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# Localization of Monoamine Oxidase A and B mRNA in the Rat Brain by In Situ Hybridization

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*ABSTRACT* Monoamine oxidases A and B (MAOA and MAOB) are the major catabolic isoenzymes of catecholamines and serotonin in the mammalian brain. Although the distribution of the monoamine oxidase protein has been mapped by ligand binding and immunohistochemistry, the sites of MAOA and MAOB synthesis have not been precisely determined. In this study, we used in situ hybridization to visualize MAOA and MAOB mRNAs in the rat brain by using specific cDNA and oligonucleotide probes. MAOA mRNA was localized in major monoaminergic cell groups, such as the dorsal vagal complex, the C1/A1 groups, the locus ceruleus, the raphe nuclei, the substantia nigra, and the ventral tegmental area. MAOA mRNA was also found in forebrain structures, such as the cortex, the hippocampus, the thalamus, and the hypothalamus. In contrast to the distribution of MAOA mRNA, high levels of MAOB mRNA were present in only three brain regions: the area postrema, the subfornical organ, and the dorsal raphe. The in situ visualization of MAO mRNA demonstrates that MAOA mRNA synthesis is wide spread in many catecholaminergic and serotonergic cell groups, whereas MAOB mRNA synthesis is far more discrete and limited. The different expression patterns of MAOA and MAOB suggests that may also have different physiological functions.

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## INTRODUCTION

Monoamine oxidases A and B (MAOA and MAOB) are the major catabolic isoenzymes of catecholamines and serotonin in the mammalian brain. The two isoenzymes have 70% amino acid identity (Bach et al., 1988), identical exon-intron organization (Grimsby et al., 1991), and are encoded by two different genes that reside closely between bands Xp11.23 to Xp22.1 of the X chromosome. The two forms are different in their substrate specificity and inhibitor sensitivity. MAOA has a higher affinity for serotonin and norepinephrine, whereas MAOB has higher affinity for trace amines, such as phenylethylamine. MAOA is inhibited by low concentrations of clorgyline, whereas MAOB is inhibited by low concentrations of pargyline and deprenyl.

MAOA and MAOB also differ in their regional distribution in the brain. The MAOs have been localized in rodent, cat, primate, and human brains by a variety of techniques, including enzyme activity (Student and Edwards, 1977; Arai et al., 1986; Shigematsu et al., 1989), in vivo metabolite accumulation (Takada et al., 1991), ligand autoradiography (Jossan et al., 1991; Saura et al., 1992), immunohistochemistry (Levitt et al., 1982; Schneider and Markham, 1987; Westlund et al., 1985, 1988, 1993; Willoughby et al., 1988), and positron emission tomography (Moerlein et al., 1986). These techniques all reveal regional, cellular, and subcellular distribution of MAO protein and activity. Northern blot analysis shows that MAOA and MAOB mRNAs are expressed in most tissues; however, there are developmental differences in expression in the brain (Grimsby et al., 1990).

In this study, we used in situ hybridization with cDNA and oligonucleotide probes to localize the sites of

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MAOA and MAOB mRNA synthesis in the rat brain. The MAOs are important regulators of monoamine systems, which have discrete origins but widespread projection sites, such as the cells of the serotonergic raphe and noradrenergic locus ceruleus. Localization of MAO mRNA synthesis by in situ hybridization can determine directly whether the MAOs are synthesized presynaptically in the monoaminergic cell groups or in the target projection sites.

## MATERIALS AND METHODS

### Animals

Adult male Sprague-Dawley rats (Charles River Laboratories, Boston, MA; n = 10; 2-3 months old) were group housed under a 12 h light-12 h dark cycle at 23°C with ad lib access to rodent chow and water.

### Probes

#### MAOA probe

To label MAOA mRNA specifically, we used a 3.5 kilobase cDNA beginning at base 135 of the rat heart MAOA cDNA (unpublished data). In addition, a 34-mer oligodeoxynucleotide probe corresponding to bases 75–108 of the human liver MAOA cDNA sequence (Bach et al., 1988; 5′-TGGAGAATCAAGAGAAGGCGAGTATC-GCGGGCCACATGTTC-3′) was employed. This region is distinctly different from the MAOB cDNA sequence.

