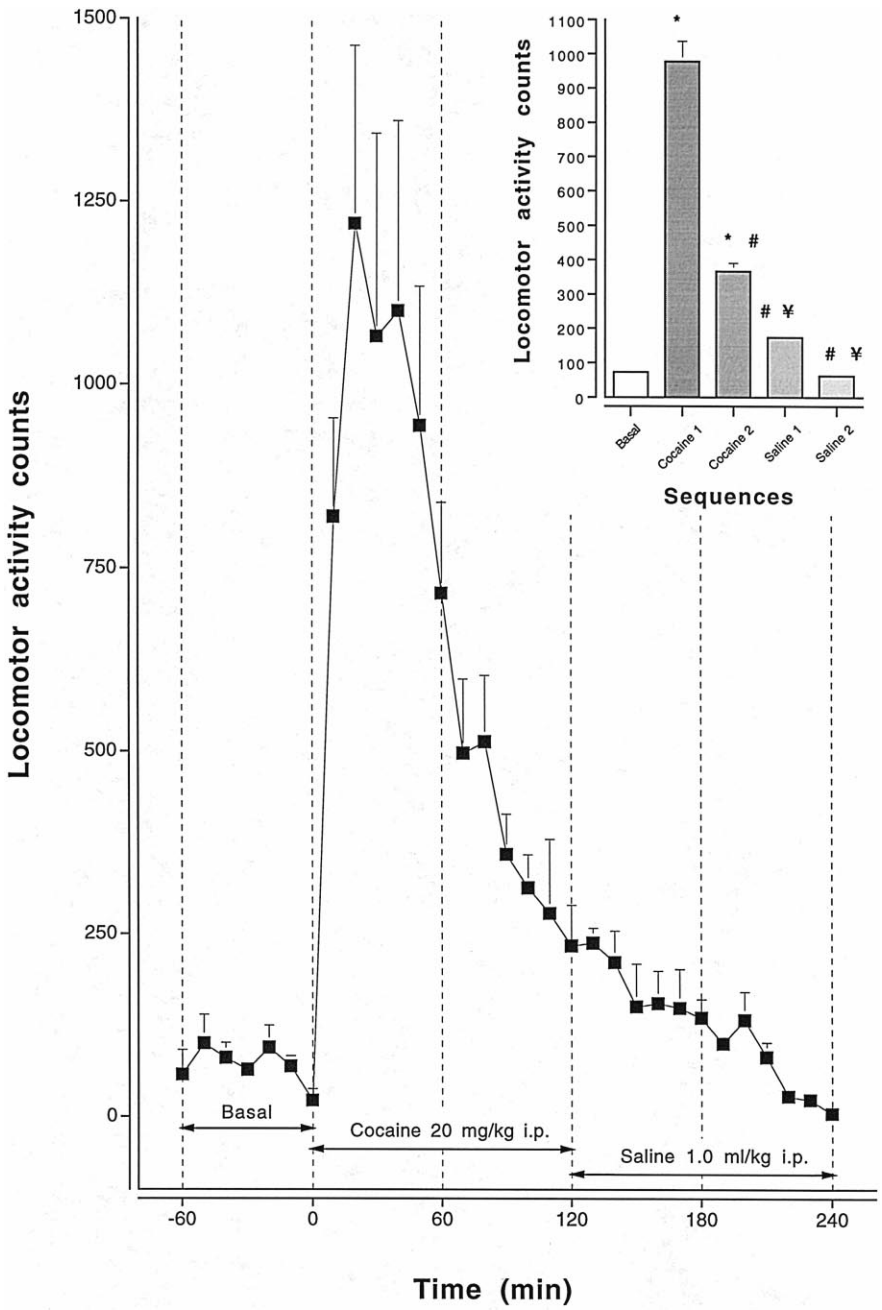

Fig. 3. Locomotor activity in response to the acute administration of cocaine. Following a 60 min habituation period, animals were first administered with cocaine (20 mg/kg i.p.) and locomotor activity was measured for 120 min. All the animals were then challenged with saline (1.0 ml/kg i.p.) and locomotor activity was measured for an additional period of 120 min. The inset shows the mean locomotor activity over five sequences of 60 min each (basal locomotor activity, cocaine 1, cocaine 2, saline 1, and saline 2). $^{*}P < 0.05$ as compared with basal locomotor activity; $\#P < 0.05$ as compared with cocaine 1; ¥$P < 0.05$ as compared with cocaine 2.

