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D_1 and D_2 dopamine receptor mRNA in rat brain

(striatum/substantia nigra/amygdala/septum/*in situ* hybridization)

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ABSTRACT **Physiological and pharmacological criteria have divided dopamine receptors into D_1 and D_2 subtypes, and genes encoding these subtypes have recently been cloned. Based on the sequences of the cloned receptors, we prepared oligodeoxynucleotide probes to map the cellular expression of the corresponding mRNAs in rat brain by *in situ* hybridization histochemistry. These mRNAs showed largely overlapping yet distinct patterns of expression. The highest levels of expression for both mRNAs were observed in the caudate-putamen, nucleus accumbens, and olfactory tubercle. Within the caudate-putamen, 47 ± 6% and 46 ± 5% of the medium-sized neurons (10–15 μm) expressed the D_1 and D_2 mRNAs, respectively, and only the D_2 mRNA was observed in the larger neurons (>20 μm). The D_1 and D_2 mRNAs were expressed in most cortical regions, with the highest levels in the prefrontal and entorhinal cortices. Within neocortex, D_1 mRNA was observed primarily in layer 6 and D_2 mRNA in layers 4–5. Within the amygdala, D_1 mRNA was observed in the intercalated nuclei, and D_2 mRNA in the central nucleus. Within the hypothalamus, D_1 mRNA was observed in the suprachiasmatic nucleus and D_2 mRNA in many of the dopaminergic cell groups. Within the septum, globus pallidus, superior and inferior colliculi, mammillary bodies, and substantia nigra only D_2 mRNA was detected. These data provide insight into the neuroanatomical basis of the differential effects of drugs that act on D_1 or D_2 receptors.**

Dopamine is a neurotransmitter that mediates many aspects of cognitive, emotive, motor, and endocrine function. Disturbances in dopaminergic neurotransmission are thought to contribute to the pathogenesis of schizophrenia and Parkinson disease. Drugs that interact with dopamine receptors are used to treat these and other neuropsychiatric and neuroendocrine disorders (1–3). Based on pharmacological and physiological criteria, dopamine receptors have been divided into D_1 and D_2 subtypes (4). For example, the D_1 receptor has high affinity for SCH-23390, has low affinity for substituted benzamides, and is able to stimulate adenylyl cyclase by coupling with the guanine nucleotide-binding protein (G protein), G_s (5, 6). Conversely, D_2 receptors have low affinity for SCH-23390, have high affinity for substituted benzamides, and inhibit adenylyl cyclase by coupling with the G protein G_i (5, 6). By virtue of sequence homology with pharmacologically related receptors, genes encoding D_1 and D_2 receptor subtypes have been cloned (7–9). These genes are members of a gene superfamily that encodes receptors mediating signal transduction by coupling to G proteins (10).

The anatomy of dopaminergic systems in the mammalian central nervous system has been well characterized. For example, dopaminergic cell groups in the mesencephalon form specialized innervations of the cerebral cortex, striatum, and various limbic and hindbrain structures (11–18). Similarly, dopaminergic neurons in the hypothalamus innervate the pituitary (11–13). Using receptor autoradiographic methods, many studies have shown that D_1 and D_2 receptor subtypes are distributed in overlapping yet distinct anatomical populations (19–23). These studies have been limited by the pharmacological selectivities of the ligands and the anatomical resolution that can be obtained by autoradiographic detection of diffusible ligands. Molecular cloning of D_1 and D_2 dopamine receptors has provided the information necessary to determine the distribution of the corresponding mRNAs by *in situ* hybridization histochemistry. In the present report we compare the cellular distribution of D_1 and D_2 receptor mRNAs in rat brain.

MATERIALS AND METHODS

Oligodeoxynucleotide Probes. Each of the mRNAs was localized using mixtures of three 48-base oligodeoxynucleotide probes prepared on an Applied Biosystems automated DNA synthesizer. The sequences of the probes for the D_1 receptor were complementary to regions of a polymerase chain reaction fragment obtained from rat striatum, and the numbering corresponds to the homologous regions of the sequence of the human D_1 receptor DNA (7): D1a, bases 735–782 (5′-TAA-AGG-AAC-TTT-CAC-ACT-GGG-CCC-ATT-CGA-CGC-GGT-TCC-CGT-TAC-CTG-3′); D1b, bases 664–711 (5′-GGA-CTG-CTG-CCC-TCT-CCA-AGG-CTG-AGA-TGC-CCC-GGA-TTT-GCT-TCT-GGG-3′); and D1c, bases 520–567 (5′-TGT-CAC-ACT-TGT-CAT-CCT-CGG-TGT-CCT-CCA-GGG-AGG-TAA-AAT-TGC-CAT-3′). The three probes to the D_2 receptor and the three probes to the α subunit of rod transducin have been described (9, 24).