#### MAOB probe

A 2.5 kilobase MAOB cDNA isolated from a human liver cDNA library was used (Bach et al., 1988). The cDNA began 78 nucleotides upstream of the ATG initiation site and included 858 nucleotides of untranslated 3′ region beyond the TAA termination codon. Northern blot analysis showed that this clone does not cross hybridize with MAOA (Bach et al., 1988).

### In situ hybridization

Rats were perfused with 4% paraformaldehyde in 0.1 M sodium phosphate buffer, pH 7.2. Brains were dissected, postfixed for 1-2 h, and cryoprotected in 30% sucrose. Free-floating coronal sections (40 μM) were cut on a freezing microtome into ice-cold 2 × saline citrate solution (SSC; 1 × SSC = 0.15 sodium chloride, 0.015 M sodium citrate). Sections were prehybridized for 1 h in 50% formamide, 10% dextran sulfate, 2 × SSC, 1 × Denhardt's solution, 10 mM dithiothreitol, and 0.5 mg/ml sonicated denatured salmon sperm DNA. Denatured MAOA cDNA probe ($^{35}$S-dATP labeled by random priming) was added to the vial (10,000,000 cpm per vial), and hybridization was carried out overnight at 48°C. Tissue sections hybridized with an MAOA specific antisense oligonucleotide probe or control sense probe (tail labeled with $^{35}$S-dATP by terminal transferase reaction) were incubated overnight at 31°C. The sections incubated with cDNA probe were washed in serial dilutions of SSC at 48°C, starting with 2 × SSC, and ending with 0.1 × SSC. For oligonucleotide probe, the incubated sections were washed at 31°C in 2 × SSC, 1 × SSC, twice in 0.5 × SSC, and 0.25 × SSC. Sections were mounted, dehydrated, and exposed onto Kodak XAR-5 film at 4°C for 3-4 days. Some slides were also dipped in Kodak photoemulsion and exposed for 1-2 weeks.

Brain regions containing major monoaminergic cell groups and their projection sites were processed. Tissue sections from the caudal medulla at the level of the nucleus of the solitary tract and C1/A1 cell groups, the pons at the level of the locus ceruleus, the midbrain at the level of the raphe and of the substantia nigra, and forebrain sections at the level of thalamus and septum were examined.

Labeling was considered specific if it was present on sections incubated with antisense oligonucleotide probes but absent on sections incubated with control sense oligonucleotide probes (see Fig. 1). The labeling by cDNA probes was considered specific if the labeling was discrete, limited to definable anatomical structures, and much darker than surrounding tissue (background levels). The anatomical regions of labeling on autoradiographic films and emulsion-dipped slides were identified by counterstaining all sections with cresyl violet and comparison to a rat brain atlas (Paxinos and Watson, 1986).

## RESULTS

### MAOA

#### Medulla

MAOA mRNA was observed in the dorsal vagal complex (Figs. 2A, 3A). The dorsal motor nucleus of the vagus was labeled intensely with MAOA cDNA and oligonucleotide probes. Scattered punctate labeling was present in the caudal nucleus of the solitary tract ventral to the area postrema; most labeling was seen medial to the solitary tract, with very little labeling observed in the nucleus of the solitary tract lateral to the solitary tract. Light labeling was present in the hypoglossal nucleus. Labeling was also observed in the C1/A1 area, with greater intensity in the more caudal aspects corresponding to the more caudal distribution of the adrenergic A1 cell group. Labeling was also observed in the inferior olive.

#### Pons

The highest density of MAOA mRNA visualized in the rat brain with both the MAOA cDNA and oligonucleotide probes was seen in the locus ceruleus (Figs. 2B, 3B). In the cerebellum, the MAOA oligonucleotide and the cDNA probe labeled cell bodies of the Purkinje and granule layers.

