Inherited Levels of A and B Types of Monoamine Oxidase Activity

by Xandra O. Breakefield and Susan B. Edelstein

Abstract

In establishing the role of inherited variations in levels of monoamine oxidase (MAO) activity in neuropsychiatric diseases, it is important to measure levels of both A and B types of activity as they appear to be under separate genetic control. Levels of A and B types of activity can be evaluated in fibroblasts and platelets, respectively. A number of genes could be involved in determining levels of activity, including those coding for the catalytic and noncatalytic subunits of the enzyme, as well as those coding for enzymes involved in covalent attachment of the flavin cofactor, other processing steps, degradation of MAO, and lipid metabolism. Different genes may be critical in controlling activity levels in various cell types depending on differential expression of the genome. In order to establish the molecular basis of variation in activity, techniques should be employed to assess the structure and conformation of the enzyme, as well as the number of enzyme molecules and their interaction with other cellular components. Only by understanding the genetic and environmental factors controlling levels of A and B types of MAO activity can we hope to evaluate and manipulate the role of MAO in human neurophysiology.

Inherited variations in enzymes involved in neurotransmitter metabolism can be assumed to modulate human behavior and disease. The measurement of these enzymes in blood from neuropsychiatric patients and controls has served as the prototype for the investigation of such modulation (Gershon et al., in press). Many investigators have focused their attention on monoamine oxidase (MAO) since this enzyme is primarily responsible for the degradative deamination of biogenic amines and can regulate concentrations of these neurotransmitters in vivo (Murphy, Belmaker, and Wyatt 1974; Sullivan, Stanfield, and Dackis 1977; Wyatt and Murphy 1976). In these studies levels of the B type of MAO have been measured in platelets. The other type of MAO activity, type A, can be measured in cultured skin fibroblasts and may be under separate genetic control from the B type of activity (Breakefield et al. 1979; Groshong, Gibson, and Baldessarini 1977; Roth, Breakefield, and Castiglione 1976). In order to assess an individual's capacity to degrade neurologically active amines, it is important to measure both A and B types of activity and to understand the molecular mechanisms that control the levels of these activities.

There are several similarities as well as differences between the A and B forms of MAO. Both are located in the outer mitochondrial membrane and require phospholipids, iron, and a covalently bound flavin cofactor for activity (Houslay, Tipton, and Youdim 1976; Murphy 1978; Youdim 1976). The active enzyme appears to be a dimer consisting of one catalytic polypeptide containing covalently bound flavin and one noncatalytic polypeptide, both of similar molecular weight (Minamiura and Yasunobu 1978; Oreland, Kinemuchi, and Stigbrand 1973; Salach 1979). The two forms of MAO deaminate a number of common amine substrates (albeit with different affinities) and are inhibited by the same drugs (albeit to varying

degrees) (Houslay, Tipton, and Youdim 1976; Murphy 1978).

It has been difficult to distinguish the two forms of MAO on the basis of physicochemical properties. However, recent studies have shown that the catalytic polypeptides of MAO A and B from rat tissues differ in apparent molecular weight with estimates of 62,000 and 59,000, respectively (Callingham and Parkinson 1979; Cawthon and Breakefield 1979). In addition, the technique of limited proteolysis and peptide mapping (Cleveland et al. 1977) has revealed that although the internal structure of the catalytic polypeptides associated with A and B types of activity are very similar, they do differ at discrete sites (Cawthon and Breakefield 1979). Such structural differences could result if the two catalytic polypeptides were encoded in separate structural gene loci which arose from a common precursor gene that underwent duplication and divergence during evolution. In this case, the A and B forms of MAO would be considered "isozymes" by the current definition (Hoffmann-Ostenhof 1978). Alternatively, the structural differences could result from differential posttranslational modification of a common catalytic polypeptide encoded in a single structural gene.

