Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 3637–3641, May 1991
Neurobiology

Human monoamine oxidase A and B genes exhibit identical exon–intron organization

(human *MAOA* and *MAOB* genes/genomic organization)

JOSEPH GRIMSBY, KEVIN CHEN, LI-JIA WANG, NANCY C. LAN, AND JEAN C. SHIH*

Department of Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California, 1985 Zonal Avenue, Los Angeles, CA 90033

Communicated by Norman Davidson, January 8, 1991 (received for review November 21, 1990)

ABSTRACT **Monoamine oxidases A and B [MAOA and MAOB; amine:oxygen oxidoreductase (deaminating) (flavin-containing), EC 1.4.3.4] play important roles in the metabolism of neuroactive, vasoactive amines and the Parkinsonism-producing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Human *MAOA* and *MAOB* genes isolated from X chromosome-specific libraries span at least 60 kilobases, consist of 15 exons, and exhibit identical exon–intron organization. Exon 12 codes for the covalent FAD-binding-site and is the most conserved exon; the *MAOA* and *MAOB* exon 12 products share 93.9% peptide identity. These results suggest that *MAOA* and *MAOB* are derived from duplication of a common ancestral gene and provide insight on the structural/functional relationship of the enzyme products.**

Monoamine oxidases A and B [MAOA and MAOB; amine:-oxygen oxidoreductase (deaminating) (flavin-containing), EC 1.4.3.4] catalyze the oxidative deamination of a number of neurotransmitters and dietary amines. Both forms are located in the outer mitochondrial membrane where they are used as marker enzymes (1). The two enzymes possess different substrate and inhibitor specificities (2–4), tissue and cell distribution (5), immunological properties (6), photo-dependent inactivation (7, 8), and amino acid sequences (9–11). Further, they are regulated differently by steroids (12). MAOA preferentially oxidizes the biogenic amines such as serotonin, norepinephrine, and epinephrine and is inactivated irreversibly by the acetylenic inhibitor clorgyline. MAOB preferentially oxidizes phenylethylamine and benzylamine and is inactivated by the irreversible inhibitors pargyline and deprenyl. Dopamine, tyramine, and tryptamine are the common substrates for both forms. Furthermore, the xenobiotic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can be oxidized by MAOB to form a neurotoxic species that can cause permanent Parkinsonian symptoms (13). Recently isolated cDNA clones that encode the human liver MAOA and MAOB showed that they share 70% amino acid identity and may be derived from separate genes (9). Transient transfection of human liver MAOA or MAOB cDNAs in COS cells resulted in expression in these virally transformed African Green monkey kidney cells of functional enzymes that observe substrate and inhibitor preferences identical to those of the respective human enzyme (14).

The tissue distribution of MAOA and MAOB mRNAs determined by RNA blot-hybridization (Northern) analysis (9, 15) is consistent with enzymatic studies (16). MAOA and MAOB are coexpressed in almost all human tissues except placenta, which predominantly expresses MAOA (11, 15, 16), and platelets and lymphocytes, which predominantly express MAOB. MAOA is expressed before MAOB in fetal brain (15, 17). Northern blot analysis reveals predominantly a MAOA mRNA species of 5 kilobases (kb) in most tissues except placenta and small intestine, which express an additional 2-kb mRNA species (11, 15). These two mRNA species arise in part from the use of alternative polyadenylylation sites (15). A 3-kb MAOB mRNA species is found in most tissues (15). These two genes are closely linked and located on the X chromosome, Xp11.23–Xp22.1. Both of them are deleted in some patients with Norrie disease (18), which is characterized by blindness, deafness, and mental retardation. However, the etiology of this disorder is still unknown.