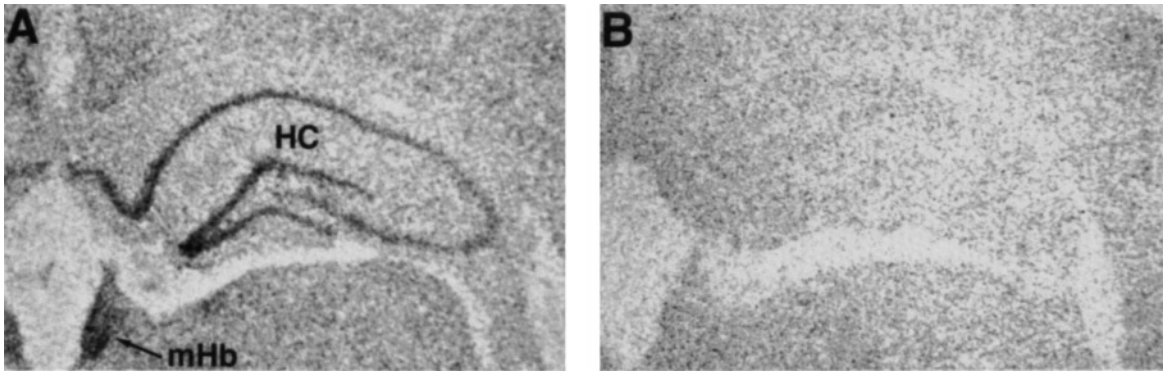


Fig. 1. Brightfield photomicrographs of in situ hybridization autoradiograms using human monoamine oxidase A (MAOA) oligonucleotide probes. **A:** Antisense oligonucleotide labeling in the hippocampus (HC) and the medial habenula (mHb). **B:** Sense oligonucleotide labeling in adjacent section hybridized in parallel with the tissue section shown in A.

