Functional Domains in Dorsal Striatum of the Nonhuman Primate Are Defined by the Dynamic Behavior of Dopamine

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The dorsal striatum comprises a continuum of distinct functional domains, limbic, associative, and sensorimotor. In the primate it exclusively subdivides further into two nuclei, the putamen and caudate. Dopamine (DA) transmission is differentially affected between these nuclei in neurodegenerative diseases such as Parkinson's and by psychostimulants such as cocaine. Because rodent systems can offer only limited insight into DA systems of the human brain, a fuller appreciation of DA transmission and its role in dysfunction requires direct study in primates.

DA behavior was explored in the major functional domains of the caudate nucleus and compared with the putamen, using fast-scan cyclic voltammetry in striatal sections from the marmoset (*Callithrix jacchus*). There was domain-specific variation in extracellular DA transients [i.e., concentration ($[DA]_o$) released by a single stimulus and the rate maximum of DA uptake, V_{max}]. Across nuclei, functional rather than anatomical regions were differentiated by these dynamics. The largest,

fastest DA transients were at motor-associated loci. Evoked $[DA]_o$ at physiological frequencies was differently frequency-sensitive between functional domains but not between anatomical nuclei. In contrast, presynaptic depression was not an index of regional differentiation, recovering with similar kinetics at all loci.

Within a given functional domain of dorsal striatum, the dynamics of DA release and uptake are similar for the putamen and the caudate nucleus. Conversely, distinct functional domains are defined by these DA dynamics, in a manner more marked in primates than in rodents. These data from the primate brain highlight differences in DA availability that may be central to DA function and dysfunction in the human.

Key words: caudate; putamen; Parkinson's disease; basal ganglia; dopamine transporter; dopamine uptake; marmoset; voltammetry; corticostriatal; nigrostriatal; striatonigral; mesostriatal; cocaine; synaptic depression; primate; ventral striatum

A distinction between putamen (Put) and caudate (Cd) nuclei, divided by the internal capsule, is a hallmark of the primate dorsal striatum. Interestingly, uneven patterns of mesostriatal dopamine (DA) cell loss render the most dorsolateral (dl) regions of the putamen most susceptible, whereas the caudate nucleus remains less affected, in both idiopathic Parkinson's disease (PD) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) parkinsonism in primate models (Hornykiewicz, 1966; Schoemaker et al., 1985; Elsworth et al., 1987; Kish et al., 1988; Maloteaux et al., 1988; Seeman and Niznik, 1990; Kaufman and Madras, 1991; Moratalla et al., 1992; Antonini et al., 1995). However, this anatomical subdivision is only one way of analyzing the primate striatum. In particular, corticostriatal connectivity defines three distinct but interrelated "functional domains" that span the caudate and putamen: ventromedial (vm)/limbic-, central/associative-, and dorsolateral/motor-associated (Kunzle, 1975, 1977; Selemon and Goldman-Rakic, 1985; Haber and McFarland, 1999). Such topographic segregation is maintained throughout the primate basal ganglia, *inter alia*, thalamostriatal (Gimenez-

Amaya et al., 1995; McFarland and Haber, 2000), amygdalostratial (Russchen et al., 1985), striatopallidal (Hazrati and Parent, 1992), and striatonigral projections (Lynd-Balta and Haber, 1994a; Haber et al., 2000) and even somatotropic organization (Crutcher and DeLong, 1984; Alexander and DeLong, 1985). Furthermore, different functional domains receive inputs from different mesostriatal DA neurons (Szabo, 1980; Parent et al., 1983; Smith and Parent, 1986; Lynd-Balta and Haber, 1994b; Haber et al., 2000). Consequently, to understand striatal DA function and, in turn, dysfunction, it is essential to explore these features in functionally rather than anatomically (caudate/putamen) segregated domains.

We have shown previously that within the putamen of a nonhuman primate there are significant differences in DA behavior that parallel the functional organization (Cragg et al., 2000). Yet this same repertoire of region-specific differences is not as apparent in the dorsal striata of rodents (Cragg et al., 2000). In this study, using fast-scan cyclic voltammetry, we have now determined the dynamic behavior of DA in the primate caudate nucleus and compared these findings with those we described previously for the putamen. In this manner, we have determined in real time the dynamics of extracellular DA in limbic- through to motor-associated functional domains throughout the dorsal striatum. We have profiled DA dynamics by single-pulse availability, uptake rate maximum (V_{max}), frequency sensitivity, and presynaptic depression. We address the hypotheses that there are differences in DA dynamics within the caudate nucleus that reflect functional subdivision, akin to that observed in the putamen, rather than the anatomical segregation of the caudate versus

