Evidence for Specific Monoamine Oxidases in Human Sympathetic Nerve and Pineal Gland (36506)

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(Introduced by E. Costa)

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Multiple forms of monoamine oxidase [MAO; monoamine:O_2 oxidoreductase (deaminating); EC1.4.3.4] are present in man and animals that can be inhibited differentially by the drug clorgyline [*N*-methyl *N*-propargyl-3-(2,4-dichlorophenoxy) propylamine hydrochloride] (1–3). Johnston (1) has designated the clorgyline-sensitive enzyme as enzyme A and the clorgyine-resistant enzyme as enzyme B. The therapeutic effectiveness of MAO inhibitor drugs is often ascribed to their ability to alter the metabolism of the transmitter amines. There is now compelling evidence that a specific form of MAO, enzyme A, is associated with the sympathetic nerves in several species (3, 4). In the rat, enzymes A and B can be readily identified because enzyme A predominates in the superior cervical ganglion whereas enzyme B predominates in the pineal gland (4). The identification of the form of enzyme associated with human sympathetic nerves may lead to the development of more effective and less toxic drugs. We therefore studied the MAO of lumbar sympathetic trunk and pineal gland of man.

Materials and Methods. Lumbar sympathetic trunk and pineal were obtained 24–48 hr after death from five male subjects that varied in age from 47 to 87 years. The sympathetic trunk contained 6–10 ganglia. Both tissues were frozen at —20° until assayed for MAO activity. The experimental design and the MAO assay procedure have been described previously (1, 4, 5). In brief, tissues were homogenized (1:15) in 67 m*M* phosphate buffer (pH 7.2) and 30 μl portions of a 700 g supernatant were preincubated at 22° with increasing concentrations of clorgyline (May and Baker, Ltd., London, England) in a total volume of 70 μl. After 15 min, 100 μl tyramine [1-^{14}C] (New England Nuclear, Boston, MA), about 6×10^5 dpm, were added resulting in a final concentration of 2.1 m*M*. After 30 min of incubation the reaction was stopped by adding 60% (w/v) perchloric acid and the tyramine metabolites were separated from tyramine by cation exchange chromatography. Protein was determined by the method of Lowry *et al.* (6).

Results. Figure 1 illustrates that about a thousand times more clorgyline was required to inhibit the MAO activity of pineal gland by half than to inhibit the MAO of sympathetic trunk. Apparently in man the clorgyline-sensitive enzyme A is also associated with sympathetic nerves while the clorgyline-resistant enzyme B is associated with pineal gland. The MAO activity of sympathetic

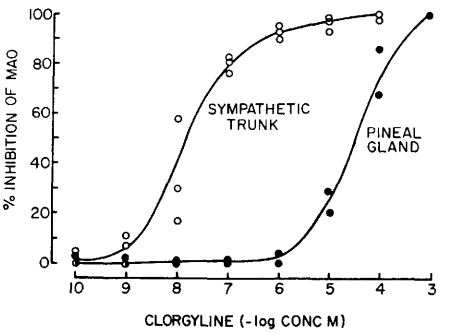

FIG. 1. Inhibition of tyramine metabolism by increasing concentrations of clorgyline in homogenates from human pineal and sympathetic trunk.

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TABLE I. Monoamine Oxidase Activity of Human Sympathetic Trunk and Pineal Gland.[a]

Tissue	Tyramine metabolized nmoles/mg protein/hr; mean ± SEM (5)
Sympathetic trunk	66 ± 26
Pineal gland	185 ± 26

[a] See text for experimental details.

trunk and pineal gland is shown in Table I.

Discussion. Enzymes A and B have different characteristics in the rat (7). Enzyme A has a high affinity for clorgyline, a lower apparent K_m for tyramine than enzyme B, is readily inactivated by trypsin digestion and is relatively heat stable. Enzyme A metabolizes the transmitter amines, norepinephrine and serotonin. In contrast, enzyme B is relatively insensitive to clorgyline, is not readily inactivated by trypsin digestion, is heat labile and probably plays only a minor role in the metabolism of the transmitter amines. The differential inhibition of MAO by clorgyline is not an artifact that occurs when tissues are homogenized, nor does it appear to be related to the diffusion of molecules through membranes to the active site of the enzyme. Enzymes A and B are probably related to the multiple forms of MAO identified by polyacrylamide gel (8–10), cellulose polyacetate (11), and density gradient column electrophoresis (12) techniques from different tissues of various species.

MAO catalyzes the oxidative deamination of norepinephrine, epinephrine dopamine, and serotonin in addition to a variety of other amines. Abnormal metabolism of the transmitter amines is associated with affective disorders and some neurological and cardiovascular diseases. MAO inhibitor drugs are often used to treat these disorders. The drugs that are used clinically are apparently not selective and therefore they probably inhibit all forms of MAO in all tissues. Following treatment with these drugs, liver which has both forms of MAO (1) can no longer metabolize ingested tyramine and as a consequence circulating tyramine can release norepinephrine from sympathetic nerves resulting in a severe hypertensive reaction (13). Our observations imply that drugs that preferentially inhibit enzyme A, the form of MAO associated with sympathetic nerves, would be more specific and less toxic than the drugs that are used currently because ingested amines might still be metabolized by enzyme B. The observation that enzyme A is associated with sympathetic nerves is consistent with the view that MAO in the nerves plays an important role in the metabolism of the norepinephrine that is destroyed intraneuronally (14).

Summary. A thousand times more clorgyline was required to inhibit the monoamine oxidase activity of human pineal gland than to inhibit the monoamine oxidase activity of sympathetic nerves. This observation is consistent with studies in other species, and it suggests that different forms of monoamine oxidase may be associated with specific cell types in man.

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