Several studies have shown that levels of type B activity in platelets are largely under genetic control (Gershon et al., in press; Nies et al. 1973; Winter et al. 1978; Wyatt, Belmaker, and Murphy 1975). Statistical analyses of levels of activity among family members indicate that the pattern of inheritance cannot be reduced to the dominant or recessive expression of a product of a single gene locus (Gershon et al., in press; Wyatt, Belmaker, and Murphy 1975). Rather, these studies suggest that

more than one gene and/or environmental factors determine levels of MAO activity. Studies of type A MAO in cultured skin fibroblasts also suggest that levels of activity can be regulated by environmental and genetic factors, as well as epigenetic factors which control the differential expression of genes in different cell types. Variations in the culture conditions (i.e., environment) such as type of medium and serum, frequency of feeding, and degree of confluency can markedly affect levels of MAO activity (Edelstein, Castiglione, and Breakefield 1978). When culture conditions are controlled, the activity for a given line remains constant from subculture to subculture. Under these conditions a wide range (>50-fold) of activities was observed in lines from control individuals (Costa et al., in press; Edelstein, Castiglione, and Breakefield 1978). Further, levels of activity in fibroblasts from three sets of monozygotic twins were found to be highly concordant suggesting genetic determination of activity (X.O. Breakefield et al., unpublished data). However, a positive correlation between the age of the donors at the time of biopsy and the levels of MAO activity was noted, suggesting a role for epigenetic control as well. This phenomenon may result from the presence of two types of fibroblasts, papillary and reticular, in cultures established from skin biopsies (Harper and Grove 1979). The proportion of each cell type in a given line can vary with the age of donor (Harper and McNicol 1977), the site of biopsy (Castor, Prince, and Dorstewitz 1962), and the initial culture conditions (Harley and Goldstein 1978). Pure papillary and reticular cultures from a female control individual (kindly provided by Dr. Robert Harper) were found to differ 7- to 10-fold in their levels of

MAO A activity. Since these two cultures were essentially identical in genetic composition and were grown under parallel conditions of culture, the difference in MAO A activity must reflect variation in the intracellular environment. Such variation could result from cell-specific differences in gene expression. Further evidence for epigenetic control of MAO is the 3- to 10-fold rise in activity as lines approach senescence in culture (Edelstein, Castiglione, and Breakefield 1978).

There is no correlation between levels of MAO B activity measured in platelets and MAO A activity measured in fibroblasts from the same individual (E. Giller et al., unpublished data; Groshong, Gibson, and Baldessarini 1977). Bond and Cundall (1977) found a highly significant correlation between levels of MAO B activity in platelets and lymphocytes from the same individual. However, a correlation remains to be demonstrated between levels of the same type of MAO activity in other cell types. Given the clear demonstration of an inherited basis for activity levels, some correlation would be expected. Thus, for a given individual, measurement of activity levels in peripheral cell types should reflect relative activity levels in vivo.

Many genes could be involved in determining levels of MAO activity in different cell types (figure 1), including:

1. Genes which code for the catalytic (C) and noncatalytic (N) subunits of MAO.

2. Genes (P) which code for enzymes involved in the processing of MAO (e.g., covalent attachment of the flavin cofactor to the catalytic polypeptide; Martinez and McCauley 1977), and other putative steps such as glycosylation (Tipton and Della

Figure 1. Gene loci controlling type and level of MAO activity

Genes: C_1 N_1 (C_2 N_2) P'' L'' D'' R''

Structural loci for MAO A and B:

$C_{1,2}$—catalytic polypeptide(s)

$N_{1,2}$—noncatalytic polypeptide(s)

Modulating loci for enzymes and factors involved in:

P — processing
L — lipid metabolism
D — degradation
R — regulation

Corte 1979) and proteolytic cleavage of a precursor polypeptide during transport from the cytosol to the outer mitochondrial membrane (e.g., analogous to other mitochondrial enzymes; Maccecchini et al. 1979; Raymond and Shore 1979).

3. Genes (L) which code for enzymes involved in lipid metabolism since lipids surrounding MAO in the mitochondrial membrane can affect activity (Ekstedt and Oreland 1975; Kandaswami and D'Iorio 1979; Olivecrona and Oreland 1971; Sawyer and Greenawalt 1979).

4. Genes (D) which code for enzymes involved in the degradation of MAO as the rate of degradation can control steady state amounts of the enzyme.

5. Other regulatory genes (R) involved directly or indirectly in determining the rates of transcription and translation of MAO and other related gene products (e.g., activators, inhibitors, cofactors, metal ions).

Theoretically, allelic variation at any of these gene loci could affect levels of MAO activity, although some loci are probably more critical than others.