Probe Specificity. The specificity of each of the probes was defined by several criteria. (*i*) Each probe was complementary to regions of the mRNAs that exhibit the lowest degree of sequence homology between the dopamine receptor subtypes, and to related receptors that couple to G proteins. To avoid hybridization to regions of the genes with unknown function, and thus unknown homology to other genes, all of the probes were complementary to coding regions. (*ii*) For a given receptor mRNA, each of the three probes hybridized to brain sections with identical patterns, and these patterns of hybridization were roughly additive when the three probes were combined. (*iii*) The probes hybridized to mRNA on Northern blots with a pattern of distribution among brain regions similar to that observed using *in situ* hybridization histochemistry. For the D_1 mRNA, there was more hybrid-

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ization in striatum than in several other brain regions (data not shown), and for the other probes these controls have been described (9, 24). (*iv*) Autoradiographic grains were confirmed to be localized above cell bodies, and >5-fold more grains were observed over positive cells than over background. (*v*) As a negative control, the patterns of hybridizations observed for the dopamine receptor subtype mRNAs were compared with that observed for the α subunit of transducin. This gene is expressed only in retinal rod cells, but not in brain (25). While the magnitude of the nonselective hybridization of the transducin and receptor probes to brain sections varied slightly between experiments, labeling patterns remained constant. In the present series of experiments, D_1 hybridizations gave a higher level of nonspecific hybridization than D_2 hybridizations.

***In Situ* Hybridization Histochemistry.** Tissue preparation and *in situ* hybridization procedures were identical to those described previously (24). In brief, male Sprague–Dawley rats (200–250 g, Taconic Farms) were decapitated, and their brains and retinas were removed and frozen on dry ice. Sections (12 μm) were cut at −20°C, mounted onto gelatin-coated slides, and stored at −70°C until use. Sections were fixed in 4% formaldehyde for 5 min, treated with 0.25% acetic anhydride in 0.1 M triethanolamine with 0.9% NaCl for 10 min, dehydrated, and delipidated.

Mixtures of the three probes for any given receptor mRNA were 3′-end-labeled (average tail length, 10–15 bases) by using terminal deoxynucleotidyltransferase (Bethesda Research Laboratories) and 2′-deoxyadenosine 5′-[α-[^{35}S]thio]triphosphate labeled (≈1500 Ci/mmol, New England Nuclear; 1 Ci = 37 GBq) and were hybridized as described (9, 24). Some of the sections were placed directly against film for 5 weeks, while others were dipped in a photographic emulsion (NTB3 from Kodak, 1:1 with water) and exposed for 2–8 weeks. Tissues were counterstained with 0.2% toluidine blue in water.

Neuronal Cell Counting. All cell counts were performed along a 200-μm-wide (medial to lateral) and 1.6- to 2.0-mm-long (dorsal-to-ventral) column in the center of the caudate-putamen at the coronal level (Fig. 1 *B* and *E*). Only cells >5 μm were included in the total cell counts, to limit inclusion of nonneuronal cells. Percentages reported in the text are means ± SD, where *n* was the number of objective fields counted. Approximately 800 cells were counted for each receptor subtype.