Abnormal levels of MAO activity have been reported in a number of mental disorders, such as depression (19), alcoholism (20), schizophrenia (21), and Alzheimer disease (22). Further, MAO inhibitors have been used as antidepressants (23). The structure of *MAOA* and *MAOB* genes will help us to understand the tissue-specific expression, the regulation, and the structural–functional relationship of their enzyme product and the possible role of these genes in mental disorders. In this report, we describe the partial structure of the *MAOA* and *MAOB* genes. These data show that both are comprised of 15 exons and 14 introns spanning at least 60 kb. The exon–intron organization is identical in both genes, which suggests that they are derived by duplication of a common ancestral gene.

MATERIALS AND METHODS

Isolation of *MAOA* and *MAOB* Genes. Genes encoding human MAOA and MAOB were isolated by screening four λ bacteriophage libraries with human liver MAOA and MAOB cDNA clones (9). These libraries were screened independently with MAOA or MAOB cDNA subfragments ^{32}P-labeled by the random priming method (24, 25). The subfragments used included the 5′ end (A8:nucleotides 1–552), the middle region (A9:nucleotides 553–1200), and the 3′ end (A10:nucleotides 1201–1958) of the MAOA cDNA and the 5′ end (B1:nucleotides 1–602), the middle region (B2:-nucleotides 603–1434), and the 3′ end (B3:nucleotides 1435–2498) of the MAOB cDNA (18). Hybridization was carried out in 50% (vol/vol) formamide in 5× SSC (1× SSC = 0.15 M NaCl/0.015 M sodium citrate) at 37°C overnight and washed at high stringency [0.1× SSC/0.1% sodium dodecyl sulfate (SDS) at 60°C]. Twenty-one *MAOA*$^+$ positive clones were isolated from a partially digested X chromosome-specific library cloned in phage λ EMBL3 (a gift from L. Hood) and λ Charon 35 (American Type Culture Collection). Forty-three *MAOB*$^+$ clones were isolated from the λ Charon 35 library and from a completely *Hin*dIII-digested (a gift from S. A. Latt) or *Eco*RI-digested (American Type Culture Collection) X chromosome-specific library cloned in λ Charon 21. Southern blot analysis of phage DNA isolated from 30 λ bacteriophage clones identified exon-containing restriction

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: MAO, monoamine oxidase; MAOA and MAOB, MAOs A and B.

*To whom reprint requests should be addressed.