(20 mg/kg i.p.) revealed that the magnitude of the extracellular dopamine response in both the shell and core subregions of the nucleus accumbens became progressively smaller as dialysate dopamine levels increased in the ventral and dorsal medial prefrontal cortices, respectively (Fig. 2A, B). Linear regression analyses applied to the 4 successive sequences of 30 min following cocaine administration (6 rats × 3 × 10 min samples each = 18 points per sequence) confirmed a significant negative relationship between dopamine levels in the ventral and dorsal medial prefrontal cortices and dialysate dopamine concentrations in the shell and core of the nucleus accumbens (*ventral medial prefrontal cortex vs. nucleus accumbens shell*: sequence 1 ($F(1, 17) = 2.7$, $P = 0.1$), sequence 2 ($F(1, 17) = 29.3$, $P < 0.0001$), sequence 3 ($F(1, 17) = 19.4$, $P < 0.0004$), sequence 4 ($F(1, 17) = 33.03$, $P < 0.0001$); *dorsal medial prefrontal cortex vs. nucleus accumbens core*: sequence 1 ($F(1, 17) = 10.2$, $P < 0.006$), sequence 2 ($F(1, 17) = 8.9$, $P < 0.008$), sequence 3 ($F(1, 17) = 5.1$, $P < 0.04$), sequence 4 ($F(1, 17) = 10.6$, $P < 0.005$)).

3.4. Effect of acute cocaine administration on locomotor activity

An analysis of variance with a main factor of subregion (ventral medial prefrontal cortex-nucleus accumbens shell vs. dorsal medial prefrontal cortex-nucleus accumbens core) and a repeated measurements factor of either 6 blocks of 10 min each (basal locomotor activity) or 12 blocks of 10 min (cocaine- or saline-induced changes in locomotion) revealed no significant differences between the two dual microdialysis groups (i.e., probes into the ventral medial prefrontal cortex-nucleus accumbens shell vs. dorsal medial prefrontal cortex-nucleus accumbens core). Therefore, the locomotor activity data of these animals were pooled for subsequent data analysis. Fig. 3 shows that cocaine (20 mg/kg i.p.) produced a significant increase in locomotor activity. A within-subjects analysis of variance with five sequences (basal, cocaine 1, cocaine 2, saline 1, and saline 2) of 6 blocks of 10 min each revealed significant effects of sequence ($F(4,44) = 45.7$, $P < 0.0001$) and time ($F(5,55) = 13.9$, $P < 0.0001$) as well as a significant sequence × time interaction ($F(20,220) = 2.9$, $P < 0.0001$).

3.5. Relationship between dialysate dopamine levels in both the prefrontal cortex and nucleus accumbens and locomotor activity in response to the acute administration of cocaine

The relationship between dialysate dopamine levels and locomotor activity produced by the acute administration of