RESULTS

The distribution of D_1 and D_2 receptor mRNAs was mapped throughout the rat brain with both macroscopic (Fig. 1) and cellular (summarized in Table 1) resolution. The highest levels of both D_1 and D_2 mRNA were observed in the striatum (Fig. 1). Both mRNAs were observed throughout the caudate-putamen, nucleus accumbens, and olfactory tubercle, and neither mRNA was observed in the islands of Calleja. Within the caudate-putamen the two mRNAs had similar distribution patterns, with slight medial-to-lateral gradients of expression. The D_1 mRNA was observed in 47 ± 5% of the neurons, and the D_2 mRNA in 46 ± 6% of neurons. The majority of neurons within the striatum are medium-sized (10–15 μm) and both mRNAs were observed primarily in these cells. Only D_2 mRNA was also expressed in rare (<3%), large (>20 μm) cells in the striatum (Fig. 3 *C* and *D*). These cells are most frequent in lateral aspects of the

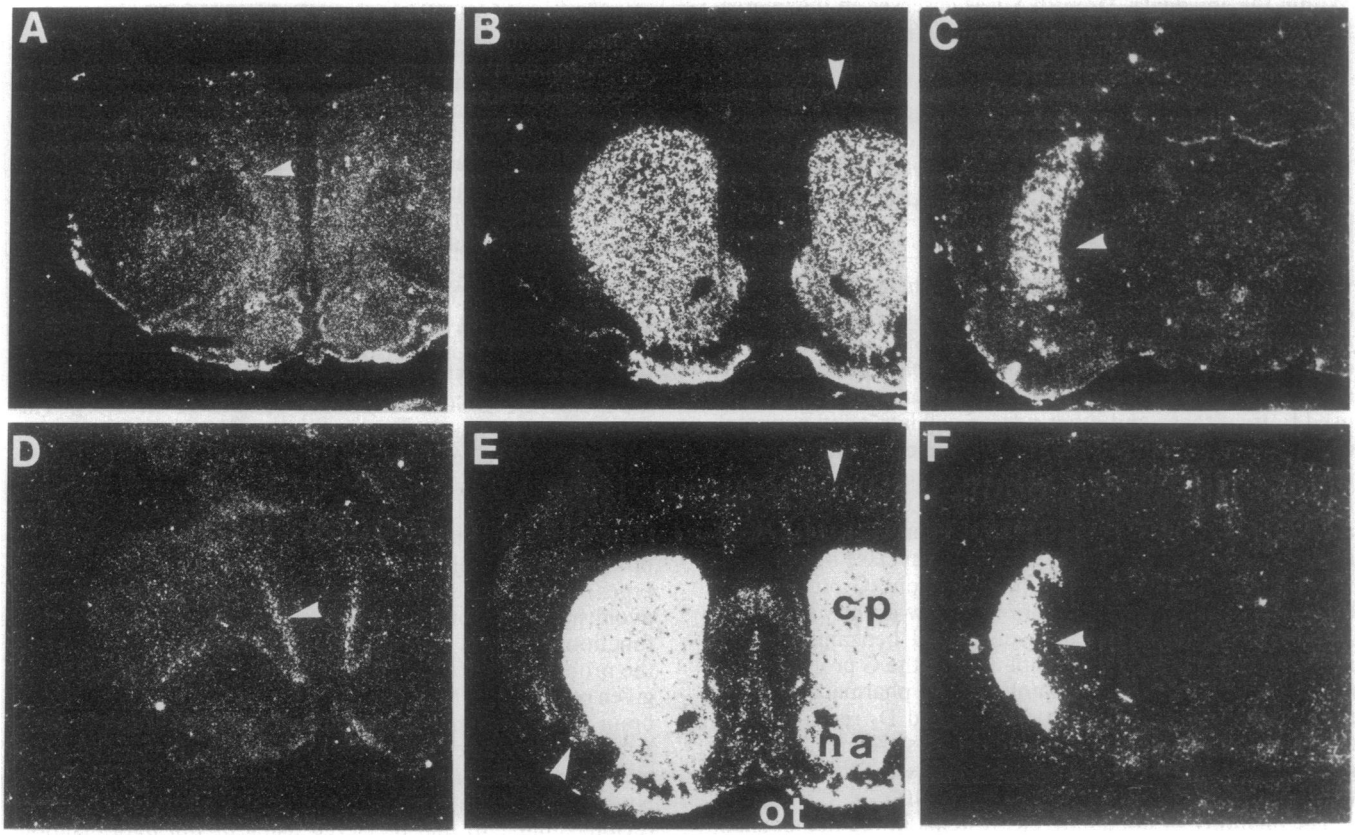

FIG. 1. Expression of D_1 (*A–C*) and D_2 (*D–F*) dopamine receptor mRNAs in rat brain. All panels are coronal left hemisections in which regions expressing mRNA appear white in the photographs. Sections for D_1 mRNA were from a different brain than was used for D_2 mRNA, but were from anatomically similar planes. Images were obtained from 5-week exposures of sections against film. Arrowheads indicate layer 6 of anteromedial prefrontal cortex in *A* and *D*, layer 6 of supragenual cortex in *B*, and layers 4–5 in *E*, and the globus pallidus in *C* and *F*. na, Nucleus accumbens; cp, caudate-putamen; ot, olfactory tubercle.