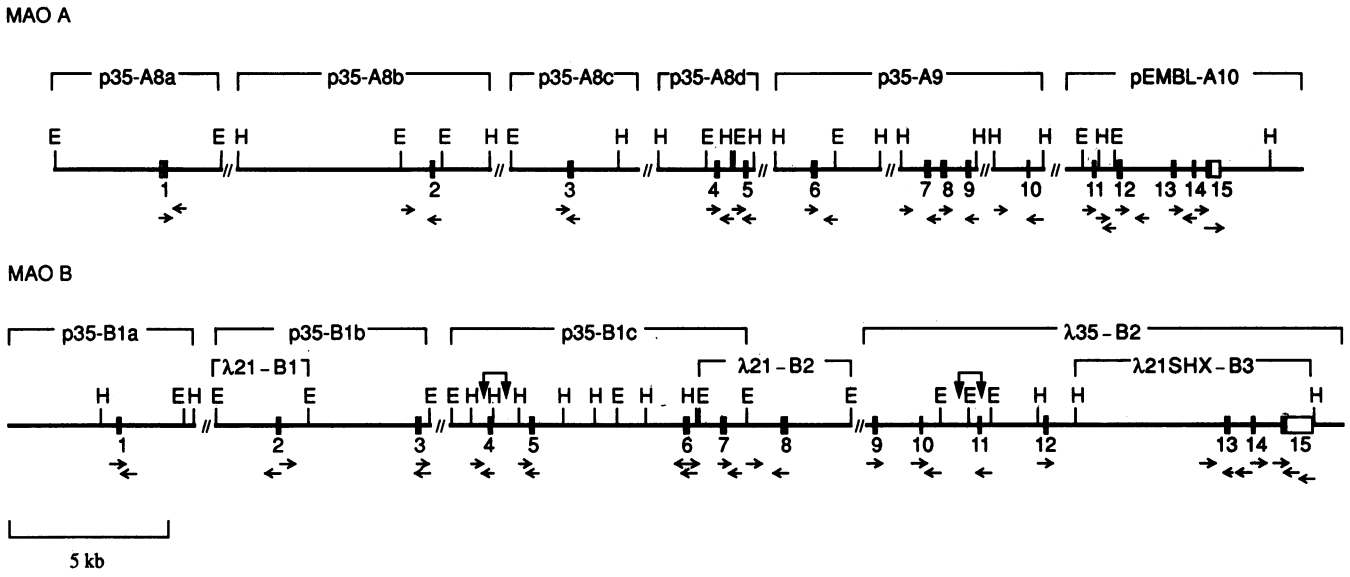

FIG. 1. Partial structural map of the *MAOA* and *MAOB* genes showing the location of exons and sequence strategy. Filled bars represent coding regions, and unfilled bars represent untranslated regions of the exons. Exon numbers are presented below the bars. The horizontal arrows represent the regions sequenced. The prefix "λ" denotes λ bacteriophage clones, and the prefix "p" denotes pUC19 subclones of λ phage DNA. E and H, *Eco*RI and *Hin*dIII restriction sites, respectively; "▼▼," equivocal assignment of an exon to either restriction fragment; "//," intron gap.

fragments: 6 MAOA$^+$ and 7 MAOB$^+$ clones that contained the most positive restriction fragments were further studied; their restriction maps for *Hin*dIII and *Eco*RI and the sequencing strategy are shown in Fig. 1. A clone containing the first exon of *MAOA* was not among the clones isolated by cDNA subfragments A8 or A8a (nucleotides 1–115) but rather by three consecutive walks from the most 5′ end of λ clone 35-A8b, which contains exon 2. The exon-containing restriction fragments (designated by the prefix "p" in Fig. 1) were subcloned into pUC19 vectors and mapped, and smaller

Table 1. Exon–intron organization of the human *MAOA* gene

Exon			Sequence of exon–intron junctions		
	Position	Size, kb	5′ boundary	Intron (gap shown in kb)	3′ boundary
1	1–146	146	ATT TCA G (146) Gly (25)	gtcagtgtgg... 23.....tttcctttag	GA CTA TCT Leu (26)
2	147–241	95	ACT ATA AGG (241) Arg (56)	gtaagtgatt...>2.0 .....tttgcag	AAT GAG CAT Asn (57)
3	242–379	138	TAT GTC AAG (379) Lys (102)	gtaaggatga...>3.8 ...tatgttctag	GGG AAA ACA Gly (103)
4	380–484	105	GGG AAG GAG (484) Glu (137)	gtaaatgtgt... 0.8 ...ttctctacag	ATT CCA ACT Ile (138)
5	485–576	92	TGG ACA AA (576) Lys (168)	g - ...>1.4 ...ctatgaacag	G ACT GCT Thr (169)
6	577–718	142	GGT GGC CAG (718) Gln (215)	- ...>2.8 ...cctcctgtag	GAA CGG AAG Glu (216)
7	719–868	150	CAT TAT GAG (868) Glu (265)	gtaactcagt... 0.2 ...tgtgttttag	TGC AAA TAC Cys (266)
8	869–1028	160	AAG AAG G (1028) Asp (319)	gtaggctgct... 0.75...cctggttaag	AT TAC TGT Tyr (320)
9	1029–1125	97	ATC ATG GG (1125) Gly (351)	gtaggttaga...>1.0 ...ctctctccag	C TTC ATT Phe (352)
10	1126–1179	54	GAA ATA AG (1179) Arg (369)	gtaagaattt...>0.9 ...tgttttatag	G AAG AAG Lys (370)
11	1180–1237	58	GCT TTA CAT (1237) His (388)	gtaagaaact... 0.6 ...tgaactgcag	CCA GTG CAT Pro (389)
12	1238–1335	98	TAT GGA AG (1335) Arg (421)	g - ... 1.6 ...tcccttgaag	G GTG ATT Val (422)
13	1336–1447	112	GCT AGG GAG (1447) Glu (458)	gtaagcagga... 0.4 ...tttctttcag	GTC TTA AAT Val (459)
14	1448–1510	63	GAA TCA AAG (1510) Lys (479)	gtaagtttgg... 0.4 ... -	GAC GTT CCA Asp (480)
15	1511–1958	≈440			