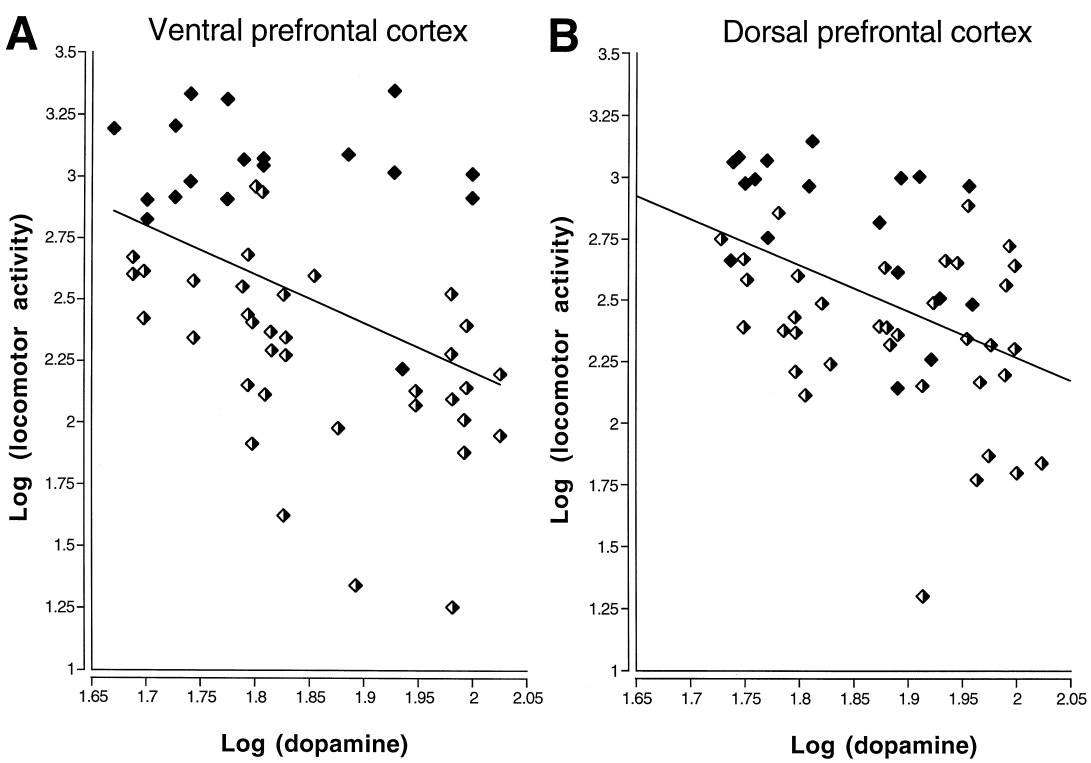

Fig. 4. Relationship between dialysate dopamine levels in subregions of the medial prefrontal cortex and locomotor activity in response to the acute administration of cocaine. The figure represents double logarithmic plots of the dependence of locomotor activity on dialysate dopamine levels in the ventral medial prefrontal cortex (panel A) and dorsal medial prefrontal cortex (panel B). For each animal, the dopamine concentration of the first 30 min (black dots, 6 rats × 3 × 10 min samples each = 18 points) and next 60 min (black and white dots, 6 rats × 6 × 10 min samples each = 36 points) following the acute administration of cocaine was compared with the acute locomotor activating effects of cocaine. *Ventral medial prefrontal cortex*: $Y = 6.16 - 1.97x$, $r = 0.4$, $r^2 = 0.2$; *Dorsal medial prefrontal cortex*: $Y = 6.03 - 1.88x$, $r = 0.4$, $r^2 = 0.2$.