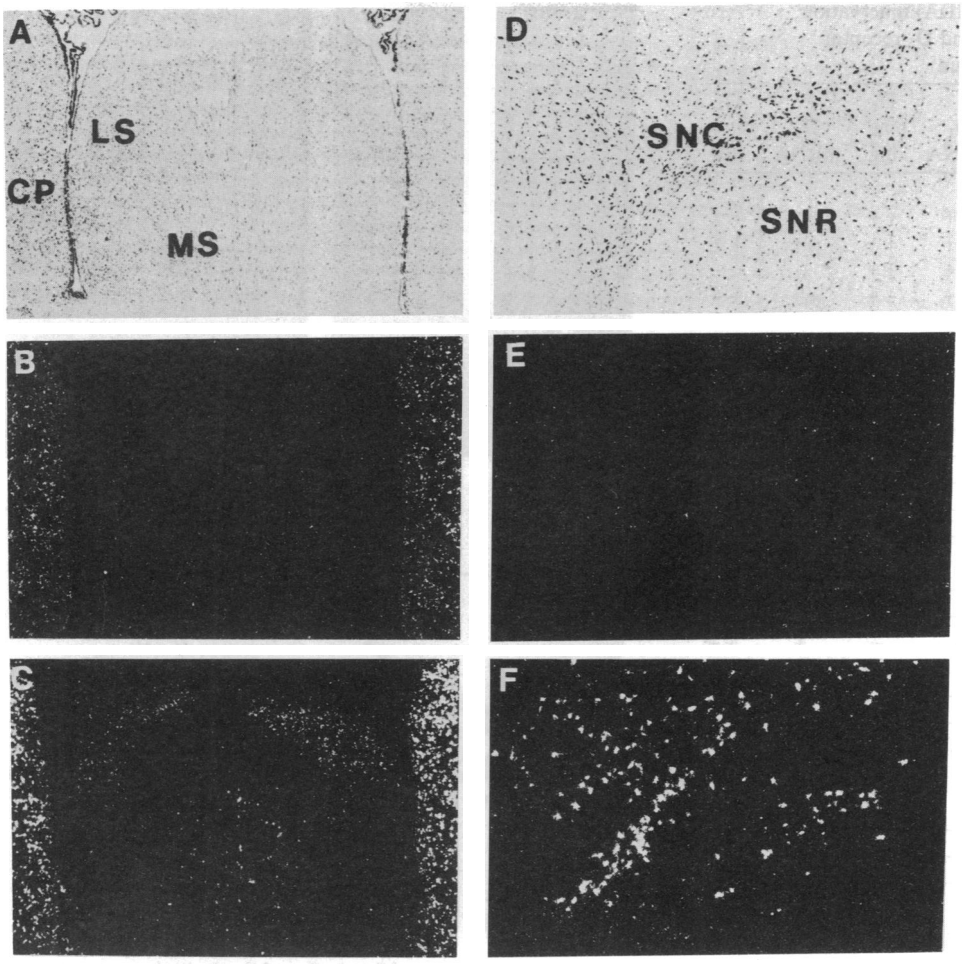

FIG. 2. Expression of D_1 (*B* and *E*), and D_2 (*C* and *F*) dopamine receptor mRNAs in rat septum (*A–C*) and substantia nigra (*D–F*). *A* and *D* are brightfield photomicrographs; *B*, *C*, *E*, and *F* are darkfield photomicrographs in which cells expressing mRNA appear white. The midbrain is oriented to the center of the figure. CP, caudate-putamen; LS, lateral septum; MS, medial septum; SNC, substantia nigra, pars compacta; SNR, substantia nigra, pars reticulata. (*A–C*, ×90; *D–F*, ×180.)

caudate-putamen. Cholinergic cells have these characteristics (27), and the distribution of these large cells is identical to that observed using probes to choline acetyltransferase mRNA (unpublished observations). The D_1 mRNA was relatively more abundant in the olfactory tubercle than in caudate-putamen and nucleus accumbens; whereas D_2 mRNA was more evenly distributed (Fig. 1 *B* and *E*). No labeling of small (<5 μm) "glial-like" cells or of vascular and ependymal structures was observed.