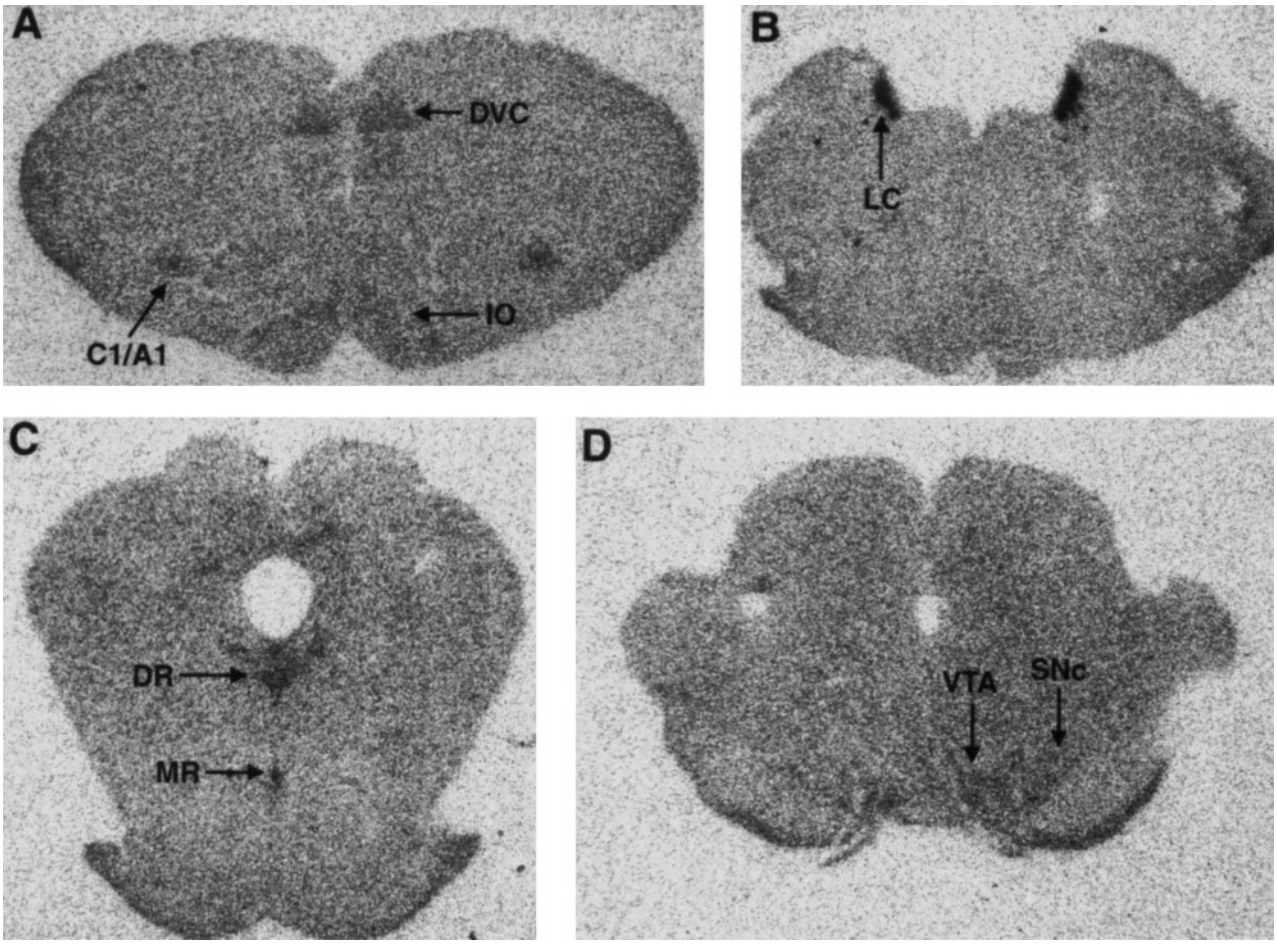


Fig. 2. Brightfield photomicrographs of in situ hybridization autoradiograms using a rat MAOA cDNA probe. **A:** In the caudal medulla, labeling was seen in the dorsal vagal complex (DVC), excluding the area postrema, the C1/A1 region, and the inferior olive (IO). **B:** In the pons, the most intense MAOA labeling observed in the brain was seen in the locus ceruleus (LC). **C:** MAOA labeling in the caudal midbrain at the level of the dorsal raphe (DR) and the medial raphe (MR). **D:** In the rostral midbrain, labeling was observed in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc).

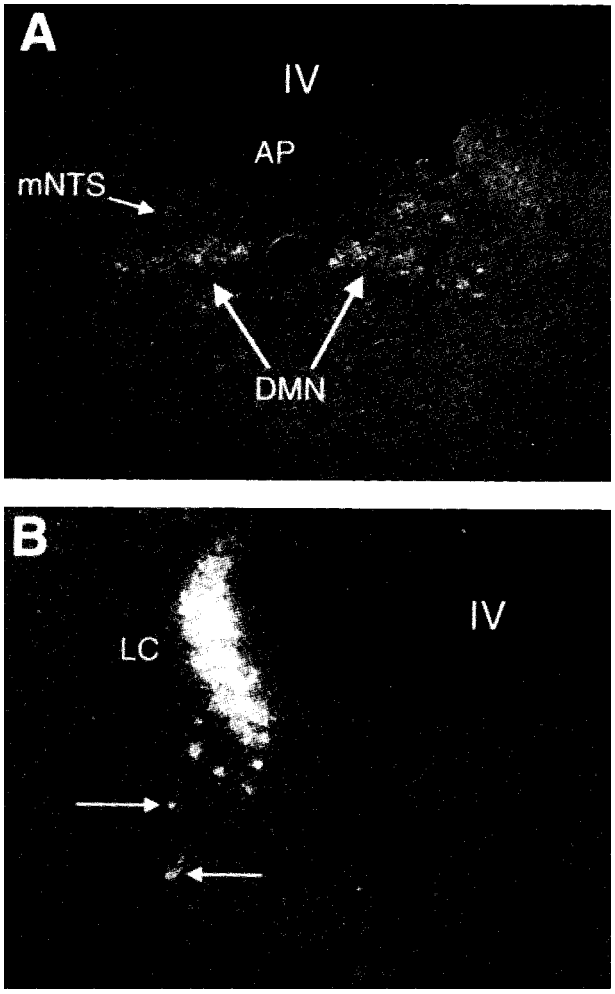


Fig. 3. Darkfield photomicrographs of photoemulsion-dipped slides after in situ hybridization with rat MAOA cDNA probe. **A:** MAOA labeling in the dorsal medulla showing cellular staining in the dorsal motor nucleus of the vagus (DMN) and in the medial nucleus of the solitary tract (mNTS) but not in the area postrema (AP). **B:** MAOA labeling in the locus ceruleus (LC). Arrows indicate isolated subcerulean cells expressing MAOA mRNA.