Nucleotide sequences of exons are shown in capital letters, whereas those of introns are in lowercase letters. The numbers following the nucleotides refer to the nucleotide positions in cDNA (6) where introns interrupt MAOA mRNA. The corresponding amino acids with their positions in parentheses are shown below the nucleotide sequences. See the text for details.

Table 2. Exon–intron organization of the human *MAOB* gene

Exon			Sequence of exon–intron junctions		
	Position	Size, kb	5′ boundary	Intron (gap shown in kb)	3′ boundary
1	1–123	123	ATC TCA G (123) Gly (16)	gttagtcgc... >15....ttctcccag	GT ATG GCA Met (17)
2	124–218	95	ACT CTT AGG (218) Arg (47)	gtaaggcat... 4.3....ggaaaacag	AAC CAA AAG Asn (48)
3	219–356	138	CAT GTA AAG (356) Lys (93)	gtaagatca...>1.0 ...atctcacag	GGC AAA TCA Gly (94)
4	357–461	105	GGG CGA GAG (461) Glu (128)	gtaaagctt...>0.4 ...tgaatgtag	ATT CCG AGT Ile (129)
5	462–553	92	TGG ACT GA (553) Glu (159)	gtaagtc..... 5.7....cctgtgcag	A TCT GCA Ser (160)
6	554–695	142	GGA GGA CAG (695) Gln (206)	gtacccatc... 1.0....tctttccag	GAG AGG AAA Glu (207)
7	696–845	150	ATG TAT GAG (845) Glu (256)	gtaactgtg... 1.7....ttctttcag	GCT AAA TAT Ala (257)
8	846–1005	160	AAG AAG G (1005) Asp (310)	gtgagtggg...>2.4 ...ttctctaag	AT TAC TGT Tyr (311)
9	1006–1102	97	ATA ATG GG (1102) Gly (342)	gtaaggcac... 1.6....attctttag	A TTT ATC Phe (343)
10	1103–1156	54	GAG GAA AG (1156) Arg (360)	gtacaaaag...>0.8 ...cattcacag	G TTG AAG Leu (361)
11	1157–1214	58	GCT CTG GAG (1214) Glu (379)	gtaaggctg...>2.0 ...atcttgcag	CCA GTG CAT Pro (380)
12	1215–1312	98	TAT GGA AG (1312) Arg (412)	gtagagtaa... 5.6....tgttccaag	G GTT CTA Val (413)
13	1313–1424	112	GCC CGA GAG (1424) Glu (449)	gtagggctc... 0.7....tcatttcag	ATC CTG CAT Ile (450)
14	1425–1487	63	GAG TCT GTG (1487) Val (470)	gtaggctat... 0.9....tgaacctag	GAT GTC CCT Asp (471)
15	1488–2498	1011			

See the legend to Table 1.

positive regions (≈1 kb) were subcloned into phage M13 and the DNA was sequenced. The exon boundaries were defined by alignment with cDNA sequences. Sequencing was performed either manually or by an Applied Biosystems model ABI 370a automated DNA sequencer by the dideoxy chain-termination method of Sanger *et al.* (26).