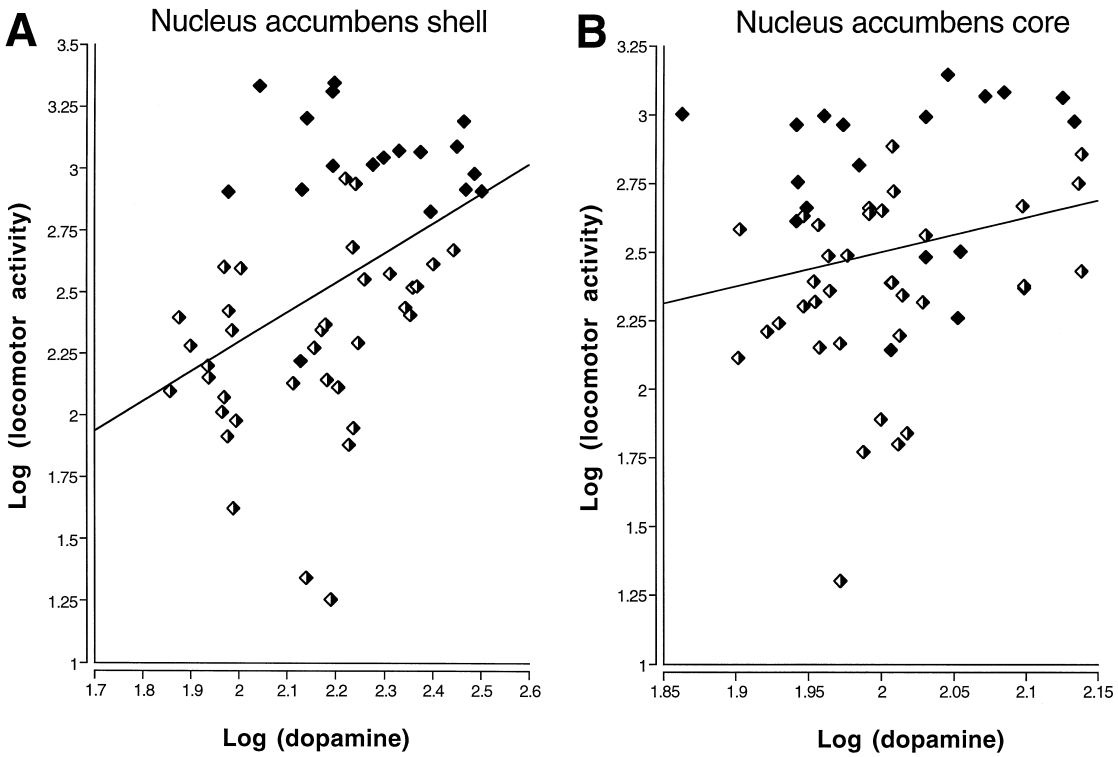

Fig. 5. Relationship between dialysate dopamine levels in subregions of the nucleus accumbens and locomotor activity in response to the acute administration of cocaine. The figure represents double logarithmic plots of the dependence of locomotor activity on dialysate dopamine levels in the shell (panel A) and core (panel B) of the nucleus accumbens. For each animal, the dopamine concentration of the first 30 min (black dots, 6 rats $\times$ 3 $\times$ 10 min samples each = 18 points) and next 60 min (black and white dots, 6 rats $\times$ 6 $\times$ 10 min samples each = 36 points) following the acute administration of cocaine was compared with the acute locomotor activating effects of cocaine. *Nucleus accumbens shell*: $Y = -0.1 + 1.2\,x$, $r = 0.4$, $r^2 = 0.2$; *Nucleus accumbens core*: $Y = 0.007 + 1.25\,x$, $r = 0.2$, $r^2 = 0.04$.

cocaine (20 mg/kg i.p.) was further explored by expressing the acute locomotor effects of cocaine as a function of dialysate dopamine levels in subregions of both the medial prefrontal cortex (ventral vs. dorsal) and nucleus accumbens (shell vs. core). To determine whether the relationship between cocaine-induced dopamine levels and loco-