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Figure 1. Regional variation in single pulse-evoked $[DA]_o$ between domains of the dorsal striatum. *a, c*, Mean $[DA]_o$ versus time evoked by a single pulse (arrows) at varying vm to dl coordinates in the Cd and Put at two ranges of AP coordinates of striatum: rostral-central, 11.9–10.5 mm (*a*) and central–postcommissural, 10.25–8.5 mm (*c*). *Inset*, Cyclic voltammogram indicating oxidation and reduction peaks for DA. Typical vm–dl recording sites are illustrated by the circles in *b*, a schematic illustration of a coronal striatal section, 10.5 mm. IC, Internal capsule; Dors, dorsal; Lat, lateral. At both coordinate ranges in *a* and *c*, there is significant regional variation in $[DA]_o$ along this ventromedial–dorsolateral axis in both the caudate (one-way ANOVA; $p < 0.001$) and the putamen ($p < 0.001$). *Post hoc t* tests: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus ventromedial; $n = 4–25$. In the putamen, there is lateral variation between each of the three territories ($^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ vs central). *d*, Geographic representation of overall mean peak $[DA]_o$ evoked from the caudate and the putamen along vm–dl axes. *** $p < 0.001$ versus ventromedial; $^{\dagger\dagger\dagger}p < 0.001$ versus central; *post hoc t* tests. Only at the dorsolateral coordinate is $[DA]_o$ significantly greater in the putamen than in the caudate nuclei (*** $p < 0.001$; $n = 11–41$). $[DA]_o$ follows the following hierarchy: dorsolateral putamen > dorsolateral caudate $\approx$ central caudate $\approx$ central putamen > ventromedial caudate = ventromedial putamen. All data are means $\pm$ SEM.

the putamen or other structural organization of the nuclei. In addition, we discuss how these data provide additional support for the hypothesis (Wu et al., 2001) that it is such dynamics that underlie the paradoxical, documented preferential action of cocaine in the limbic- rather than motor-associated striatum (Carboni et al., 1989; Cass et al., 1992; Kuczenski and Segal, 1992; Bradberry et al., 2000). These data illustrate the function-associated repertoire of DA dynamics in the striatum of a non-human primate of central relevance to basal ganglia function in health and disease.

MATERIALS AND METHODS

Brain slice preparation. Male marmosets (1–2 years) from an established colony were killed with an overdose of pentobarbitone (i.p.). Striatal slices (400 μm) were prepared in ice-cold, HEPES-buffered physiological saline saturated with 95% O_2 and 5% CO_2 , as described previously (Rice et al., 1997; Cragg et al., 2000) using a Vibratome (Lancer Series 1000; Lancer, St. Louis, MO). Striatal coordinates were midcommissural to rostral [anteroposterior (AP), 8.5–11.5 mm] (Stephan et al., 1980). All recordings were made at 32°C in bicarbonate-buffered artificial CSF (aCSF; 95% O_2 and 5% CO_2) as described previously (Cragg et al., 2000).

Anatomical definitions. By dorsal striatum, we mean the striatum excluding the nucleus accumbens. According to corticostriatal connectivity (Selemon and Goldman-Rakic, 1985; Haber and McFarland, 1999), three major functional domains of the striatum can be delineated along a ventromedial to dorsolateral axis: ventromedial, central, and dorsolateral. Each domain is associated, respectively, with one of the following functions (and distinct frontal inputs): limbic (orbital and medial prefrontal cortex), cognitive/associative (dorsolateral prefrontal cortex), and sensorimotor (premotor and motor cortex). In both the caudate and the putamen, we defined three recording sites for comparison along the ventromedial–dorsolateral axis: vm, central (or mid), and dl, respectively (Fig. 1b). These regions correspond approximately to the three functionally defined territories, with the exception of the caudate nucleus, in which both the central and dorsolateral regions sampled are predominantly cognitive-associated, central striatum. Therefore, note that the dorsolateral loci in the caudate sampled in this study, unlike dorsolateral loci in putamen, do not constitute a component of the dorsolateral striatum (DLS) as defined by Haber et al. (2000).

Voltammetry and microelectrodes. $[DA]_o$ was measured using fast-scan cyclic voltammetry at a 6 μm carbon-fiber microelectrode beveled to a point (tip length, ~30 μm; MPB Electrodes, London, UK) using a Millar Voltammeter (PD Systems, West Moseley, UK) as described previously (Cragg and Greenfield, 1997; Cragg et al., 2000). The scan rate was 800 V/sec, from -0.7 to 1.3 V to -0.7 V versus Ag/AgCl, and the sampling frequency was 4–8 Hz. Illustrated voltammograms are faradic currents obtained by subtraction of background current. Identification of the released substance as DA was confirmed by comparison *in situ* and in DA calibration of oxidation and reduction potentials (+540 and -180 mV vs Ag/AgCl, respectively). Contributions from the monoamine oxidase (MAO)-metabolite DOPAC or norepinephrine (NE) were determined as minimal from experiments including MAO inhibition (pargyline) and NE uptake inhibition (desipramine). Electrodes were calibrated in 1–2 μM DA in aCSF. Sensitivity to DA is linear at these concentrations and typically 2–7 nA/μM. The minimum detection limit for $[DA]_o$ (~2× currents for noise) was roughly 20–40 nM.

Electrical stimulation. Electrical stimulation was at local, surface bipolar electrodes (50 μm diameter), as described previously (Cragg et al., 2000). Stimulus pulses (0.1 msec pulse width, half-maximal at 10 V) were applied in one of three paradigms: singly; in trains at 1–20 Hz for 3 sec; or in pairs with interstimulus intervals ranging from 50 msec to 40 sec (and interpair intervals of 5 min). Evoked release was TTX-sensitive and Ca^{2+} -dependent (data not illustrated).

