Some Current Matters of Monoamine Oxidase Biochemistry

by Theodore L. Sourkes

Abstract

Some problems in the basic biochemistry of monoamine oxidase (MAO) and the regulation of its concentration in tissues are considered. The substrate preferences of muscle MAO do not conform to the current distinction between A and B forms of the enzyme. Examples of this are given for skeletal and cardiac muscle. Although the enzyme concentration is low in this tissue, its relatively great mass suggests that it has a role to play in monoamine metabolism. The significance of riboflavin and iron for MAO activity is discussed.

For those of us in the neurosciences, discussion of the function of monoamine oxidase (MAO) centers first of all around its role in brain and nerve—indeed, in specific regions of the brain. Clinicians have a more specific and practical interest in the effects of inhibition of MAO as an initial step in the amelioration of mental depression by treatment with certain drugs. Diagnosticians want to know whether platelet MAO concentration is a predictor of schizophrenia or affective psychosis: whether MAO is a variable that depends upon one of those states, or a nonconcomitant parameter lacking a significant commonality of causes with the psychoses.

For the metabolic specialist, the intestinal mucosa and the liver have been of great concern because of their role in inactivation (detoxification) of the biogenic monoamines. Recent new data suggest that muscle also makes an important contribution in this regard. Many years ago Spinks and Burn (1952) found that hyperthyroid animals had significantly reduced levels of MAO in the liver, whereas hypothyroid animals tended to have a small increase. Over the years this has been confirmed, although conditioning factors of age and sex may play a role in determining the response of hypothyroid rats (Sourkes 1979). We found, like others before us, that rats made hyperthyroid by administration of thyroxine (T₄) have a decrease in liver MAO activity. Others rendered hypothyroid by extirpation of the adrenal gland have a slight, but not significant, increase in hepatic MAO activity.

For some years we have been using a physiological test in conjunction with determination of MAO in various organs. We follow the conversion of intraperitoneally administered ¹⁴C-pentylamine to ¹⁴CO₂ in the rat, a process that seems to depend upon the activity of MAO in vivo. Almost all our studies have indicated that this test is measuring the same property as when we determine MAO in tissues of animals (Sourkes 1972; Sourkes and Missala 1976, 1977; Symes, Missala, and Sourkes 1971). However, we have found one important exception in the particular case of the hypothyroid animal given replacement treatment. When thyroidectomized rats are injected with 20 µg of T₄ per kilogram body weight daily, they become euthyroid within 13 days. Interestingly enough, their liver MAO activity declines in that period to 75 percent that of the controls, i.e., as though the hormone administration had rendered them hyperthyroid.

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Thus, we end up with rats that have normal levels of circulating thyroid hormone but a depressed concentration of hepatic MAO (Sourkes et al. 1977).

We might expect the overall metabolism of monoamines to suffer under the above condition, but in fact, the rate of oxidation of pentylamine in vivo increases progressively with the Ti treatment from the subnormal values observed in hypothyroidism to control values in about 2 weeks, i.e., at the time the animals have attained the euthyroid state. Thus, despite the low hepatic MAO activity, there can be a normal rate of oxidation of a classical MAO substrate.

This discrepancy led us to investigate the activity of MAO in skeletal muscle. This tissue, little studied in the past, has now begun to receive attention, notably through studies in biological psychiatry initiated by Meltzer (Arora and Meltzer 1977; Meltzer, Jackman, and Arora 1980, this issue). The low MAO activity, which has been recognized for many years, must be thought of as acting in a tissue that represents about half the mass of the adult animal body. Thus, the contradiction described above is only apparent, being readily resolved by recognizing the role of muscle MAO. In contrast to hepatic MAO, muscle MAO increases in the hyperthyroid state and decreases in the hypothyroid state (Sourkes et al. 1977). This greater activity of muscle MAO could explain the fact that the aliphatic monoamine we have studied is oxidized at an increased rate in the hyperthyroid rat.

To summarize this point, muscle MAO, by reason of its large, but distributed mass, may play a significant role in the termination of activity of circulating monoamines.

The second matter that I wish to discuss is the question of types of MAO. Edwards (1980, this issue) and Domino (1980, this issue) have both presented evidence for the concept of two types of MAO, A and B, defined in relation to the inhibitory activities of clorgyline and deprenyl. There is a tendency on the part of some to reify the differential inhibitory potencies of these two drugs into two isoenzymes. Although two such enzymes may exist, it is well to remember that at the present time they do so only on the basis of an operational definition deriving from kinetic experiments. The inherent uncertainties of this pragmatic situation will persist until two physical entities, differing in their action on monoamines in some significant respects, have been separated from one another. Edwards (1980, this issue) has pointed out how difficult it has been thus far to establish different electrophoretic mobilities for the postulated two enzymes.

Our recognition of the small but significant activity of MAO in skeletal muscle led us to investigate the substrate specificity of this enzyme in mitochondrial preparations. Our definition of the presence of the A type of MAO has been "susceptibility to inhibition by 10^{-6}M clorgyline to the extent of 80% or more" (Kwatra and Sourkes 1979). On this basis, rat skeletal muscle contains both A and B forms (serotonin, tryptamine, and kynuramine readily inhibited by clorgyline; benzylamine only partially blocked). Phenylethylamine (studied in the presence of semicarbazide as in the case of benzylamine) is different from the other substrates. The oxidation of low concentrations (5 x 10^{-6}M) is not sensitive to clorgyline, but the oxidation of high concentrations (10^{-5}M) is sensitive to this inhibitor. Hence, phenylethylamine is a B type substrate at low concentrations and an A type at high. In the case of heart muscle preparations, high concentrations of phenylethylamine are treated like an A substrate; low concentrations would be characterized as oxidation by MAO-A and B, mixed (Kwatra and Sourkes 1979).

To summarize this part, our examination of the properties of muscle MAO in regard to substrates indicates that at least for phenylethylamine, the type of MAO action is concentration-dependent.

The last matter I wish to take up is the question of cofactors of MAO. The initial purification of mitochondrial MAO (Youdim and Sourkes 1966, 1972) revealed the presence of iron and riboflavin. The role of the vitamin had been long suspected because of the decrease of MAO activity in the liver of animals that had been made riboflavin-deficient (Hawkins 1952; Wiseman and Sourkes 1961; Wiseman-Distler and Sourkes 1963). Iron has since been found in the pig mitochondrial enzyme (Oreland 1971) and most recently in beef mitochondrial MAO (Salach 1979). In following up our finding of the presence of iron in purified MAO, we investigated the effect of iron deficiency in rats and found that there was a decrease of MAO activity in the liver of anemic rats (Sourkes 1972; Symes et al. 1969). The effect of the deficiency is even more pronounced when our physiological test with pentyamine is applied (Symes, Missala, and Sourkes 1971). Later on, it was found that the platelet MAO of patients with simple hypochromic iron-deficiency anemia is low in MAO activity, and this activity is restored toward normal as the patients are successfully treated with iron preparations (Youdim, Wood, and Mitchell 1975). The failure of Heinze et al.


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