Southern Blot Analysis. Phage DNA isolated from 21 $MAOA^+$ clones, and 30 $MAOB^+$ clones were digested completely with *Hin*dIII and *Eco*RI and subjected to electrophoresis in 0.8% agarose gels. DNA fragments were then transferred to a nylon filter as described by Southern (27) and hybridized with appropriate ^{32}P-labeled MAOA or MAOB cDNA fragments.

Materials and Reagents. DNA-modifying enzymes were obtained from Boehringer Mannheim, and Southern blotting materials and nylon filters were from Bio-Rad.

RESULTS AND DISCUSSION

Alignment of the cDNA and the genomic sequences demonstrates that the coding regions of both the *MAOA* and *MAOB* genes are interrupted by 14 introns and possess identical exon–intron organization (Fig. 1 and Tables 1 and 2). The fact that all of the introns interrupt the coding sequences for MAOA and MAOB at exactly the same position (Tables 1 and 2) suggests that these two forms of MAO are derived from duplication of an ancestral gene. The structures of rat genes for aldolase isozyme B and human aldolase isozyme C also exhibit identical exon–intron organization (28). The exons of the *MAOA* and *MAOB* genes range in size from 54 to ≈440 base pairs (bp) and from 54 to ≈1000 bp, respectively. All intron donor and acceptor sites are consistent with the classical G-T/A-G splice junction rules (29) (Tables 1 and 2). Comparison of the sizes that we determined for introns 7, 12, 13, and 14 (Tables 1 and 2) shows no conservation between the two genes; however, both *MAOA* and *MAOB* possess a large first intron.

The genomic DNA sequences of all exons are identical to the cDNA sequences in the 5′ untranslated and coding regions for both *MAOA* and *MAOB*; however, 13 mismatches are found between genomic DNA and cDNA in the 3′ untranslated region in exon 15 of *MAOB*. The significance of this divergency is not clear at the present time; a similar observation was reported for the α-amylase gene of *Aspergillus oryzal* (30). Genomic DNA sequences upstream from the first ATG of *MAOA* match perfectly with our liver cDNA (9). Further, in this report we show that corresponding phage λ restriction maps (Fig. 1) and in some cases the sequences of several clones isolated from different libraries are identical. This result suggests that genes encoding only one species of MAOA and of MAOB are present on the X chromosome. The existence of more than two forms of MAO has been suggested because MAOs in some tissues do not have all of the characteristics of either *MAOA* or *MAOB* (4). Whether alternative splicing events are involved in the multiplicity of MAOA and MAOB can now be investigated.

The study of the relationship between gene structure and the three-dimensional structure of its protein product has just begun. Burke *et al.* (31) have shown that 17 of 19 amino acids encoded at exon–intron boundaries are located at the surface of human glycogen phosphorylase. When the splice site-encoded amino acids in MAOA (Table 1) are compared with those in MAOB (Table 2), 11 of 14 amino acids encoded at the 5′ boundary and 9 of 14 encoded at the 3′ boundary of the introns are identical. The amino acid changes between MAOA and MAOB, respectively, at the 5′ boundary are: lysine to glutamic acid (exon 5 product), histidine to glutamine (exon 11 product), and lysine to valine (exon 14 prod-

Table 3. Comparison of the peptide identity between products of *MAOA* and *MAOB* exons