Analysis of data and dopamine kinetics. Voltammetric data were acquired and analyzed on a personal computer running the Strathclyde Whole Cell Program (Dr. J. Dempster, University of Strathclyde, Strathclyde, UK). Data simulations for analysis of Michaelis–Menten kinetics used software provided by Dr. R. M. Wightman (University of North Carolina, Chapel Hill, NC) to fit each experimental data curve (concentration vs time) with theoretical curves. The kinetic analysis is based on the assumption that DA released into the extracellular space after a single pulse appears as an instantaneous concentration increase, $[DA]_p$, followed by a rapid decline that is predominantly attributable to transporter-mediated uptake (Gros et al., 1996), operating with Michaelis–Menten kinetics. Concentration–time (*t*) profiles can be described by the following equation: $d[DA]/dt = [DA]_p - V_{max}/\{[K_m/(DA)] + 1\}$, where K_m is the affinity constant of the dopamine transporter (DAT) and V_{max} is the maximum velocity of uptake. This method of analysis has been described in detail previously (Wightman and Zimmerman, 1990; Kawagoe et al., 1992; Jones et al., 1995) and incorporates a factor *d* that introduces a delay to compensate for electrode response time attributable to surface coatings or other interactions at uncoated electrodes. In

the present studies, d (140–220 nm) was comparable with that reported previously (Cragg et al., 2000). K_m was set at a constant value of 210 nM (Ross, 1991; for review, see Cragg et al., 2000). For each accepted simulation, R^2 was >0.9 . In cases in which small changes in variable parameter values could sometimes give equal degrees of fit (equivalent R^2), both sets were included for analysis (n = number of simulations). Data simulations were undertaken blind with respect to recording site. Linear regressions, Pearson correlations, and slope comparisons used GraphPad software (GraphPad Software Inc., San Diego, CA).

Paired-pulse data were used to determine time constants for recovery of release at a given site using a double exponential curve fit (Kennedy et al., 1992) of the form $y = y_0 + a(1 - \exp^{-bx}) + a(1 - \exp^{-cx})$, where x is time and a , b , and c are variables. We include a y -intercept term, y_0 , because this relationship may not necessarily approach zero at time 0 in a simple manner (our unpublished observation). We constrained a and $y_{\max}$ to a relationship in which $y_{\max} = y_0 + 2 \times a = 1$. Time constants were $[\ln 2]/b$ and $[\ln 2]/c$.

Data are means $\pm$ SEM and the sample size is the number of recording sites, unless otherwise stated. Some data from the putamen have been published in part previously (Cragg et al., 2000); we have included expanded data about the putamen, where appropriate, from sets that match those for the caudate to make comparisons with the caudate. The number of animals in each experiment is 3–12. Comparisons for differences in means were assessed by one- or two-way ANOVA and *post hoc* multiple comparison t tests (Newman–Keuls). In pulse train experiments, “net” or “steady-state” refers to $[DA]_o$ at a period during the stimulation during which $[DA]_o$ approaches an apparent steady state (2–3 sec). Note that the steady state may be a complex state and is not necessarily seen at high frequencies.

Solutions. All drugs and solutions were obtained from Sigma (Poole, UK).

RESULTS

Single-pulse evoked $[DA]_o$ within and between striatal domains

A single, electrical stimulus pulse in marmoset striatum evoked the rapid release and removal of the electroactive substance, DA. The substance was identified as DA by a characteristic voltammogram with peak potentials for oxidation (~ 500 mV) and reduction currents (~ 200 mV vs Ag/AgCl) (Fig. 1a, inset) that are identical for exogenously applied DA and DA signals obtained previously, including in marmoset putamen (Cragg et al., 2000). The metabolite DOPAC did not contribute significantly to evoked signals in the putamen (Cragg et al., 2000) or in the caudate nucleus: inhibition of monoamine oxidases A and B for up to 5 hr (pargyline, 20 μ M), had no effect on the magnitude of the signal observed ($n = 4$; data not shown).

There was significant regional variation in evoked $[DA]_o$ within both the caudate and the putamen attributable to vm–dl coordinates at both central–rostral locations (Fig. 1a,b) (one-way ANOVAs; $p < 0.001$; caudate, $n = 9$ –16; putamen, $n = 7$ –25) and central–postcommissural locations (Fig. 1c) (one-way ANOVAs; $p < 0.001$; caudate, $n = 6$ –12; putamen, $n = 4$ –15). Throughout the AP range of the striatum investigated, evoked $[DA]_o$ in dorsolateral positions was significantly greater than that released ventromedially, by more than twofold in the caudate and, most markedly, by threefold in the putamen. The more marked regional variation within the putamen than within the caudate was attributable to the most elevated $[DA]_o$ of all of those occurring in the dorsolateral putamen.