Only D_2 mRNA was observed in the substantia nigra (Fig. 2 *D–F*), septum (Fig. 1 *B* and *E*; Fig. 2 *A–C*), and hindbrain regions. Within the substantia nigra, D_2 mRNA was found in nearly all the large neurons of the pars compacta and in an occasional cell of the pars reticulata. An identical distribution of cells has been observed in the substantia nigra with probes to tyrosine hydroxylase mRNA (28). Within the septum, D_2 mRNA was localized in several subdivisions of the lateral septal nucleus. The D_2 mRNA was also observed in scattered cells in the medial septal nucleus, and within the nucleus of the diagonal band (Fig. 1*E*; Fig. 2*C*). The distributions of D_2 mRNA and choline acetyltransferase mRNA are very similar in these structures (unpublished observations).

The D_1 and D_2 mRNAs were observed in most regions of the cerebral cortex, but at much lower levels than in striatum. For most of the cerebral cortex, D_1 mRNA was seen deep within layer 6 (Fig. 1 *A* and *B*), and D_2 mRNA in layers 4 and 5 (Fig. 1 *D–F*). The highest levels of both mRNAs were observed in prefrontal (Fig. 1 *A* and *D*), perirhinal, and entorhinal cortex. In the prefrontal cortex, expression was limited to the anteromedial and suprarhinal pregenual regions (Fig. 1 *A* and *D*). In the entorhinal cortex, there was expression in layers 2 and 3. Only D_1 mRNA was observed within the piriform cortex, being most abundant in the polymorphic cell layer (Fig. 1*B*). Both mRNAs were observed in the dorsal endopiriform nucleus (Fig. 1 *B* and *E*).

D_1 and D_2 mRNAs had markedly different distributions in the amygdala (Fig. 1 *C* and *F*; Fig. 3 *A* and *B*). Only D_1 mRNA was found in the intercalated nuclei, and to a lesser extent in the basolateral and medial regions. Conversely, only D_2 mRNA was in the central nucleus.

The remaining brain regions observed to express D_1 and D_2 mRNAs are summarized in Table 1. Within the hypothalamus, D_2 mRNA was seen in most of the dopaminergic cell groups, except for the periventricular area and arcuate nucleus. The D_2 mRNA was also observed in the anterior parvocellular part of the paraventricular hypothalamic nucleus. D_1 mRNA was observed only in the paraventricular and suprachiasmatic nuclei (Fig. 1*C*). Many mid- and hindbrain regions express only the D_2 mRNA, most notably the mesencephalic dopaminergic cell groups and the dorsal raphe serotonergic cell groups. Neither mRNA was detected in hippocampus or cerebellum [the low signal in hippocampus for D_1 (Fig. 1*C*) could not be differentiated from controls with transducin probes]. Finally, both D_1 and D_2 mRNAs were observed in the inner nuclear layer of the retina.

DISCUSSION

The distribution of D_1 and D_2 receptor mRNA distribution is in remarkably good agreement with the innervation patterns of the various brain regions by dopaminergic neurons and with the distribution of dopamine D_1 and D_2 binding sites (Table 1). For example, mesencephalic dopaminergic neurons form their densest innervation of the brain within the striatum (11, 12, 18), and the striatum has the highest levels of D_1 and D_2 mRNA and binding sites (19–23). Areas of

Table 1. Distribution of dopaminergic (DA) innervation, dopamine D_1 and D_2 binding sites, D_1 and D_2 receptor mRNAs in various regions of the rat brain