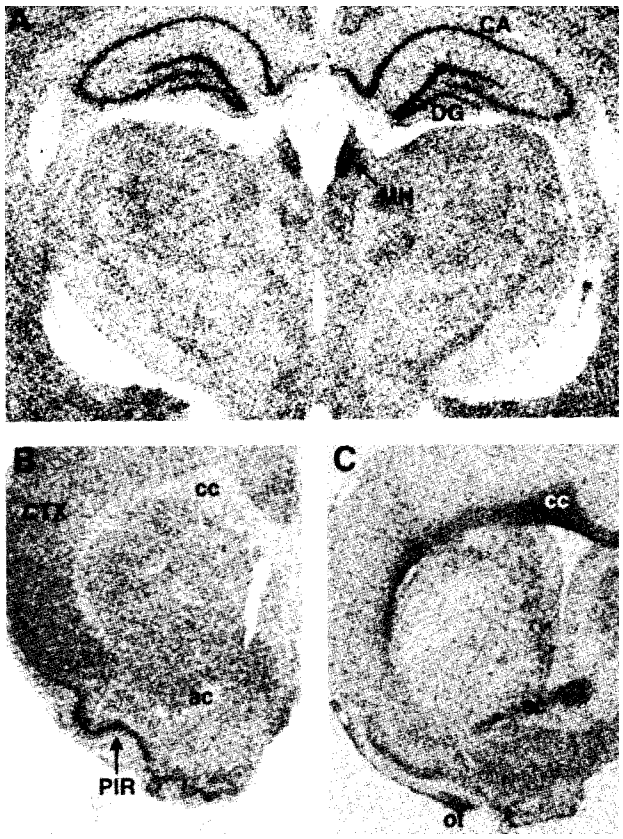


Fig. 4. Brightfield photomicrographs of in situ hybridization autoradiograms using a human MAOA oligonucleotide probe (A,B) and a rat MAOA cDNA probe (C) in the forebrain. **A:** High levels of MAOA mRNA were observed in the medial habenula (MH) and in the CA1–3 and dentate gyrus (DG) regions of the hippocampus. Less intense labeling was observed in several subnuclei of the thalamus. **B:** High levels of MAOA mRNA in the piriform cortex (PIR) and moderate levels in the cerebral cortex (CTX). Note that the human MAOA oligonucleotide probe did not label fiber tracts, such as the corpus callosum (cc) and the anterior commissure (ac). **C:** The rat MAOA cDNA probe, in contrast to the human oligonucleotide probe, labeled fiber tracts in the forebrain, such as the cc, the ac, and the olfactory tract (ot).

### Midbrain

MAOA labeling was observed in the dorsal raphe extending ventrally along the midline. Below the superior cerebellar peduncle, the median raphe was also labeled (Fig. 2C). The dopaminergic regions of the ventral tegmental area and the substantia nigra pars compacta were labeled (Fig. 2D; the substantia nigra pars reticulata was not labeled). The periaqueductal gray dorsal to the ventral tegmental area was also lightly labeled. The MAOA cDNA probe, but not the MAOA oligonucleotide probe, also labeled the cerebral peduncle fiber tract.

### Forebrain

The thalamus showed a complex anatomical distribution of MAOA hybridization with diffuse but differential regional labeling (Fig. 4A). The paraventricular, central lateral, parafascicular, ventral posteromedial, and ventral posterolateral nuclei contained MAOA mRNA. The mediodorsal and most of the posterior complex lacked MAOA labeling. Ventromedial to the thalamus, the posterior hypothalamic nuclei and the ventromedial hypothalamus were diffusely labeled. Ventrolateral to the thalamus, the external medullary lamina and the zona incerta contained no MAOA mRNA. The subthalamic nucleus did contain MAOA mRNA, however.