No significant effect of the AP coordinate was detected in either the caudate or the putamen (two-way ANOVAs). There was a trend in ventromedial putamenal regions toward higher evoked $[DA]_o$ more caudally. At these loci, the most medial coordinate of the putamen is more lateral than in rostral regions (Stephan et al., 1980). For all subsequent data analysis, AP data were pooled. Within the caudate nucleus, the mean evoked $[DA]_o$

in central and dorsolateral regions was twice that seen in ventromedial areas (Fig. 1d) ($193 \pm 17\%$ and $197 \pm 15\%$ of ventromedial, respectively; $p < 0.001$; $n = 17$ –28). In contrast, within the putamen, there was significant variation between each of the three subregions measured, such that there was more than a threefold vm–dl variation in evoked $[DA]_o$ (Fig. 1d) (dorsolateral $313 \pm 18\% >$ central $181 \pm 8\%$ of ventromedial; $p < 0.001$; $n = 11$ –41).

A comparison of putamen versus caudate nuclei reveals that internucleus variation (20–30%) is a far smaller source of variation than intranucleus variation (300%). At similar vm–dl coordinates in the caudate and the putamen, $[DA]_o$ is similar in all but the most lateral regions: The only significant source of variation between the caudate and the putamen (two-way ANOVA; $p < 0.05$) is at this dorsolateral coordinate, where the mean $[DA]_o$ in the putamen ($1.83 \pm 0.11 \mu$ M; $n = 41$) exceeds that in the caudate by 33% ($1.38 \pm 0.11 \mu$ M; $p < 0.001$; $n = 28$). This region-specific availability of DA parallels the segregation of the functional organization of the striatum, as delineated by corticostriatal topography.

Dopamine uptake pharmacology

Single-pulse evoked $[DA]_o$ and extracellular lifetime were unaltered by application of desipramine (300 nM), a competitive inhibitor of the NE transporter in the caudate nucleus (Fig. 2a) ($n = 7$; three applications) as well as the putamen (Cragg et al., 2000). In contrast, uptake by the DAT avidly regulated the extracellular concentration and lifetime of DA (Fig. 2b): during competitive inhibition of the DAT by GBR 12909 (500 nM), maximum $[DA]_o$, the clearance rate, and thus the extracellular lifetime of single-pulse evoked $[DA]_o$ throughout the caudate were significantly elevated (one-way ANOVA; $p < 0.001$; $n = 19$; four applications), as seen in the putamen previously (Cragg et al., 2000). Together, these data also verify that the substance measured is not NE but DA.

Regional variation in $V_{\max}$ of dopamine uptake between striatal domains

Each experimental observation of $[DA]_o$ versus time was modeled with simulations of Michaelis–Menten kinetics to evaluate the maximal uptake rate, $V_{\max}$, via the DAT, and the underlying release per pulse, $[DA]_p$ (Fig. 2c–f). $V_{\max}$ and $[DA]_p$ varied in a manner that was positively correlated (Fig. 2d) in the caudate (Pearson test; $p < 0.001$; $r = 0.50$; $n = 67$) and in the putamen ($p < 0.001$; $r = 0.68$; $n = 91$).

Analysis of the distribution of the values of $[DA]_p$ and $V_{\max}$ within a vm–dl axis in each nuclei revealed significant effects of coordinate (Fig. 2e,f), as seen for $[DA]_o$ (Fig. 1d). $[DA]_p$ varied significantly within the caudate (Fig. 2) [$1.67 \pm 0.10 \mu$ M (vm) to $2.70 \pm 0.14 \mu$ M (dl); one-way ANOVA; $p < 0.001$; $n = 16$ –30] and within the putamen (Fig. 2e) [$1.45 \pm 0.07 \mu$ M (vm) to $3.35 \pm 0.16 \mu$ M (dl); one-way ANOVA; $p < 0.001$; $n = 23$ –38]. The central and dorsolateral caudate did not differ. The source of variation between the caudate and the putamen, when compared at paired coordinates (two-way ANOVA; $p < 0.05$), was attributable to 25% greater $[DA]_p$ in the dorsolateral putamen than in the caudate. $[DA]_p$ in the dorsolateral putamen significantly exceeded release in all other regions.

$V_{\max}$ varied significantly within the caudate (Fig. 2f) [$3.51 \pm 0.15 \mu$ M/sec (vm) to $4.20 \pm 0.14 \mu$ M/sec (dl); one-way ANOVA; $p < 0.001$; $n = 16$ –30] and within the putamen (Fig. 2f) [$3.27 \pm 0.13 \mu$ M/sec (vm) to $4.94 \pm 0.13 \mu$ M/sec (dl); one-way ANOVA;