Because of the large number of ways in which MAO activity can be regulated, it is important to examine other properties of the enzyme in order to understand the molecular basis of variation in activity. Differences in levels of enzyme activity could result from altered conformation of the enzyme, lower concentration of active enzyme molecules, the presence of inhibiting or the absence of activating factors, and/or reduced availability of cofactor(s) and metal ion(s). Such phenomena may be explained by several biochemical mechanisms, and various experimental approaches are available to analyze these mechanisms. For example, a difference in the structure or conformation of the enzyme could result from changes in the amino acid sequence of the catalytic or noncatalytic polypeptides, in processing of these molecules or in the microenvironment of the enzyme. Such alterations in the enzyme could be revealed by accompanying changes in a number of properties:

1. Differences at the active site of the enzyme could modify the kinetics of the catalytic reaction and could be revealed by determining the apparent substrate affinity (K_m, concentration of substrate resulting in half maximal activity) for several substrates. For example, Berrettini, Vogel, and Clouse (1977) have described the existence of two forms of MAO B in platelets which differ in their affinity for tryptamine.

2. Structural differences could also modify the susceptibility of MAO to degradation and could change its susceptibility to heat denaturation or proteolysis *in vitro*. Recently T.P. Bridge et al. (unpublished data) have discovered a temperature sensitive form of platelet MAO which appears to be inherited and is associated with low activity.

3. Structural variations, furthermore, could affect the molecular weight and/or ionic charge of MAO. Such changes in the catalytic polypeptides of MAO A and B can be resolved by labeling them with the irreversible inhibitor ^{3}H-pargyline and carrying out electrophoresis under solubilizing and denaturing conditions in sodium dodecyl sulfate polyacrylamide gels or nonequilibrium pH gradient gels (Costa and Breakefield 1979, in press; Edwards and Pak 1979; McCauley 1976; Pintar et al. 1979). Autoradiograms of these gels are shown in figure 2 for platelet MAO from six control individuals. Intact MAO molecules can be analyzed by other methods such as gel filtration and isoelectric focusing when sufficient amounts of material are available (White and Glassman 1977).

4. Some structural differences do not result in changes in molecular weight or ionic charge of the enzyme. In such cases, internal differences could be revealed by limited proteolysis and peptide mapping (Cleveland et al. 1977). For example, the catalytic polypeptides of MAO labeled with ^{3}H-pargyline can be isolated from preparative sodium dodecyl sulfate polyacrylamide gels and exposed to site-specific proteases. The resulting labeled peptide fragments can then be separated on the basis of molecular weight, resulting in a reproducible pattern which reflects the