Dorsal to the thalamus, the medial habenula contained very high levels of MAOA labeling (Figs. 1A, 4A). In the hippocampus, the granular cell layer of the dentate and the pyramidal layers of the CA1–3 regions were labeled (Figs. 1A, 4A).

The piriform cortex contained very high levels of MAOA labeling, which appeared to be localized to layer

2 (Fig. 4B,C). The cerebral cortex was labeled by the MAOA oligonucleotide in levels 1–6 (Fig. 4B). The MAOA cDNA probe labeled the cerebral cortex only lightly (Fig. 4C). MAOA mRNA was detected in the medial septum; no labeling was observed in the adjacent diagonal band.

The labeling observed with the MAOA antisense oligonucleotide probe was specific, because no labeling was observed in any brain region after hybridization with the MAOA sense oligonucleotide probe (see, e.g., Fig. 1). In all regions where MAOA antisense oligonucleotide labeling was observed, MAOA cDNA labeling was also observed. However, the MAOA cDNA consistently labeled major fiber tracts, such as the olfactory tract, the anterior commissure, fimbria, the stria medullarus, and the corpus callosum in six out of ten rats examined (Fig. 4C). The cDNA probe also labeled the striatum, but no distinction could be made between labeling of striatal fibers and cell bodies from the autoradiographic films. No labeling was seen in fiber tracts below the midbrain (e.g., the cerebellar peduncle). Fiber labeling was conspicuously absent from sections hybridized with the MAOA oligonucleotide probe (Fig. 4B). The labeling of fiber tracts was specific to the MAOA cDNA probe, because fiber tracts were not labeled by cDNA probes for MAOB (see below) or for catecholaminergic enzyme expression (e.g., tyrosine hydroxylase) hybridized in parallel on adjacent tissue sections (data not shown).

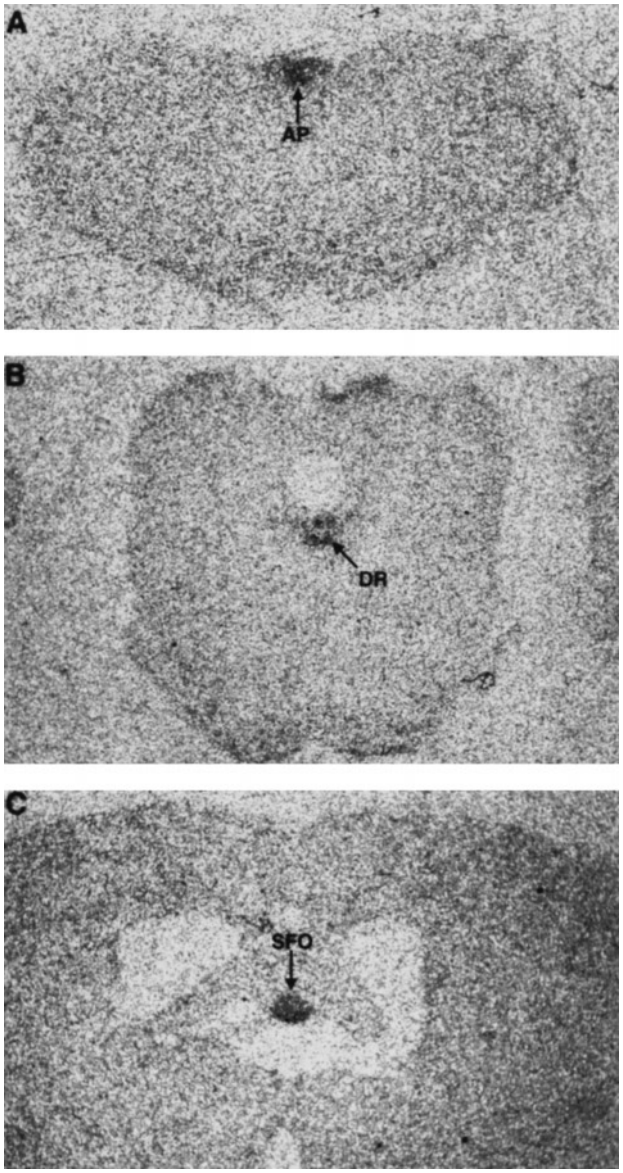


Fig. 5. Brightfield photomicrographs of in situ hybridization autoradiograms using a human monoamine oxidase B (MAOB) cDNA probe. **A:** Coronal section of the medulla at the level of the area postrema (AP). **B:** Coronal section of the midbrain at the level of the dorsal raphe (DR). **C:** Coronal section of the forebrain at the level of the subfornical organ (SFO). MAOB in situ hybridization labeling was observed only in these three brain regions.