Figure 2. DA uptake: pharmacology and $V_{\max}$. *a, b*, Mean $[DA]_o$ versus time after a single pulse (arrow) in the caudate nucleus in the control (circles) and with an uptake transporter inhibitor for norepinephrine (*a*; desipramine, 300 nM; triangles) or DA (*b*; GBR 12909; 500 nM; squares). *a*, Desipramine had no effect on the peak $[DA]_o$ or the removal rate ($n = 7$). *b*, GBR 12909 slowed the rate of removal and significantly enhanced $[DA]_o$ ($n = 19$; $***p < 0.001$). *c*, Data points of a typical observation in the central caudate (Mid Cd) after a single pulse (arrow). Superimposed is a simulated data curve that describes the $[DA]_o$ detected after release and uptake with Michaelis–Menten kinetics. In this example, $[DA]_p = 2.15 \mu\text{M}$, $V_{\max} = 3.1 \mu\text{M}/\text{sec}$, $R^2 = 0.99$, $K_m = 210 \text{ nM}$, and $d = 180 \text{ nm}$. *d*, $V_{\max}$ versus $[DA]_p$ from all simulations in the caudate (triangles; $n = 67$) and the putamen (circles; $n = 91$). Positive correlations (dotted lines) within the putamen ($r = 0.68$) and the caudate ($r = 0.5$) are significantly different from zero ($p < 0.001$). The mean $[DA]_p$ (*e*; $***$) and mean $V_{\max}$ within the caudate (*f*; bars) compared with the putamen (dashed and/or dotted lines; means $\pm$ SEM) across vm–dl axes are shown. $[DA]_p$ and $V_{\max}$ increase significantly with an increasing dorsolateral coordinate in both nuclei (one-way ANOVAs; $p < 0.001$; *post hoc t* tests; $***p < 0.001$ vs ventromedial) but only in the putamen is there a lateral variation between each of the three territories (Cragg et al., 2000). Only at the dorsolateral coordinate are either $[DA]_p$ or $V_{\max}$ significantly greater in the putamen than in the caudate ($^{++}p < 0.01$; $^{+++}p < 0.001$; $n = 16$ –38). All data are means $\pm$ SEM.

$p < 0.001$; $n = 23$ –38]. The central and dorsolateral caudate did not differ. The source of variation between the caudate and the putamen, when compared at paired coordinates (two-way ANOVA; $p < 0.05$), was attributable to $\sim 20\%$ greater $V_{\max}$ in the putamen than in the caudate at dorsolateral regions. Indeed, the highest $V_{\max}$ observed was in the dorsolateral putamen, where $V_{\max}$ was significantly greater than in all other regions.

It should be noted that the values of $[DA]_p$ and $V_{\max}$ obtained using this approach were validated by an alternative means of estimating $V_{\max}$ (Cragg et al., 2000). After an intense stimulation (e.g., 100 Hz, 0.5 sec train) that generates sufficiently high $[DA]_o$ ($\gg K_m$ of the DAT), the clearance rate of DA approaches a constant, $V_{\max}$ (i.e., zero-order kinetics). The values of $V_{\max}$ obtained using this method were not different from those obtained by the data simulations and, furthermore, demonstrated regional heterogeneity (data not shown).

Frequency dependence of dopamine_o during pulse trains

Steady-state $[DA]_o$ was compared in ventromedial versus dorsolateral regions of both the caudate and the putamen during pulse trains, over a range of frequencies (2–20 Hz) at which DA neurons may fire action potentials *in situ* (Grace and Bunney, 1983, 1984a,b; Schultz et al., 1983; Schultz, 1984, 1986). These data have been reported in part previously for the putamen (Cragg et al., 2000). As for the putamen, evoked $[DA]_o$ in the caudate nucleus peaked initially ($t \approx 0.5 \text{ sec}$) after the start of the stimulus (Fig. 3*a,b*) to a concentration resembling that observed after a single pulse (Fig. 1). Subsequently, $[DA]_o$ either declined, remained constant at, or increased to an approximately steady-state concentration (at $t = 2$ –3 sec) as a function both of the frequency of stimulation (Fig. 3*a–c*) (two-way ANOVA; $p < 0.001$; $n = 4$ –10) and of the region ($p < 0.001$). In the ventromedial, limbic-associated caudate, each increase in the stimulation frequency

increased $[DA]_o$ at steady-state times (compared with previous frequency) (e.g., Newman–Keuls multiple comparison *t* tests; $p < 0.01$ for 20 Hz vs 10 or 5 Hz) with a facilitative (nonlinear) relationship, as in the ventromedial putamen (Fig. 3*c*). In the dorsolateral caudate, each increase in the stimulation frequency increased the steady-state $[DA]_o$ (compared with the previous frequency) up to 10 Hz (e.g., Newman–Keuls multiple comparison *t* tests; $p < 0.05$ for 2 Hz vs 10 or 20 Hz): at 20 Hz, no significant increase in $[DA]_o$ compared with 10 Hz was observed, as in the dorsolateral putamen (Fig. 3*c*).

Consistent with the regional differences in $[DA]_o$ observed after a single pulse, net $[DA]_o$ at low frequencies ($< 10 \text{ Hz}$) was significantly greater (approximately twofold) in the dorsolateral than in the ventromedial caudate (*t* tests; $p < 0.01$; $n = 4$ –5). However, at higher frequencies, steady-state $[DA]_o$ in the ventromedial caudate becomes equal to (10 Hz) and eventually significantly greater than (20 Hz; more than twofold) $[DA]_o$ in the dorsolateral regions (Fig. 3*c*) ($p < 0.01$; $n = 6$ –10). An identical effect has been described previously for the putamen (Cragg et al., 2000), as illustrated for the comparison in Figure 3*c*.

