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L. MONOAMINE OXIDASE INHIBITORS

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Numerous substances belonging to a great variety of chemical classes interfere with monoamine oxidase (MAO) *in vitro* and in part also *in vivo* (34, 35). This review deals only with compounds causing strong and long-lasting inhibition of the enzyme *in vivo*.

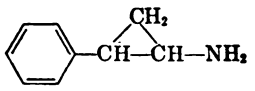
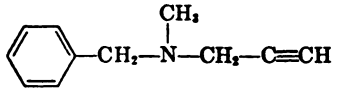
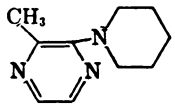
CHEMISTRY AND ACTION ON MAO

Since the introduction of iproniazid into medicinal therapy in 1957, further MAO inhibitors of the hydrazine class as well as nonhydrazine inhibitors have been developed (table 1). *In vitro*, these inhibitors and the substrates generally compete for the enzyme as long as the inhibition is not complete. Once this has been established, however, it becomes uncompetitive and almost irreversible. Tranylcypromine is an exception because it may induce competitive or noncompetitive inhibition depending on the substrate (34, 35). There exist also some other differences between the various groups of MAO inhibitors. Thus, hydrazine derivatives, pargyline, and modaline on the one hand cause maximal inhibition *in vitro* only after aerobic preincubation in the absence of substrates. This progression seems to be due to their transformation into compounds which represent the actual inhibitors reacting with the active center of the enzyme. It has been shown, for instance, that the active metabolite of iproniazid is a volatile compound, possibly an oxidation product of isopropylhydrazine (26, 48). Tranylcypromine on the other hand causes maximal inhibition of MAO *in vitro* without aerobic preincubation. This indicates chemical affinity of the drug to the active site of MAO without previous metabolism, possibly because of similar electronic properties of tranylcypromine and the intermediary forms of the monoamines during oxidation (3, 4, 42, 53).

Prior exposure of MAO to reversible inhibitors like harmine derivatives and amphetamine prevents the inhibition of the enzyme by MAO inhibitors of the hydrazine type and by modaline, but not by tranylcypromine (11, 21, 22, 31). Reversible inhibitors and hydrazines or modaline seem to compete for the same active site of the enzyme, whereas the reason for the different behavior of tranylcypromine is not clear.

Intensity, onset and duration of action of MAO inhibitors *in vivo* differ according to the individual compound and to the mode of administration (oral or parenteral). The inhibition of the enzyme in the brain generally lasts longer than in the other organs. The onset of action of tranylcypromine is quicker and its duration of action shorter than that of most hydrazine derivatives (34, 35). Because of the long-lasting effect (days to weeks), repeated therapeutic doses of MAO inhibitors such as hydrazine derivatives and pargyline may lead to almost complete inactivation of MAO in man, *e.g.*, in the brain, liver and jejunal mucosa (13, 27).

TABLE 1
MAO-Inhibitors

Chemistry	Generic Name	Trade Name
Hydrazine-derivatives		Marsilid
	Isocarboxazid	Marplin
	Nialamide	Niamid
	Phenelzine	Nardil
		Stinerval
R_1—NH—NH—R_2	Pheniprazine	Catron
		Catroniazid
		Cavodil
	Iproclozide	Sursum
	Mebamazine	Actomol
	Phenoxypropazine	Drazine
Phenylcyclopropylamine 	Tranylcypromine	Parnate
N-Benzyl-N-methylpropargylamine 	Pargyline	Eutonyl
2-Methyl-3-piperidinopyrazine 	Modaline	

EFFECT ON OTHER ENZYMES

Some MAO inhibitors of the hydrazine type interfere with a variety of enzymes other than MAO, *e.g.*, amphetamine oxidase, diamine oxidase, choline oxidase, cholinesterase, decarboxylase of aromatic amino acids, diphosphopyridine nucleotidases, *etc.* The compounds may act *in vitro*, *in vivo*, or in both; their intensity of action depends on the chemical structure. Nonhydrazine MAO inhibitors affect these enzyme systems in general much less if at all. The inhibitory action of the hydrazines seems in general not to parallel their effect on MAO (12, 19, 34, 35).