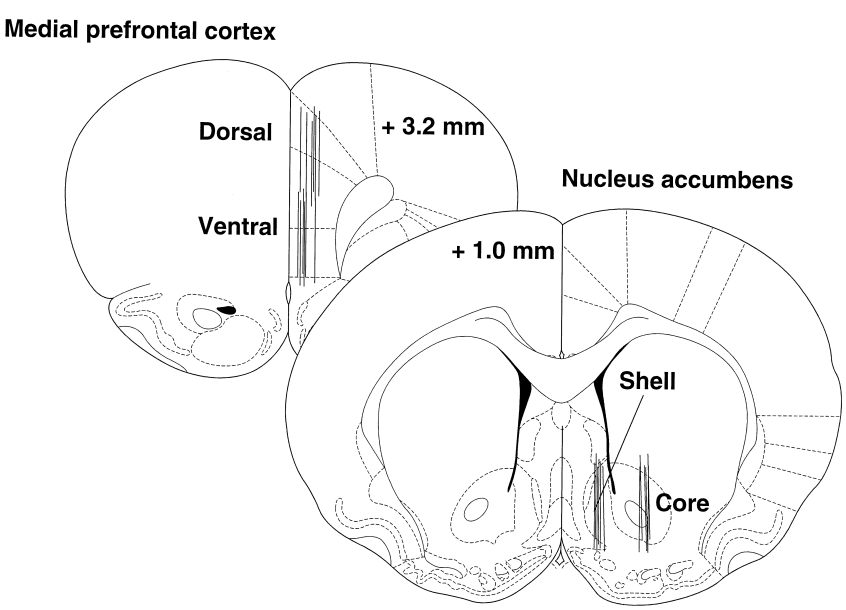

Fig. 6. Location of microdialysis membranes in the dorsal and ventral prefrontal cortices, shell and core of the nucleus accumbens. Silhouettes of probe tracks were drawn onto representative sections of the rat brain (Paxinos and Watson, 1986). The numbers indicate millimeters rostral to bregma.

motor activity differs as a function of subterritories within both the prefrontal cortex and nucleus accumbens, log-transformed data were subjected to linear regression analyses. For each animal, the dopamine concentration of the first 30 min (6 rats × 3 × 10 min samples each = 18 points) and next 60 min (6 rats × 6 × 10 min samples each = 36 points) following the acute administration of cocaine was compared with the acute locomotor activating effects of cocaine. A plot of residuals vs. fitted values of the dependent variable showed a band of constant width, independent of the fitted values, indicating that the assumptions of the general linear model were met. Fig. 4 represents double logarithmic plots of the dependence of locomotor activity on dialysate dopamine levels in both the ventral medial prefrontal cortex (panel A) and dorsal medial prefrontal cortex (panel B) in response to cocaine. Panels A and B illustrate that, in both the ventral and dorsal medial prefrontal cortices, the magnitude of the locomotor response to cocaine was inversely related to dialysate dopamine levels. Linear regression analyses confirmed a significant negative relationship between dopamine levels in the ventral and dorsal medial prefrontal cortices and locomotor activity in response to cocaine administration ($F(1,53) = 11.5$, $P < 0.001$ and $F(1,53) = 12.4$, $P < 0.0009$, respectively). In contrast, Fig. 5 shows that, in the shell of the nucleus accumbens (panel A), the magnitude of the locomotor response to cocaine became progressively bigger as dopamine levels increased ($F(1,53) = 12.0$, $P < 0.001$). Finally, only a trend to a significant relationship between cocaine-induced locomotor activity and dialysate dopamine levels was found in the core of the nucleus accumbens ($F(1,53) = 2.4$, $P = 0.1$) (panel B).

3.6. Histology

Fig. 6 depicts the location of the dialysis membrane in the dorsal medial prefrontal cortex (dorsal anterior cingulate cortex {cingulate area 1 or area 24b} and dorsal prelimbic cortex {cingulate area 3 or area 32}), ventral medial prefrontal cortex (ventral prelimbic and infralimbic cortex {area 25}), shell and core of the nucleus accumbens. Silhouettes of probe tracks were drawn onto representative sections of the rat brain (Paxinos and Watson, 1986).