Comparison of net, steady-state $[DA]_o$ in the caudate with the putamen at paired coordinates indicates no significant difference between the two nuclei (two-way ANOVAs for frequency and nucleus; $p < 0.001$ and $p > 0.05$, respectively) at either of the two coordinates.

Recovery from presynaptic depression

To characterize further the presynaptic properties of DA neurons innervating the striatal region most vulnerable to parkinsonian degeneration (i.e., the dorsolateral putamen), we evaluated and compared the recovery of the releasability of DA after presynaptic depression at the dorsolateral loci of the putamen and the caudate. At a given dorsolateral site in both the putamen and the caudate nuclei in each of four different animals, paired pulses of

Figure 3. Frequency sensitivity of $[DA]_o$ during pulse trains. *a, b*, $[DA]_o$ versus time during 3 sec stimulation trains (*stim*, solid bar) over a range of frequencies (2–20 Hz) in the vm (*a*) and dl (*b*) caudate nucleus, $3 < n < 10$. SEMs are excluded for clarity. The steady-state $[DA]_o$, between dotted lines, varies differently with the frequency in each region. *c*, Steady-state $[DA]_o$ versus frequency in ventromedial (*open symbols*) and dorsolateral (*filled symbols*) regions of both the caudate (*triangles*) and, for comparison, putamen (*circles*). $[DA]_o$ is a function of the frequency of stimulation (two-way ANOVA; $p < 0.001$) and subregion ($p < 0.01$). As in the putamen (*dotted lines*), in the dorsolateral caudate each increase in frequency up to 10 Hz increased $[DA]_o$ (*post hoc t* tests; $p < 0.001$ – 0.05 ; $n = 5$ – 8); in the ventromedial caudate, $[DA]_o$ increased supralinearly with the frequency ($p < 0.01$ – 0.05 ; $n = 4$ – 10). $[DA]_o$ in the ventromedial regions significantly exceeded that in the dorsolateral regions at frequencies of >10 Hz (20 Hz; $**p < 0.01$). There was no significant difference between the caudate and the putamen (two-way ANOVA). Data are means $\pm$ SEM.

varying interpulse intervals (50 msec to 40 sec) were administered repeatedly and in random order, 5 min apart (Fig. 4*a*). The recordings sites were typical for each nucleus: Mean peak $[DA]_o$ evoked by a single pulse was $2.08 \pm 0.03 \mu M$ in the putamen, which more importantly was consistently greater than evoked $[DA]_o$ in the caudate ($1.64 \pm 0.23 \mu M$; $p < 0.05$; $n = 4$). In both nuclei, a strong depression of release was observed at the second, paired pulse, which was inversely related to the interpulse interval (Fig. 4*a, b*). Full recovery of $[DA]_o$ occurs only after ~ 30 sec (Fig. 4*a, b*). The relationships between the paired-pulse ratio of $[DA]_o$ [pulse 2 (P2)/pulse 1 (P1)] and interpulse interval in both the caudate and the putamen could be fitted well with double exponentials ($R^2 > 0.99$), as described previously for rodent striata (Kennedy et al., 1992; Abeliovich et al., 2000). The time constants derived from both fast and slow components were: caudate, 2.7 and 9.4 sec; putamen, 2.8 and 7.7 sec, shorter than those described in rodents. Although a two-way ANOVA (for time and region) indicates significant variation in $[DA]_o$ attributable to interpulse interval ($p < 0.001$), there is no significant difference in relative recovery between the caudate and the putamen ($n = 4$), despite the difference in absolute $[DA]_o$.

DISCUSSION

These data indicate region-specific heterogeneity in the dynamic regulation of $[DA]_o$ throughout the dorsal striatum of a nonhuman primate. Different functional domains are defined by corresponding differences in DA dynamics. Within a given functional domain, the anatomically segregated putamen and caudate nuclei nonetheless share similar DA dynamics.

Single-pulse evoked dopamine_o and striatal domain

$[DA]_o$ evoked locally by a single pulse was a function of the vm–dl coordinate in the caudate nucleus, as seen previously in the putamen (Cragg et al., 2000). From the three-site analysis of $[DA]_o$ (and $[DA]_p$) within each nucleus, a marked gradient in DA availability is apparent (Fig. 5): evoked $[DA]_o$ increases from the ventromedial striatum through the central striatum to the DLS by twofold (caudate) to threefold (putamen).

Notably, intranuclear variation in $[DA]_o$ reflected the func-

tional domain. For example, within the caudate nucleus, evoked $[DA]_o$ was lower in the ventromedial compared with the central sites, yet it was similar in the central and the dorsolateral sites: this heterogeneity parallels the segregation of these three loci into primarily two functional domains, the ventromedial/limbic Cd (vm Cd) and the central/associative (mid and dl Cd) (Haber et al., 2000). Interestingly, this finding is mirrored in basal $[DA]_o$ seen within the caudate nucleus in rhesus monkeys (Bradberry et al., 2000). In contrast, in the putamen the significant difference in evoked $[DA]_o$ between each of the three loci in turn parallels the division into three functional domains, including the dorsolateral/motor Put (dl Put). Moreover, mean evoked $[DA]_o$ within each functional domain was common to the putamen and the caudate. In other words, functional domains, which span anatomical segregation into the caudate and the putamen, can be delineated by DA availability.