EFFECT ON THE METABOLISM OF MONOAMINES

In animals and man, MAO inhibitors, regardless of their chemical structure, generally increase the content of endogenous monoamines as well as of mono-

TABLE 2

Dose of various MAO inhibitors (in milligrams per kilogram) causing a 50% increase in brain 5HT (ED50) in different mammalian species

	Iproniazid	Isocarboxazid	Tranylcypromine	Pargyline
Mouse	540 (280–930)	44 (37–49)	23 (20–26)	405 (350–475)
Rat	176 (157–196)	28 (17–37)	6 (2–9)	81 (56–112)
Guinea pig	64 (36–98)	14 (8–20)	28 (14–48)	224 (143–303)
Rabbit	290 (150–400)	74 (30–107)		

From Medicina Experimentalis, 4: 113, 1961.

Intraperitoneal administration of the drugs 16 hr before sacrifice. Figures in parentheses: fiducial limits for 95% probability (36).

amines from exogenous sources, *e.g.*, injected monoamines or their precursors such as dopa and 5-hydroxytryptophan. This is true for 5-hydroxytryptamine (5HT), catecholamines, normetanephrine, and octopamine in the brain, for 5HT and norepinephrine (NE) in autonomic ganglia, for NE in the heart and adipose tissue, for 5HT in blood platelets and small intestine, for phenethylamine, tyramine, and tryptamine in various tissues, *etc.* (34, 35).

Concomitantly, MAO inhibitors enhance the urinary excretion of free and conjugated monoamines (such as O-methylated and nonmethylated catecholamines, 5HT, tryptamine, tyramine, phenethylamine, *etc.*) and diminish the elimination of deaminated products (such as 3-methoxy-4-hydroxymandelic acid, homovanillic acid, 3,4-dihydroxymandelic acid, 3,4-dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid as well as 3-methoxy-4-hydroxyphenylglycol and -ethanol). In some tissues, *e.g.*, brain, 5-hydroxyindoleacetic acid, homovanillic acid, and 3,4-dihydroxyphenylacetic acid are also decreased after MAO inhibition (34, 35).

Intensity, onset and duration of action depend on the species (table 2) and on the chemical structure of the inhibitors. The catecholamines in the central nervous system seem, for instance, to be less influenced in cats and dogs than in rodents and monkeys. In cats, the cardiac catecholamines are even decreased by tranylcypromine, pargyline and iproniazid, whereas in rats and possibly also in man these amines may increase. This difference might be due to the fact that in cats the cardiac catecholamines are mainly metabolized by 3-O-methyltransferase, whereas in rats and man oxidative deamination is the main catabolic pathway (20, 28, 36, 41, 45, 49). Several hydrazines (*e.g.*, isoniazid) have no influence on the monoamine content, whereas others (*e.g.*, pheniprazine) are about 15 times more potent than iproniazid. The nonhydrazine compounds

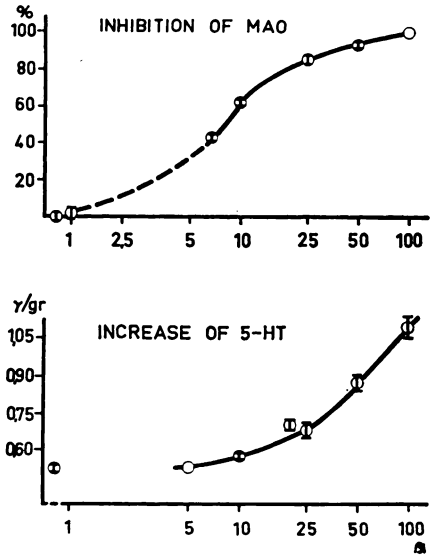


FIG. 1. Influence of increasing doses of iproniazid on the MAO activity and the 5HT content of rat brain. Ordinates: percent inhibition of MAO (brain mitochondria) (above) and 5HT content of the whole brain in micrograms per gram fresh tissue (below); abscissae: dose of iproniazid in milligrams per kilogram (intraperitoneal 16 hr before decapitation) (34, 35). (From Progress in Drug Research, Vol. II, p. 417, 1960.)

pargyline and tranylcypromine are very effective in increasing monoamines, the latter at least as much as the strongest MAO inhibitor of the hydrazine series. The onset of action seems in general to be more rapid with nonhydrazine inhibitors (*e.g.*, tranylcypromine and pargyline) than with hydrazines such as iproniazid, whereas the duration of action of most inhibitors is rather long (lasting up to several days); this fact explains their cumulative effect (34, 35).