	Amino acids in exon products				% identity of peptides				
	MAOA		MAOB		H MAOA*	H MAOA	H MAOA	H MAOB	
Exon	Position	No.	Position	No.	H MAOB*	B MAOA†	R MAOA‡	R MAOB§	Function
1	1–25	25	1–16	16	62.5	76.0	68.0	93.8	N-terminus and FAD binding domain
2	26–56	31	17–47	31	71.0	80.6	80.6	87.1	FAD binding domain
3	57–102	46	48–93	46	73.9	91.3	93.5	93.5	
4	103–137	35	94–128	35	77.1	97.1	91.4	85.7	
5	137–168	31	129–159	31	67.7	80.6	80.6	90.3	
6	169–215	47	160–206	47	76.6	93.6	93.6	95.7	
7	216–266	50	207–257	50	74.0	80.3	80.4	84.3	
8	267–319	54	258–310	54	69.8	94.3	90.6	86.8	
9	320–351	32	311–342	32	65.6	96.9	93.8	75.0	
10	352–369	18	343–360	18	66.7	88.9	88.9	94.4	
11	370–388	19	361–379	19	78.9	89.5	89.5	78.9	
12	389–421	33	380–412	33	93.9	97.0	100.0	97.0	FAD covalent binding site
13	422–458	37	413–449	37	89.2	94.6	94.6	89.2	
14	459–479	21	450–470	21	47.6	66.7	81.0	90.5	
15	480–527	48	471–520	50	62.5	79.2	76.6	84.0	C-terminus
				Total	72.6	87.9	87.4	88.3	

*H MAOA and H MAOB denote human MAOA and human MAOB, respectively.
†B MAOA denotes the amino acid sequence of bovine adrenal MAOA cDNA taken from Powell *et al.* (29).
‡R MAOA, §R MAOB denotes the amino acid sequences of rat liver MAOA and MAOB taken from T. Kuwaharaet (30) and Ito *et al.*, respectively (31).

uct). Those at the 3′ boundary are: leucine to methionine (exon 1 product), threonine to serine (exon 5 product), cysteine to alanine (exon 7 product), lysine to leucine (exon 10 product), and valine to isoleucine (exon 14 product). A change from cysteine to alanine may alter disulfide bridges, or a change from lysine to leucine, which contributes a charge difference, may confer different catalytic properties of MAOA and MAOB by influencing the conformations of the enzyme. Whether these differences contribute to the substrate and inhibitor specificities of these two forms of MAO awaits elucidation by mutagenesis studies.

The number of amino acids encoded by corresponding exons in *MAOA* and *MAOB* are identical except those encoded by exons 1 and 15. Nine more amino acids are encoded by exon 1 of *MAOA* than by exon 1 of *MAOB*, whereas two more amino acids are encoded by exon 15 of *MAOB* than by exon 15 of *MAOA* (Table 3).

Exons 1 and 2 of both *MAOA* and *MAOB* encode the AMP-binding site (amino acid residues 15–29 and 6–20 for MAOA and MAOB, respectively), which shares extensive sequence identity with several other flavoproteins, including lipoamide dehydrogenase, glutathione reductase, thioredoxin reductase, D-amino acid oxidase, *p*-hydroxybenzoate hydroxylase, and lactic dehydrogenase (9). This region may be involved in FAD noncovalent binding, which may be important for MAO catalytic activity. Exon 12 in both *MAOA* and *MAOB* codes for 33 amino acids including the pentapeptide Ser-Gly-Gly-Cys-Tyr through which the cofactor FAD is covalently bound to cysteine (32, 33). This is the most conserved exon between human *MAOA* and *MAOB*, and the products share 93.9% amino acid identity, suggesting that the peptide encoded by this exon is important for the interaction with FAD. The product of exon 14 has the lowest amino acid identity (47.6%) between MAOA and MAOB. Whether these divergent regions encode the distinctive characteristics of each form of MAO remains to be studied.

The hydropathy plots of MAOA and MAOB show seven hydrophobic regions, but when the requirement of α-helix structure is taken into consideration, only two possible transmembrane domains (residues 7–30 and 491 to the C terminus) were revealed (9). Both of these regions contain uninterrupted uncharged residues flanked by a few basic amino acids, which might be important for targeting and anchoring of the protein (34). These two domains are encoded by exons 1 and 15, respectively, of *MAOA* and *MAOB* and share 62.5% peptide identity between the two MAO forms (Table 1). It is tempting to speculate that these divergent sequences may alter the anchoring to the outer mitochondrial membrane, thus conferring substrate and/or inhibitor specificities of MAOA and MAOB.