## MAOB

Strong MAOB labeling was present only in the area postrema, the medial dorsal raphe, and the subfornical organ (Fig. 5). No MAOB labeling above background was observed in the locus ceruleus, where MAOA labeling was most intense, or in other brain regions.

## DISCUSSION

This study demonstrated the localization of MAOA and MAOB mRNAs in the rat brain by in situ hybridization. MAOA mRNA was found to be distributed widely in the brain, whereas MAOB mRNA was expressed intensely in only three brain regions: the area postrema, the dorsal raphe, and the subfornical organ.

## MAOA

MAOA mRNA was present in major monoamine groups of the brain, such as the dorsal vagal complex, the C1/A1 groups, the locus ceruleus, the raphe nuclei substantia nigra, and the ventral tegmental area. It was also present in important brain structures of the forebrain, such as the cerebral cortex, the hippocampus, the medial habenula, the thalamus, and the hypothalamus; these are major projection sites of the monoamine groups of the midbrain and hindbrain. Thus, MAOA mRNA was found in serotonergic and noradrenergic cell groups as well as in dopaminergic groups. The presence of MAOA mRNA in these groups is consistent with a role for MAOA in oxidizing serotonin, noradrenaline, and dopamine.

The distribution of MAOA mRNA corresponds closely to the binding of MAOA ligand (e.g., $^{3}$H-Ro 41-1049) in some areas, such as the medial habenula, the hypothalamus, the raphe nuclei, the locus ceruleus, the inferior olive, the C1/A1 groups, and the dorsal vagal complex (Saura et al., 1992). Both positive and negative mismatches between in situ hybridization and previously

reported ligand binding are also apparent. Intense ligand binding has been reported in the interpeduncular nucleus (Saura et al., 1992), but MAOA mRNA was not observed there in the present study. Furthermore, only low levels of binding were reported in the cortex and the hippocampus (Saura et al., 1992), where high levels of MAOA mRNA expression were seen. These differences may reveal patterns of posttranslational transport of MAOA after synthesis, differences in sensitivity between ligand binding and in situ hybridization, or they may indicate that, in some brain regions (e.g., the cortex and the hippocampus), the MAOA gene is transcribed to mRNA but is not translated into protein that can be labeled by the radioligand.

In the pons and the medulla, nearly identical labeling was observed by using either a rat heart MAOA cDNA or an oligonucleotide corresponding to human liver MAOA cDNA. In the forebrain, however, the patterns of labeling by the cDNA probe and the oligonucleotide probe were different, mainly in the labeling of fiber tracts by the cDNA probe. The labeling of fiber tracts was specific to the MAOA cDNA probe, because other cDNA probes that were used on adjacent tissues sections in parallel did not label fiber tracts. The labeling of fiber tracts may be an artifact of the specific MAOA cDNA probe utilized (Higgins and Wilson, 1987). Conversely, the presence of MAOA mRNA in fiber tracts may indicate glial cell expression (Levitt et al., 1982) or axonally transported mRNA, which has been observed in some other systems (Jirikowski et al., 1990). Further characterization of fiber tracts, e.g., by Northern blot, is required to determine the specificity of the fiber labeling by MAOA cDNA probe.