4. Discussion

The results of the present study demonstrate that basal levels of dopamine were significantly higher in the ventral medial prefrontal cortex compared with the dorsal medial prefrontal cortex and higher concentrations of dopamine were also observed in the core of the nucleus accumbens compared with its shell counterpart. These observations corroborate recent results indicating that there are lower basal dialysate dopamine levels in the shell relative to the core (Pierce and Kalivas, 1995; King et al., 1997; Heidbreder and Feldon, 1998). Several morphometric (Tan et al., 1995), immunohistochemical (Zahm, 1992), and in vivo electrochemical (Wieczorek and Kruk, 1995; Jones et al., 1996; David et al., 1998) studies of the dopamine systems in subterritories of the nucleus accumbens are also consistent with a higher dopamine overflow in the core of the nucleus accumbens compared with its shell counterpart. Our results also indicate that basal dopamine levels were higher in the ventral medial prefrontal cortex compared with the dorsal medial prefrontal cortex. This finding is corroborated by the observation that the deep layers of the prefrontal cortex (ventral prelimbic and infralimbic cortices) along the medial edge of the corpus callosum, correspond to the portion of the prefrontal cortex that has the greatest dopamine innervation density (Ciliax et al., 1995). Furthermore, recent studies have demonstrated that the dopamine transporter is densely distributed in the dorsal anterior cingulate cortex and distributed only sparsely in the deep layers of the prelimbic cortex (Sesack et al., 1998). These findings together with the results of the present study demonstrate that both the ventral prelimbic and infralimbic cortices have a lower content of dopamine transporter and, hence, a reduced but selective dopamine uptake capacity and a higher concentration gradient of extracellular dopamine. In contrast, the distribution of dopamine transporter-labelled axons is higher in the dorsal anterior cingulate cortex, which has an increased but less selective dopamine uptake capacity and a lower concentration gradient of extracellular dopamine. One alternative explanation to the differential basal release properties of dopamine in subregions of both the nucleus accumbens and medial prefrontal cortex is that the serotonin and norepinephrine transporters participate in the uptake and clearance of dopamine. A major role of the serotonin transporter in the clearance of dopamine is unlikely since it has a lower affinity for dopamine compared with both the dopamine and norepinephrine transporters (Hoffman et al., 1991). However, the potential role of the norepinephrine transporter to both the uptake and clearance of dopamine cannot be ruled out. There is a greater distribution of dopamine β-hydroxylase fibers in the shell compared with the core of the nucleus accumbens (Berridge et al., 1997). There also seems to be a dorso-ventral gradient for dopamine uptake in the medial prefrontal cortex. Thus, in the anterior cingulate cortex, dopamine is taken up primarily by norepinephrine terminals through the norepinephrine transporter whereas the dopamine transporter is the major actor in clearing the extracellular dopamine in the infralimbic cortex (Cass and Gerhardt, 1995). The question of whether the norepinephrine transporter affects the clearance rate of dopamine under basal conditions in subregions of both the nucleus accumbens and medial prefrontal cortex requires further investigations.

Cocaine has been shown to bind with high affinity to dopamine, norepinephrine, and serotonin uptake sites, preventing the reuptake of all three monoamines from the