MAO inhibitors also differ in their action on the various amines: in the brain, 5HT is often more markedly increased than NE, and there may be differences with regard to NE and dopamine (6, 9, 32, 51).

There is no absolute parallelism between *MAO inhibition and monoamine increase.* Thus, the enzyme has to be inhibited at least to 85% before the monoamine content of brain and possibly other tissues rises (fig. 1). Furthermore, the monoamine accumulation is of shorter duration than the MAO inhibition. This might indicate that MAO is present in great excess so that only a high degree of inhibition leads to an accumulation of its substrates (10, 17).

The *antagonism towards monoamine releasers* such as reserpine and benzoquinolizine derivatives represents a typical effect of MAO inhibitors regardless of their chemical structure (34, 35). In addition, NE release by other compounds (*e.g.*, nicotine, insulin, histamine, guanethidine, α-methyl-meta-tyrosine) as well as by nervous stimulation is diminished, whereas the liberation of catecholamines by sympathomimetic amines like amphetamine does not seem to be antagonized by MAO inhibitors (16, 23, 38, 43).

The *recovery of monoamines* after their depletion by monoamine releasers

(*e.g.*, reserpine) is accelerated by all types of MAO inhibitor. Potency and speed of this enhancement depend on the chemical structure of the inhibitors and the nature of the amines. Pheniprazine, tranylcypromine, and pargyline, for instance, have a faster action than iproniazid in the brain, and the repletion of 5HT seems to be more markedly enhanced than that of NE. Owing to this latter difference, it was possible to prepare animals with brains in which 5HT was normal, but NE was depleted (34, 35).

OTHER METABOLIC EFFECTS

MAO inhibitors, especially hydrazine derivatives, show various metabolic actions which are connected not with MAO inhibition, but rather with an influence on other enzyme systems (34, 35). A typical action of the inhibitors is the rise of the lactate and pyruvate level in the blood. This might be due to an increase in the metabolic action of endogenous catecholamines and 5HT, since the accumulation of lactate and pyruvate in blood due to exogenous NE and 5HT is enhanced by iproniazid (18). Furthermore, in animals and in man, hypoglycemic effects of MAO inhibitors have been described (34, 35, 39) which, together with the increase of pyruvate and lactate in blood, might indicate an acceleration of glycolysis.

MODE OF ACTION

It has been well established that the effect of MAO inhibitors on the metabolism of endogenous and exogenous amines is mainly the consequence of *MAO inhibition.* The inhibitors act on the monoamines which are primarily metabolized by MAO, *e.g.*, NE and 5HT in the brain, NE in the heart, tyramine and tryptamine in the circulating blood. If, however, metabolic routes bypassing MAO are available (*e.g.*, 3-O-methylation, conjugate formation), the MAO inhibitors have less or no effect as in the case of circulating 5HT and NE (1, 24, 34, 35, 52).

MAO inhibitors probably increase both the *intra- and extraneuronal monoamines* in tissues such as heart and brain. The intraneuronal accumulation seems to be directly due to inhibition of MAO, since the major part of the intraneuronal amines is probably metabolized by this enzyme. The accumulation of extraneuronal monoamines might be the consequence of the intraneuronal increase, because there seems to be an equilibrium between the two compartments, because monoamines may spill over from completely filled intraneuronal stores, or both (33). Evidence for an increase of extraneuronal monoamines, which probably stimulate the adrenergic receptors, has been gained by biochemical and histochemical investigations in brain (7, 8) as well as by experiments with the isolated perfused cervical ganglion (15).

With regard to the *reserpine-induced release of monoamines* from tissue stores, a new hypothesis has been put forward recently. According to this, reserpine competes with NE for a carrier mechanism which is responsible for the uptake of the amine into the storage organelles. MAO inhibitors seem to allow the endogenous NE (which is no longer metabolized) to "displace" reserpine from this

carrier, and this process attenuates the monoamine depletion (46). Besides this mechanism, which is probably of major importance, MAO inhibitors might also have some other effects, *e.g.*, a direct action on cellular membranes (37). It remains to be investigated why MAO inhibitors counteract the amine-liberating effect of various other compounds such as insulin, histamine, nicotine, guanethidine as well as of nervous stimulation (see above).