### MAOB

In contrast to MAOA mRNA, the distribution of MAOB mRNA in the brain was very circumscribed. There were only three brain regions in which the amount of MAOB mRNA exceeded the limits of detection: the area postrema, the dorsal raphe, and the subfornical organ. The area postrema and the subfornical organ are both circumventricular organs that contain a wide variety of neurotransmitters, including monoamines (Armstrong et al., 1981; Kelly, 1982). MAOB expression, therefore, may play a role in the oxidation of local neurotransmitters. The area postrema and the subfornical organs also lack blood-brain barriers and are exposed to blood-borne substances; they are functionally important as detectors of humoral factors and toxic substances in the blood (Kelly, 1982). It is possible that MAOB may aid in the degradation of blood-borne factors in these circumventricular organs.

Although MAOB mRNA was observed in the serotonergic cell group of the dorsal raphe, MAOB was not present in the median raphe or in any major catecholaminergic cell group, such as the C1/A1 groups, the nucleus of the solitary tract, the locus ceruleus, the substantia nigra, or the ventral tegmental area. MAOB mRNA was also not observed in projection sites of the monoaminergic groups in the forebrain. This was unexpected, because the MAOB enzyme has lower affinity for serotonin as a substrate than MAOA. Similar patterns of MAOA in catecholaminergic cells and MAOB in serotonergic cells have been described immunohistochemically in rat (Levitt et al., 1982) and in monkey (Westlund et al., 1985). We cannot rule out, however, the possibility that low levels of MAOB mRNA below the level of detection by $^{35}S$ in situ hybridization autoradiography may be present in neurons or glia. It is also possible that the human MAOB cDNA probe employed in this study does not hybridize with all forms of rat MAOB mRNA.

The patterns of MAOB and MAOA mRNA expression were mutually exclusive almost everywhere, even when those regions were immediately adjacent to each other. For example, MAOA mRNA was present in the nucleus of the solitary tract, whereas MAOB was found in the area postrema. Even in the dorsal raphe, where MAOA and MAOB mRNA overlapped, MAOA expression extended farther laterally and ventrally. The differential pattern of expression suggests that, despite homology between MAOA and MAOB at the level of protein and gene sequences, the regulation of tissue-specific expression is very different.

Like the case of MAOA, both correspondences and disparities were observed between the expression of MAOB mRNA and the distribution of MAOB ligand-binding sites (e.g., $^{3}H$-Ro 19-6327). High levels of ligand binding have been reported in the subfornical organ, the area postrema, and the dorsal raphe (Saura et al., 1992); high levels of MAOB mRNA were seen in all of these areas. However, MAOB mRNA expression was limited to these three areas, whereas MAOB ligand binding has been reported in numerous other brain regions, such as the arcuate nucleus, the hippocampus, the organum vasculosum lamina terminalis, the interpeduncular nucleus, and the inferior olive (Saura et al., 1992). These differences may reflect the differential sensitivity of the ligand binding vs. in situ hybridization. Differences in mRNA localization and protein localization may also reflect posttranslational processing and axonal transport, resulting in ligand binding at sites distant from the place of MAOB synthesis.

Unlike earlier studies of MAO protein distribution in the brain, in situ hybridization localizes the site of mRNA synthesis, which may be distant from the final site of mitochondrial incorporation. This is particularly relevant, because the monoamines are distributed from several cell groups with wide-ranging projections, such as the locus ceruleus and the raphe nuclei. This study has demonstrated that high levels of MAOA mRNA expression are present in the monoamine cell groups and in their projection sites, whereas MAOB mRNA expression is far more limited. Further work is needed

to identify the phenotype of cells expressing MAO mRNA. For example, double-labeling studies could demonstrate colocalization with monoamine transmitters or could determine neuronal vs. glial distribution.

The MAOs have proven to be critical substrates of psychiatric disorders, such as depression, that are treatable with MAO inhibitors. The deletion of both MAO genes is associated with mental retardation in humans (Collins et al., 1992), and the disruption of functional MAOA synthesis is associated with aggression in humans (Brunner et al., 1993) and in transgenic mice (Cases et al., 1995). Understanding the functional significance of MAO mRNA expression will require elucidation of interactions between monoaminergic synthetic enzymes, monoamine transporters, and the control of MAO protein synthesis and transport. The ability to visualize MAOA and MAOB mRNA expression at the cellular level by using in situ hybridization should help determine the time course and regional differences in the pharmacological regulation of MAO gene expression.

## ACKNOWLEDGMENTS

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