Brain region†	DA innervation	D_1 mRNA	D_1 binding	D_2 mRNA	D_2 binding
Cortex					
Anteromedial prefrontal	++	++	++	++	++
Suprarhinal prefrontal	++	++	++	++	++
Piriform	+	++	++	–	–
Entorhinal	++	++	++	++	++
Dorsal endopiriform nu.	+	++	++	+	+
Basal ganglia					
Caudate-putamen	+++	+++	+++	+++	+++
Nucleus accumbens	+++	+++	+++	+++	+++
Olfactory tubercle	+++	+++	+++	+++	+++
Islands of Calleja	++	–	++	–	+++
Globus pallidus	+	–	++	sc	+
Entopeduncular nu.	+	–	++	+	–
Subthalamic nu.	++	–	++	–	–
Septum					
Lateral	++	–	+	+	++
Medial	–	–	–	+	++
Nuclear diagonal band	++	–	–	+	++
Amygdala					
Basolateral	+	+	+	–	–
Central	+++	–	–	++	++
Medial	+	+	+	–	–
Intercalated	+++	++	++	–	+
Hypothalamus					
Dorsal	*	–	–	++	+
Posterior	*	–	–	++	+
Ventromedial	±	–	–	++	+
Lateral	+	–	–	++	+
Zona incerta	*	–	+	++	+
Arcuate	*	–	–	–	–
Periventricular	*	–	–	–	–
Paraventricular	+	±	–	+	–
Suprachiasmatic	±	+	+	–	–
Lateral mammillary	–	–	–	++	++
Medial mammillary	–	–	–	++	++
Mid- and hindbrain					
Lateral habenula	++	–	–	++	+
SN, pars compacta	*	–	+++	+++	+++
SN, pars reticulata	*	–	+++	sc	+
Ventral tegmental area	*	–	–	+++	+++
Retrorubral field	*	–	–	+++	+++
Cranial nerves 3 and 6	–	–	–	++	++
Dorsal raphe	+	–	–	++	+
Locus coeruleus	+	–	–	±	++
Central gray	+	–	–	++	++
Inferior colliculus	±	–	–	++	+
Superior colliculus	±	–	–	+	+
Pontine reticular	–	–	–	++	+
Dorsal tegmental nu.	–	–	–	+++	+++
Medial parabrachial	–	–	–	++	+++
Retina					
Inner nuclear layer	+	+	ND	+	+
Outer nuclear layer	+	–	ND	–	++

±, Uncertainty; + to +++, low to high relative levels; *, dopaminergic cell groups; ND, not determined; sc, scattered cells. The table is based on those represented in refs. 23 and 26, where the index of dopaminergic innervation was gathered from refs. 11, 13–18, 20, 23, and 26), and the distribution of D_1 and D_2 binding sites was obtained from refs. 19–23.

†nu., Nucleus; SN, substantia nigra.

apparent discrepancy between the distribution of D_1 mRNA and binding sites are the striatal projection areas including the