RELATION BETWEEN MAO INHIBITION AND PHARMACOLOGIC EFFECTS

MAO inhibitors exert a variety of pharmacologic effects. Thus, they modify the functional changes induced by monoamine releasers, by monoamines, monoamine precursors and other drugs (*e.g.*, enhancement of hypnotics); furthermore, they may influence behavior, electroencephalogram, synaptic transmission, convulsive seizures, cardiovascular and gastrointestinal functions. Some of these actions are not the consequence of MAO inhibition but of other mechanisms, *e.g.*, the inhibition of enzymes not related to MAO or a direct action on receptors (34, 35).

Three actions are of main practical importance: psychostimulation, lowering of blood pressure, and antianginal effect. A causal relation between these properties and MAO inhibition has not been fully established but is likely for the following reasons. 1) Only hydrazine derivatives exerting marked MAO inhibition *in vivo* (*e.g.*, iproniazid) have a psychostimulant, hypotensive, and antianginal action; chemically related hydrazines (*e.g.*, isoniazid) which do not influence the enzyme are generally devoid of these effects. 2) Long-acting MAO inhibitors not belonging to the hydrazine class (*e.g.*, pargyline, tranylcypromine) also cause psychostimulation and hypotension. 3) In general, the MAO inhibition and the pharmacologic action have a similar time course. Both appear only slowly after repeated therapeutic doses of MAO inhibitors, but persist for some time after discontinuation of the drugs. A correlation between pharmacologic effects and MAO inhibition in man, however, has not been found by all investigators. This is not necessarily an argument against a causal connection since estimations of MAO have been mainly made in peripheral tissues (*e.g.*, by measuring the urinary excretion of 5-hydroxyindoleacetic acid and tryptamine or by direct determination of MAO in the jejunal mucosa). MAO inhibition in the periphery does not necessarily reflect MAO inhibition in the central nervous system (27, 30, 44, 50). 4) Alteration of other enzymes, *e.g.*, decarboxylase of aromatic amino acids, diphosphopyridine nucleotidase, diamine oxidase, choline oxidase, is probably not a major cause for the above-mentioned pharmacologic effects. Isoniazid and some other hydrazides inhibit these enzymes at least to the same extent as iproniazid without having its pharmacologic action. On the other hand, pargyline and tranylcypromine either generally do not influence these enzymes or influence them distinctly less than the hydrazides (19, 34, 35) (table 2).

The mechanism by which changes in the monoamine metabolism lead to the above-mentioned effects remains to be further investigated. The following hypotheses have been proposed: a) nonspecific central stimulation by accumulation

of endogenous sympathomimetic amines in the central nervous system; correction of a possible metabolic disturbance, *e.g.*, of monoamines or carbohydrates (39, 40) present in mental depression (psychostimulation); b) interference with ganglionic transmission, with the release of NE from sympathetic nerve endings, or with the action of the amine on vascular muscles (2, 5, 14); preferential accumulation of dopamine or octopamine (weak pressor agents) which might compete with NE at receptors involved in the regulation of blood pressure (25, 47) (hypotensive action); and c) coronary dilatation by an increase of 5HT ("benign" coronary dilator) in the blood (29); oxygen sparing, *e.g.*, by activation of glycolysis; improvement of myocardial energy production in consequence of increased supply of easily utilized substrates, *e.g.*, pyruvate and lactate from the blood (antianginal effect).

SUMMARY

MAO inhibitors of various chemical classes (hydrazine derivatives, tranylcypromine, pargyline, modaline) in general cause competitive, followed by noncompetitive, irreversible inhibition of the enzyme. For this purpose, the drugs, except tranylcypromine, have to be metabolized to form the actual inhibitors. Enzymes not related to MAO are affected more markedly by hydrazine than by nonhydrazine MAO inhibitors.

All types of MAO inhibitor cause some typical effects *in vivo*, such as increase of endogenous and exogenous monoamines, antagonism towards monoamine releasers, or change in the excretion pattern of monoamines and their metabolites. A rise of endogenous monoamines occurs only when MAO has been inhibited to a high degree. Intensity, onset and duration of action depend on the species, the tissue, the amine, the mode of administration, and the chemistry of the drug.

The action of MAO inhibitors bears mainly on those amines which are preferentially metabolized by MAO. Thereby, the intra- as well as the extraneuronal amines seem to be increased. For some clinical effects a relationship with MAO nihibition is probable.

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