These data suggest that functions assigned to a striatal subregion are more accurately described by mediolateral coordinates than by the nucleus. In particular, mesostriatal features assigned preferentially to the putamen and not the caudate may reside in dorsolateral projections (e.g., onset of parkinsonian degeneration), whereas features assigned preferentially to the caudate may result from a greater component of central/associative functions. The greatest $[DA]_o$ is evoked in the dorsolateral putamen, the only motor domain sampled, and notably, the region most susceptible to parkinsonian degeneration. Greater apparent DA availability/turnover in dorsolateral regions may, in turn, generate a greater accumulation of potentially toxic DA metabolites. Given the concordance between the degree of degeneration associated with each region in PD (Kish et al., 1988; Antonini et al., 1995) and DA availability, our observations indirectly support DA autotoxicity as a contributing factor in PD (for review, see Jenner and Olanow, 1996; Olanow and Tatton, 1999).

Dopamine uptake and striatal domain

The DAT was the dominant uptake mechanism governing $[DA]_o$ and lifetime in the caudate, as observed in the putamen (Cragg et al., 2000). Like $[DA]_o$ and $[DA]_p$, uptake V_{max} varied in a region-

Figure 4. Recovery from presynaptic depression. *a*, A typical series for $[DA]_0$ versus time after paired stimulus pulses (arrows) delivered at interpulse intervals ranging from 2 to 20 sec (dotted lines), recorded at a single site in the dorsolateral caudate. Plots are standardized to 100% of the release by the first pulse. Release is restored only after at least 20 sec. *b*, Mean $[DA]_0$ released by the second, paired pulse as a fraction of the first ($P2/P1$) versus the interpulse interval for the dorsolateral caudate (triangles) and the putamen (circles). Curve fits (solid lines) are double exponentials of the form $y = y_0 + a(1 - e^{-bx}) + a(1 - e^{-cx})$, where $y_0 + 2 \times a = 1$. Time constants of fast and slow components of illustrated fits are, respectively: Cd, 2.7 and 9.4 sec; Put, 2.8 and 7.7 sec. The two-way ANOVA indicates variation attributable to time ($p < 0.001$) but not region ($n = 4$).

specific manner that paralleled the segregation of the caudate and the putamen into, respectively, two versus three functional domains: V_{max} in dorsolateral locations was greater than that in ventromedial locations by 20% in the caudate and 50% in the putamen.

Within each functional domain, the mean V_{max} was similar in the caudate and the putamen. V_{max} was greatest in the dorsolateral putamen, the only motor domain sampled, and exceeded V_{max} in the dorsolateral caudate by 20%. Thus, uptake, as for release, reflects the functional striatal domain, as defined by corticostriatal connectivity, primarily independently of anatomical segregation into the caudate versus the putamen.

Previous findings from techniques with less-defined spatial resolution show that overall DAT protein levels or ligand-binding density, B_{max} ($[^{125}I]$ altropine, $[^3H]$ mazindol, $[^3H]$ CFT, and $[^{125}I]$ RTI-55), in primate, including human, striatum are highest in the putamen (Donnan et al., 1991; Kaufman and Madras, 1992; Miller et al., 1997; Madras et al., 1998). These data can now be reinterpreted as a specific consequence of the greater motor component of the putamen compared with the caudate, and its associated greater V_{max} . Moreover, the regional heterogeneity in uptake will be an additional contributing factor in neurodegeneration; it explains the greater accumulation and regional neuro-

Figure 5. Summary of regional availability of DA. The gradient fill within the dorsal striatum enclosed by the dashed lines illustrates the relative regional availability of DA as determined by mean $[DA]_0$ evoked by a single pulse in the striatum, here indicated by a key, in micrometers. Representative recording locations along the vm–dl axes used to define this gradient in both the Cd and the Put are indicated (circles). Regional differences in DA availability obey a vm–dl organization that spans the two nuclei. This territorial delineation parallels the known functional domains of the striatum defined by corticostriatal connectivity (for review, see Haber and McFarland, 1999; Haber et al., 2000). IC, Internal capsule.

toxicity of the MPTP metabolite and DAT substrate, 1-methyl-4-phenylpyridinium (Elsworth et al., 1987; Moratalla et al., 1992), and may be a component of regional methamphetamine-induced toxicity (Harvey et al., 2000).

However, the distribution of DAT activity is inversely correlated with the effect of the DAT antagonist cocaine. Paradoxically, cocaine preferentially elevates $[DA]_0$ in limbic rather than motor-associated striata (Carboni et al., 1989; Cass et al., 1992; Kuczenski and Segal, 1992; Bradberry et al., 2000). The competitive antagonistic action of cocaine will be differently apparent when the DAT is differently saturated by endogenous DA. Wu et al. (2001) have suggested that lower rates for both dopamine release and uptake together underlie the preferential increase in $[DA]_0$ in the nucleus accumbens rather than the caudatoputamen of rats after the systemic injection of cocaine. According to this hypothesis, the greater action of cocaine in the ventromedial striatum rather than in the DLS documented in the nonhuman primate (Bradberry et al., 2000) could also be explained by our findings that both $[DA]_p$ and V_{max} are lowest in limbic-associated regions.