Figure 2. Autoradiograms of ^{3}H-pargyline-labeled MAO from control platelets separated by two types of polyacrylamide gel electrophoresis
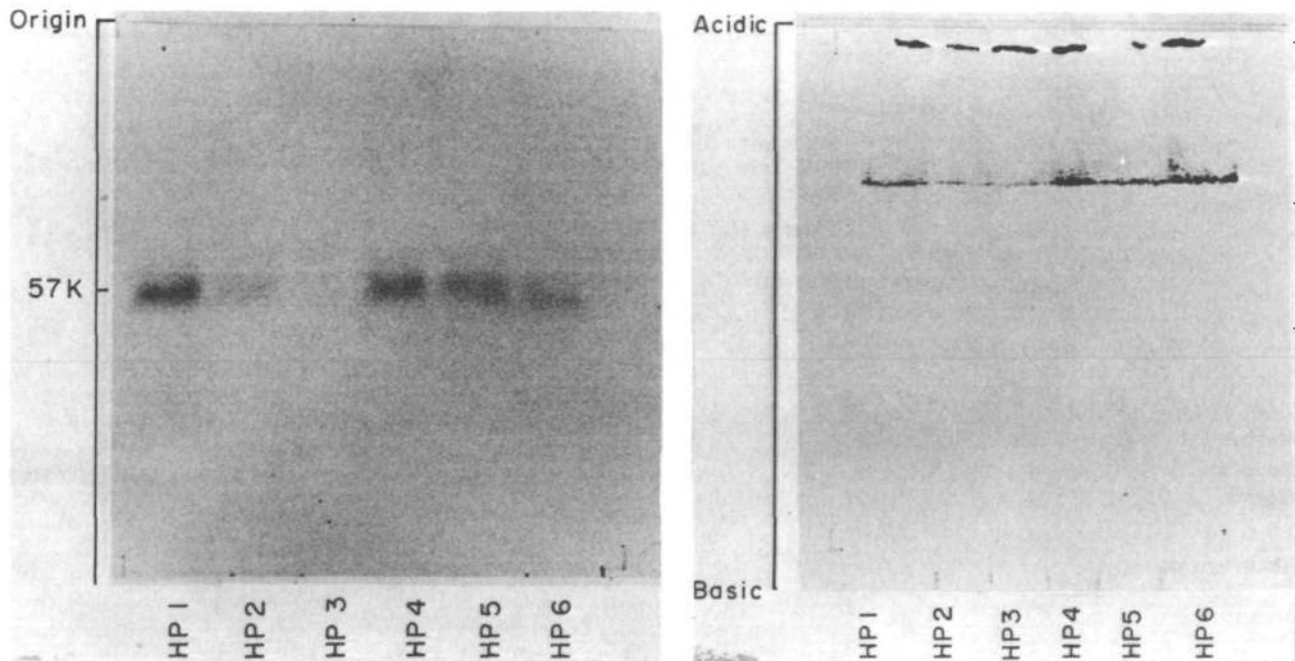
Particulate platelet fractions were prepared from peripheral venous blood of six control donors by differential centrifugation and sonication. These fractions were incubated with 0.6 μM ^{3}H-pargyline (New England Nuclear), then washed by centrifugation and solubilized prior to sodium dodecyl sulfate polyacrylamide gel electrophoresis (left panel) or nonequilibrium pH gradient gel electrophoresis (right panel). Gels were treated for fluorography, dried and exposed to pre-flashed X-omatic R film for 14 days at $-70°C$. These techniques are described in Costa and Breakefield (1979, in press).
Note: In right panel, band at top (acidic) represents unsolubilized MAO.

number, position, and availability of specific cleavage sites (Cawthon and Breakefield 1979).

In addition to structural alterations, variations in the level of activity also could be due to changes in the rate of synthesis and/or degradation of the enzyme. The number of active enzyme molecules can be determined using inhibitors which bind stoichiometrically at the catalytic site. Type B MAO can be titrated with the irreversible inhibitors ^{3}H-pargyline and ^{14}C-deprenyl (Chuang, Patek, and Hellerman 1974; Salach, Detmer, and Youdim 1979; Youdim and Salach 1978). Similarly, type A MAO can be titrated using either the ir-

reversible inhibitor ^{14}C-clorgyline (Salach, Detmer, and Youdim 1979; Youdim and Salach 1978) or the reversible inhibitor ^{3}H-harmaline (Nelson et al. 1979). Unlabeled irreversible inhibitors also can be used to measure the number of enzyme molecules by establishing the exact amount of inhibitor necessary to completely block enzyme activity (Egashira et al. 1976; Oreland and Ekstedt 1972). Alternatively, specific antibodies to MAO could be used to titrate the number of enzyme molecules (Dennick and Mayer 1977; Hartman, Yasunobu, and Udenfriend 1971). Unlike inhibitors, antibodies can interact with precursor

molecules and/or noncatalytic subunits as well as catalytic subunits.

Finally, levels of enzyme activity may be modulated by indirect mechanisms. Alterations in the intracellular concentration of activators, inhibitors, cofactors, and/or metal ions could influence activity. The presence of such components might be revealed by a number of methods including mixing experiments, dialysis, fractionation, or addition of specific chelators (Berrettini and Vogel 1978; Murphy et al. 1976; Youdim 1976). Differences in the lipid microenvironment of the enzyme can also affect activity (Ekstedt and Oreland 1975; Kandaswami and

D'Iorio 1979; Olivecrona and Oreland 1971; Sawyer and Greenawalt 1979). Analysis of lipid composition is difficult to perform, but studies of the structure and conformation of MAO should reveal differences in the microenvironment.

Clearly, levels of MAO activity are determined by genetic, epigenetic, and environmental factors. If an inherited alteration of MAO is hypothesized to have an etiologic role in neuropsychiatric disease, it is important to establish the molecular nature of this alteration. Only by a thorough understanding of the factors controlling MAO activity can we unravel the primary or secondary role of MAO in neuropsychiatric diseases.

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Community Support Systems

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