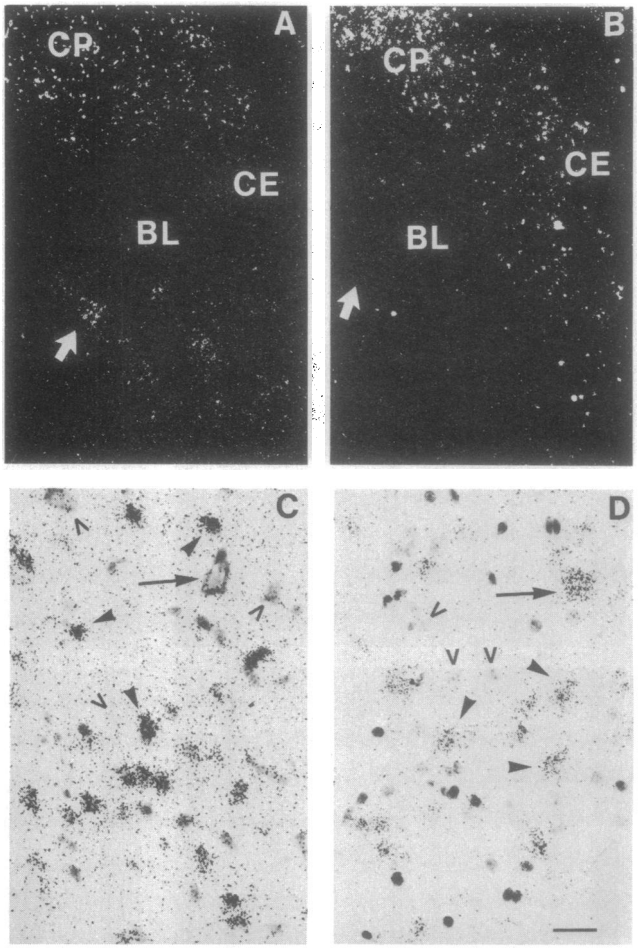

FIG. 3. Expression of D_1 (*A*, *C*) and D_2 (*B*, *D*) dopamine receptor mRNA in amygdala (*A* and *B*) and striatum (*C* and *D*). Cells expressing mRNA appear white in the darkfield (*A* and *B*) and as black grains in the brightfield (*C* and *D*) photomicrographs. *A* and *B* are from coronal sections through the amygdala; arrows indicate one of the intercalated nuclei of the amygdala. *C* and *D* show neurons from the caudate-putamen, where solid arrowheads indicate positive cells, open arrowheads indicate negative cells, and the arrows highlight a representative large interneuron. BL, basolateral amygdaloid nucleus; CE, central amygdaloid nucleus; CP, caudate-putamen. (Bar = 20 μm.)

globus pallidus, endopeduncular nucleus, and substantia nigra. These regions have very high levels of D_1 binding but no D_1 mRNA. However, these data can be reconciled if D_1 receptors are synthesized in the striatum and then transported to these regions, as suggested by lesion studies (29).

Within the cerebral cortex, the densest dopaminergic innervation is in prefrontal and entorhinal regions (15, 16) areas with the highest mRNA levels and binding sites (19–23). The laminar patterns of mRNA expression and binding sites also correlate, with D_1 mRNA and binding sites highest in layer 6 (20), and D_2 mRNA and binding sites highest in layers 3–5 (23). Within the amygdala, the highest levels of dopaminergic innervation is in the central and intercalated nuclei (16). The highest levels of D_1 mRNA and binding (20) are present in the intercalated nuclei, and D_2 mRNA and binding are highest in the central nucleus (23).

The majority of dopaminergic cell groups express D_2 but not D_1 mRNA (Table 1). Exceptions include the arcuate and periventricular dopaminergic cell groups of the hypothalamus (as previously reported for D_2; ref. 30), which express neither mRNA. These data suggest that D_2 but not D_1 receptors are likely to function as presynaptic receptors in most dopaminergic neurons. This is consistent with various

physiological (31) and anatomical (32) studies, which have indicated that presynaptic dopamine receptors have a D_2 pharmacology.

In general, the present anatomical data must be interpreted with extreme caution regarding its relevance for the potential existence of additional dopamine receptor genes. With the exceptions of photoreceptors in the retina (D_2 binding, no mRNA; refs. 9 and 33) and the hippocampus (D_1 and D_2 binding, no mRNA; refs. 20 and 23), the present data seem to account for the known distribution of dopamine receptors in neuronal tissues. This does not exclude the possible expression of other dopamine receptor genes in these tissues. Consider for example the case of muscarinic receptors, which are encoded by five different genes (m1–m5). Of these genes, analysis of m1 and m2 receptor distribution alone would have appeared to account for the majority of muscarinic receptor distribution. In fact, the majority of m4 mRNA is coexpressed with m1 mRNA, and m5 mRNA has a very limited distribution (34).

Within the striatum, D_1 and D_2 mRNAs show very similar distribution patterns, and both mRNAs are expressed by ≈50% of the medium-sized neurons. These data are consistent with the mRNAs being extensively coexpressed in this structure. However, additional experiments are required to determine the precise extent of this colocalization. A cellular coexpression of D_1 and D_2 receptors was predicted by various biochemical and behavioral studies. For example, in membrane preparations, D_2 receptors are able to inhibit D_1-stimulated adenylyl cyclase (35). The widespread coexpression of these mRNAs within the striatum is also consistent with the additive and synergistic effects of D_1 and D_2 receptors on psychomotor behavior (36).

The expression of only D_2 mRNA by cells with the appearance, distribution, and frequency of cholinergic cells in the striatum and basal forebrain is consistent with the innervation of these cells by dopaminergic neurons (37) and the inhibition of these cholinergic systems by D_2 but not D_1 receptors (38, 39). These data are also consistent with an involvement of cholinergic systems in certain D_2 (but not D_1)-mediated behavior (40). If recent hypotheses that adaptive changes in cholinergic systems are involved in the pathophysiology of tardive dyskinesia (40) are true, then one may predict from these data that chronic blockade of D_1 receptors may not induce this disorder.

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