The positive correlations observed between $[DA]_p$ and V_{max} in both the caudate and the putamen, together with the regional variation in DA content (Cragg et al., 2000), suggest that the largest and fastest dopamine transients at dorsolateral coordinates result primarily from the densest dopaminergic innervation (Bjorklund and Lindvall, 1984). However, the faster V_{max} is not necessarily wholly attributable to fiber packing density, because dorsolaterally projecting mesostriatal DA neurons have the greatest DAT expression levels (Shimada et al., 1992; Blanchard et al., 1994; Hurd et al., 1994; Sanghera et al., 1994; Haber et al., 1995). Moreover, a dissociation is apparent between the parameters $[DA]_p$ and V_{max} , where $[DA]_p$ tends toward zero before V_{max} . Unless there is increased DAT density per releasing bouton with the ventromedial coordinate [a hypothesis contradictory to both expression studies (above) and ultrastructural findings in rodents (Nirenberg et al., 1997; Sesack et al., 1998)], this dissociation suggests that $[DA]_p$ is governed by factors beyond packing density. Other differences between DA neurons [e.g., membrane

ionic conductances (for review, see Meir et al., 1999; Wolfart et al., 2001; Liss et al., 2001) or calcium-buffering properties (Gerfen et al., 1987; Haber et al., 1995)] may generate regional variation in release probability.

Frequency sensitivity

Net $[DA]_o$ during pulse trains reflects the release per pulse ($[DA]_p$) minus the reuptake (Wightman et al., 1988; Wightman and Zimmerman, 1990; Limberger et al., 1991; Kawagoe et al., 1992). At frequencies observed *in vivo* (e.g., 1–20 Hz) (Bunney et al., 1973; Grace and Bunney, 1983, 1984a; Schultz et al., 1983), the frequency sensitivity of $[DA]_o$ varied significantly within both nuclei. There was a supralinear effect of the frequency in the ventromedial caudate but a frequency insensitivity in the dorsolateral regions of >10 Hz. These two effects strongly resemble those seen previously within the putamen (cf. Cragg et al., 2000). We have already demonstrated that because of weaker uptake and presynaptic autoinhibition of release by D_2 -like receptors, levels of evoked $[DA]_o$ in the ventromedial putamen can exceed those dorsolaterally during pulse trains despite the lower levels of DA available for release (Cragg et al., 2000): it is possible that a similar scenario operates within the caudate nucleus. The similarity in net $[DA]_o$ between related domains of the caudate versus the putamen could have been predicted given the approximately similar $[DA]_p$ and V_{max} of uptake. By related mechanisms, similar net $[DA]_o$ could be generated in dorsolateral regions of the caudate and the putamen (central vs dorsolateral territories), despite the greater release and uptake during any single release transient. These differences in homeostatic control of $[DA]_o$ between domains in both the putamen and the caudate are consistent with a different temporal precision of DA signaling (low vs high) that has been proposed to be appropriate for limbic- versus motor-associated functions, respectively (Horvitz, 2000).

Recovery from presynaptic depression

After a single stimulus, DA release exhibited a fast depression. Slow recovery was described by a double exponential function, which (in rodents) results from, among others (Kennedy et al., 1992), DA autoreceptors (Kennedy et al., 1992; Benoit-Marand et al., 2001), $[Ca^{2+}]_i$, α -synuclein (Abeliovich et al., 2000), and by analogy to other neurotransmitters, rates of vesicle refill/redock/priming (for review, see Thomson, 2000). Recovery time constants are faster than those reported previously in rodents; however, it is unclear whether this discrepancy reflects experimental or important species differences. According to these time constants, the net constraints on presynaptic recovery in the caudate and the putamen were equivalent. Therefore, greater initial DA availability and reuptake do not confer greater apparent presynaptic re-releasability.

Conclusions

We have described distinct differences within the primate dorsal striatum in DA dynamics, in particular, in availability for release, avidity of uptake, and their interactions. Consequently, striatal functional domains are differentiated by this dynamic availability of DA, independently of caudate/putamen anatomical segregation. Caudate/putamen differences (e.g., susceptibility to degeneration) are probably attributable to their mediolateral organization and consequent limbic versus motor dopaminergic components.

These data indicate how DA may be used in different manners, quantitatively and qualitatively, for different functions within the striatum. Interestingly, DA behavior may be necessarily correlated with properties of sites of action: for example, the density of

striatonigral projection neurons varies in parallel along the same axis (ventromedial > dorsolateral) (Haber et al., 2000). The heterogeneity in the dynamic behavior of DA surpasses that seen in the rodent caudatoputamen (Cragg et al., 2000). This unparalleled heterogeneity may reflect the increased functional specialization of the primate brain, in particular the greater repertoire of functions modulated by DA, including movements and affect. Furthermore, these data may underlie the regional specificity of the primate striatum to psychostimulant drugs and neurodegenerative disease.

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