Human liver MAOA (9, 11) and MAOB cDNAs (9), bovine adrenal MAOA cDNA (35), and rat liver MAOA (36) and MAOB cDNAs (37) have been cloned thus far. Table 3 shows the comparison of the peptide sequences encoded by each exon between human (9) and bovine MAOA (35), between human and rat MAOA (36), and between human and rat MAOB (37). The amino acid sequences of human and bovine MAOA and of human and rat MAOA are highly conserved (overall 87.9% and 87.4% identity, respectively). The amino acid sequences of human and rat MAOB are also highly conserved (overall 88.3% identity). The strong conservation of the amino acid sequence of each form of MAO among mammalian species may reflect evolutionary pressure to maintain the specific physiological function of each MAO. The most remarkable conservation is seen in the product of exon 12, which contains the FAD covalent binding domain. The peptide identities are 97%, 100%, and 97% between human and bovine MAOA, human and rat MAOA, and human and rat MAOB, respectively. This finding suggests selective evolutionary conservation of a particular exon encoding a functional domain.

In summary, both MAOA and MAOB are encoded by 15 exons exhibiting identical exon–intron organization. These results (*i*) suggest that *MAOA* and *MAOB* are derived from the same ancestral gene and (*ii*) provide further insights on the structural–functional relationship of these important isoenzymes.

We thank Minnie McMillan, Ph.D., and Steve Chamberlain at the University of Southern California Cancer Center Microchemical Core Laboratory for assistance in DNA sequencing. This work was supported by Grants R37 MH39085 (merit award), Research Scientist Award KO5 MH00796, and RO1 MH 37020 from the National

Institutes of Mental Health. The support from the Boyd and Elsie Welin Professorship is also greatly appreciated.