synaptic cleft (Heikkila et al., 1975; Reith et al., 1986). The known pharmacological actions of cocaine indicate that its ability to enhance extracellular dopamine levels depends on extracellular dopamine that is released either by a spike-dependent phasic mechanism or by impulse-independent presynaptic processes (Giorguieff et al., 1977; Clow and Jhamandas, 1989). Moreover, the systemic administration of cocaine (20 mg/kg i.p.) has been shown to produce a non-selective increase in dopamine, norepinephrine, and serotonin in the ventral tegmental area (Reith et al., 1997). Finally, extracellular levels of cocaine in the ventral tegmental area have been reported to be significantly higher than the concentrations of cocaine in the prefrontal cortex following the intravenous administration of 3 mg/kg cocaine (Pan et al., 1994). Thus, by increasing extracellular dopamine at somatodendritic dopamine D_2 autoreceptors in the ventral tegmental area (Robertson et al., 1991), cocaine would inhibit dopamine cell firing (Einhorn et al., 1988) and could be considered an inhibitor of phasically released dopamine. Although the inhibitory effect of cocaine on impulse flow is only partly mediated by presynaptic mechanisms, one way by which cocaine decreases dialysate dopamine levels in the prefrontal cortex would be via a decrease in impulse flow, which would result from the immediate effects of cocaine at the dopamine cell bodies located in the ventral tegmental area. It is also known that dopamine inhibits the activity of pyramidal cells in the prefrontal cortex (Bunney and Aghajanian, 1976; Ferron et al., 1984) primarily through an action on γ-aminobutyric acid (GABA) interneurons (Penit-Soria et al., 1987; Pirot et al., 1992). Furthermore, it has been shown that the postsynaptic sensitivity to GABA in the cerebral cortex seems to be correlated with the regional density of dopamine innervation (Beauregard and Ferron, 1991). Thus, under conditions of low dopamine tonus, GABA neurons would transmit less inhibitory information whereas enhanced dopamine release would make them more inhibitory. In the case of a decrease in dopamine levels in the prefrontal cortex as a result of cocaine-induced changes in the ventral tegmental area, the activity of prefrontal cortex pyramidal cells would be increased and their excitatory influence on subcortical structures would be reinforced. Thus, it seems reasonable to proceed on the working hypothesis that since both dopamine D_1 and D_2 receptors are co-localized in non-pyramidal cells of the prefrontal cortex and particularly in the infralimbic area of the prefrontal cortex (Vincent et al., 1993) and since these non-pyramidal cells most likely correspond to GABA interneurons, one consequence of the cocaine-induced decreased dopamine levels and the resulting dampened activity of GABA interneurons would be to increase the activity of projection neurons to the nucleus accumbens and particularly to the nucleus accumbens shell. This was, in fact, the case in the present set of data that indicates an increase in dopamine levels in the shell subregion of the nucleus accumbens.

Our conclusions that cocaine decreases dialysate dopamine in both subregions of the prefrontal cortex are opposite to those suggested in a recent microdialysis study in which both amphetamine (0.25 and 0.5 mg/kg, s.c.) and cocaine (5 and 10 mg/kg, i.p.) were reported to elevate extracellular dopamine in the prefrontal cortex to a larger extent than in the nucleus accumbens (Tanda et al., 1997). There is no obvious explanation for these discrepant findings, but there are sufficient procedural differences between the two studies to preclude a direct comparison. The most obvious difference beyond the dose of cocaine is in the methods used to measure changes in dialysate dopamine levels in the prefrontal cortex. In our study, discrimination between dorsal and ventral subregions of the prefrontal cortex was made possible by the use of a smaller probe and by the experimental design. In contrast, Tanda et al. (1997) used a 3-mm probe with 20-min sampling periods. Thus, it is possible that the increases in dialysate dopamine levels within the prefrontal cortex reported by Tanda and colleagues reflect the activity of dopamine neurons that innervate sites other than those sampled in the present study. In fact, we have recently reported (Hedou et al., 1999) that reverse microdialysis of amphetamine in the ventral medial prefrontal cortex produced a significant dose-dependent decrease in dialysate dopamine levels, whereas no significant alterations in dopamine levels were observed following amphetamine microinfusion in the dorsal medial prefrontal cortex. Finally, microdialysis probes were implanted contralaterally in the Tanda's study, whereas ipsilateral preparations were used in the present study. A left-biased asymmetry seems to account for the differential role of the mesocortical dopamine system in the ability to cope with stressors (Carlson et al., 1993; Sullivan and Szechtman, 1995), the self-administration of cocaine (Glick et al., 1994), and the utilization of subcortical dopamine (Carlson et al., 1996). Increases in dialysate dopamine levels in response to the acute administration of either cocaine or amphetamine are more pronounced in the left medial prefrontal cortex than in its right counterpart (Maisonneuve et al., 1990). Furthermore, we have recently shown that repeated cocaine administration is associated with a significant decrease in serotonin levels in the left anterior cingulate and pyriform cortices (Heidbreder et al., 1999b). The question of whether cocaine's effects on dopamine dynamics in the medial prefrontal cortex-nucleus accumbens axis are dependent on ipsilateral vs. contralateral preparations remains to be investigated.

Self-stimulation of the prefrontal cortex is known to trigger a syndrome of behavioral inhibition, which is most intense in the prelimbic area of the prefrontal cortex and becomes progressively less pronounced as the stimulation occurs in more caudal sites (i.e., posterior cingulate cortex) (Wilcott, 1981; Spence et al., 1985). In contrast, electrolytic lesions of the ventral tegmental area produce a significant depletion of dopamine in the medial prefrontal

cortex, which is associated with a behavioral syndrome of locomotor hyperactivity (Le Moal et al., 1969). The extent of dopamine depletion in the medial prefrontal cortex is also correlated positively with the amplitude of locomotor hyperactivity (Tassin et al., 1978). Thus, a seesaw between hyper- and hypoarousal states seems to be closely related to the dopamine tone within the medial prefrontal cortex. A similar relationship was observed in the present study with a significant negative relationship between dopamine levels in the ventral and dorsal medial prefrontal cortices and locomotor activity in response to cocaine administration. In contrast, the magnitude of the locomotor response to cocaine became progressively larger as dopamine levels increased in the shell of the nucleus accumbens. Thus, if dopamine exerts a tonic stimulatory control on a subpopulation of GABA interneurons in the ventral prelimbic/infralimbic area of the medial prefrontal cortex (Rétaux et al., 1994), then cocaine-induced decreases in dialysate dopamine levels in this cortical area could produce a decreased activity of GABA interneurons and a behavioral hyperactivity syndrome. This reduction in the GABA tone could, in turn, trigger an increased activity of infralimbic efferents to the shell of the nucleus accumbens by removing the inhibition of pyramidal cells. The resulting increase in dopamine neurotransmission in the shell of the nucleus accumbens, which parallels the locomotor activating effects of cocaine, would then represent the end product of a chain reaction that was triggered by cocaine at the level of the ventral tegmental area. Finally, our results demonstrate that dopamine levels in both the ventral and dorsal medial prefrontal cortices in response to cocaine are inversely related to dialysate dopamine levels in both the shell and core subregions of the nucleus accumbens. Thus, the higher the dopamine levels in the medial prefrontal cortex, the lower the dopamine concentrations in the nucleus accumbens. These results are compatible with the observation that enhancement of dialysate dopamine levels in the medial prefrontal cortex by the local injection of amphetamine decreases basal extracellular levels of both dorsal and ventral striatal dopamine (Louilot et al., 1989; Karreman and Moghaddam, 1996). Furthermore, the local infusion of dopamine D_1, but not D_2 receptor antagonists, results in an enhancement of locomotor activity elicited by intra-nucleus accumbens injections of amphetamine (Vezina et al., 1991; Weihmuller et al., 1991).

In summary, the results of the present series of experiments support the view of a dissociation in the pattern of dopamine release in the medial prefrontal cortex and nucleus accumbens in response to the acute administration of cocaine. Given the obvious relevance of the mesocorticolimbic dopamine system to both psychopathological disorders and drug addiction, the development along these lines of a complex model of monoamine function and interaction between subregions of the medial prefrontal cortex and nucleus accumbens may have important implications for our understanding of how integrated response strategies organized in the medial prefrontal cortex are translated into actions via the nucleus accumbens. This view is further supported by the recent discovery that the dorsal prefrontal cortex participates in the reorganization of behavior within the context of a well-learned task strategy whereas the ventral prefrontal cortex would use mnemonic information to generate and revise planned actions or foraging strategies (Seamans et al., 1995).

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