1. Greenawalt, J. W. & Schnaitman, C. (1970) *J. Cell Biol.* **46,** 173–179.
2. Knoll, J. & Magyar, K. (1972) *Adv. Biochem. Psychopharmacol.* **5,** 393–408.
3. Johnston, J. P. (1968) *Biochem. Pharmacol.* **17,** 1285–1297.
4. Fowler, C. J., Callingham, B. H., Mantle, T. J. & Tipton, K. F. (1978) *Biochem. Pharmacol.* **27,** 97–101.
5. Westlund, K. N., Denney, R. M., Kochersperger, L. M., Rose, R. M. & Abell, C. W. (1985) *Science* **230,** 181–183.
6. Denney, R. M., Fritz, P. R., Patel, N. T. & Abell, C. W. (1982) *Science* **215,** 1400–1403.
7. Chen, S., Shih, J. C. & Xu, Q.-P. (1984) *J. Neurochem.* **43,** 1680–1687.
8. Chen, S., Shih, J. C. & Xu, Q.-P. (1985) *Biochem. Pharmacol.* **34,** 781–788.
9. Bach, A. W. J., Lan, N. C., Johnson, D. L., Abell, C. W., Bembenek, M. E., Kwan, S.-W., Seeburg, P. H. & Shih, J. C. (1988) *Proc. Natl. Acad. Sci. USA* **85,** 4934–4938.
10. Shih, J. C. & Lan, N. C. (1990) *Neurol. Neurobiol.* **57,** 147–155.
11. Hsu, Y.-P. P., Weyler, W., Chen, S., Sims, K. B., Rinehart, W. B., Utterback, M., Powell, J. F. & Breakefield, X. O. (1988) *J. Neurochem.* **51,** 1321–1324.
12. Youdim, M. B. H., Banerjee, D. K., Kelner, K., Offutt, L. & Pollard, H. B. (1989) *FASEB J.* **3,** 1753–1759.
13. Chiba, K., Trevor, A. & Castagnoli, N., Jr. (1984) *Biochem. Biophys. Res. Commun.* **120,** 574–578.
14. Lan, N. C., Chen, C. & Shih, J. C. (1989) *J. Neurochem.* **52,** 1652–1654.
15. Grimsby, J., Lan, N. C., Neve, R., Chen, K. & Shih, J. C. (1990) *J. Neurochem.* **55,** 1166–1169.
16. Egashira, T. (1976) *Nippon Yakurigaku Zasshi* **26,** 493–500.
17. Lewinsohn, R., Glover, W. & Sandler, M. (1980) *Biochem. Pharmacol.* **29,** 1221–1230.
18. Lan, N. C., Heinzmann, C., Gal, A., Klisak, I., Orth, U., Lai, E., Grimsby, J., Sparkes, R. S., Mohandas, T. & Shih, J. C. (1989) *Genomics* **4,** 552–559.
19. White, K., Shih, J. C., Fong, T. L., Young, H., Gelfand, R. & Boyd, J. (1980) *Am. J. Psychiatry* **37,** 1258–1259.
20. Sullivan, J. L., Cavenar, J. O., Jr., Maltbie, A. A., Lister, P. & Zung, W. W. K. (1979) *Biol. Psychiatry* **14,** 385–394.
21. Wyatt, R. J. & Murphy, D. L. (1976) *Schizo. Bull.* **2,** 77–89.
22. Oreland, L., Arai, Y. & Stenstrom, A. (1984) in *Monoamine Oxidase and Disease*, eds. Tipton, K. F., Dostert, P. & Strolin-Benedetti, M. (Academic, London), pp. 291–295.
23. Murphy, D. L., Garrick, N. A., Abibakh, C. S. & Cohen, R. M. (1984) *J. Clin. Psychiatry* **45,** 37–43.
24. Maniatis, T., Fritsch, E. F. & Sambrook, J. (1989) in *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Lab., Cold Spring Harbor, NY).
25. Feinberg, A. P. & Volgelstein, B. (1983) *Anal. Biochem.* **132,** 6–13.
26. Sanger, F., Nicklen, S. & Coulson, A. R. (1977) *Proc. Natl. Acad. Sci. USA* **74,** 5463–5467.
27. Southern, E. M. (1975) *J. Mol. Biol.* **98,** 503–517.
28. Rottmann, W. H., Deselms, K. R., Nicolas, J., Camerato, T., Holman, P. S., Green, C. J. & Tolan, D. R. (1987) *Biochimie* **69,** 137–145.
29. Brethnach, R. & Chambon, P. (1981) *Annu. Rev. Biochem.* **50,** 349–383.
30. Wirsel, S., Lachmund, A., Wildhardt, G. & Ruttkowski, E. (1989) *Mol. Microbiol.* **3,** 3–14.
31. Burke, J., Hwang, P., Anderson, L., Lebo, R., Gorin, F. & Fletterick, R. (1987) *Proteins: Struct. Funct. Genet.* **2,** 177–187.
32. Kearney, E. B., Salach, J. I., Walker, W. H., Seng, R. L., Kenney, W., Zeszotek, E. & Singer, T. D. (1971) *Eur. J. Biochem.* **24,** 321–327.
33. Yu, P. H. (1981) *Can. J. Biochem.* **59,** 30–37.
34. Hase, Y. T., Muller, U., Riezman, H. & Schatz, G. (1984) *EMBO J.* **3,** 3157–3164.
35. Powell, J. F., Hsu, Y.-P. P., Weyler, W., Chen, S., Salach, J., Andrikopoulos, K., Mallet, J. & Breakefield, X. O. (1989) *Biochem. J.* **259,** 407–413.
36. Kuwahara, T., Takamoto, S. & Ito, A. (1990) *Agric. Biol. Chem.* **54,** 253–257.
37. Ito, A., Kuwahara, T., Inadome, S. & Sagara, Y. (1988) *Biochem. Biophys. Res. Commun.* **157,** 970–976.