The relationship of early studies of monoamine oxidase to present concepts

I. J. Kopin

Scientist Emeritus, NINDS, NIH, Bethesda, USA

Summary The development of our understanding of monoamine oxidase (MAO), of its role in the metabolism of amines and of the therapeutic usefulness of MAO inhibitors (MAOIs) have evolved, slowly at times and rapidly at other times, with leaps propelled by new discoveries, new techniques and new insights. Moussa Youdim was one of the major contributors to propulsion of several of these leaps, including the detection of multiple forms of MAO, the descriptions of their properties, active sites and substrates, the use of MAOIs for enhancement of DOPA in treating Parkinson’s disease and the evolution of MAO-B inhibitors from mere enzyme inhibitors to lead compounds in the discovery of neuroprotective agents for use in degenerative neurological diseases. Since others will be describing the more recent developments in this field, I thought it would be of interest and instructive to recount the unfolding of our early understanding of MAO, dating from its discovery until the events that first suggested that drugs that inhibit MAO might be neuroprotective. While even the earliest observations about MAO were valid, they were often misinterpreted or confusing, whereas others were predictive of several of our newer concepts of MAO and of side effects encountered in patients treated with MAOIs.

1. Discovery of monoamine oxidase

Nearly 100 years ago, Dale and Dixon (1909) found that 4-hydroxyphenylethylamine (tyramine) was the major in pressor amine found in putrified meat; it seemed to produce adrenaline-like effects. This sparked interest of their colleagues at Cambridge in the metabolic fate of this amine and the following year Ewins and Laidlaw (1910) showed that tyramine was quantitatively converted to p-hydroxyphenylacetic acid by perfused dog liver. Furthermore, orally administered tyramine gave rise to urinary excretion of the acid. They believed that the amine moiety of tyramine was replaced by a hydroxyl and that the resulting alcohol was then metabolized to the corresponding acid:

\[ R-\text{CH}_2-\text{NH}_2 \rightarrow R-\text{CH}_2-\text{OH} \rightarrow R-\text{COOH} \]

Interestingly, tyramine disappeared when perfused through the heart without any evidence of production of the expected acid; they speculated (incorrectly) that the benzene ring of tyramine had been destroyed. The tyramine was probably removed by uptake into the sympathetic nerves, converted to octopamine which remained in the storage vesicles (see below).

Using a Barcroft differential manometer to measure oxygen utilization by liver homogenates, Hare (1928), while a student at Cambridge, was able to show that oxygen uptake corresponded to exactly one atom of oxygen per molecule of tyramine, but only half the expected amount of ammonia was recovered. Furthermore, she demonstrated the production of hydrogen peroxide during the reaction. The thermolability of the reaction indicated that an enzyme, which she named tyramine oxidase, catalyzed the oxidative deamination of tyramine. However, she did not find the expected product, p-hydroxyphenylacetic acid. Several years later, at Duke University, she found that the number of oxygen molecules used in the oxidation of tyramine depended upon factors such as the pH, the age of the preparation and its concentration (Bernheim, see Hare, 1931). With fresh tissue, at physiological pH, two oxygen atoms were required to metabolize tyramine and the product was, as expected, p-hydroxyphenylacetic acid. She explained the discrepancy between the production of ammonia and the disappearance of tyramine in her earlier experiments by suggesting that one molecule of tyramine was converted to p-hydroxyphenylacetaldehyde and that this reacted with a second molecule of tyramine to form a covalent linkage:

\[ 2R-\text{CH}_2-\text{NH}_2 + O_2 \rightarrow 2R-\text{CH}=\text{NH} + H_2O_2 \]
\[ R-\text{CH}=\text{NH} + H_2O \rightarrow R-\text{CHO} + NH_3 \]
\[ R-\text{CH}_2-\text{NH}_2 + R-\text{CHO} \rightarrow R-\text{CH}_2-N=\text{CH} \rightarrow R+H_2O \]
Under most conditions, however, the oxidation proceeds further, producing the acid. Ewins and Laidlaw (1910) had shown that both the mono-N-methyl and the dimethyl derivatives of tyramine (hordenine) could be transformed to p-hydroxyphenylacetic acid, albeit at a slower rate. In 1937, several investigators confirmed the production of hydrogen peroxide, ammonia and an aldehyde as a result of oxidative deamination of several primary, secondary and tertiary amines (Kohn, 1937; Richter 1937; Blaschko et al., 1937). The aldehyde was trapped using 2,4-dinitrophenylhydrazine. Covalent linkage of the reactive aldehydes formed from catecholamines will show up again, about 60 years later (see below). The competitive interactions among “tyramine oxidase”, “adrenaline oxidase” and “aliphatic amine oxidase”, suggested that they were all substrates for the same enzyme, subsequently named MAO. The three products formed by the deamination process, hydrogen peroxide, ammonia and an aldehyde, are all potentially toxic.

Bernheim (1931) recognized the potential toxicity of H$_2$O$_2$, but assumed that catalase rapidly destroyed this oxidizing agent to generate H$_2$O + O$_2$. Although Fenton (1894) had described Fe$^{++}$ catalysis of H$_2$O$_2$ oxidation reactions, the cycling Haber-Weiss reactions (Haber and Weiss, 1932) and superoxide dismutase (McCord and Fridovich, 1969) had not been discovered. Sixty years after Hare’s description of H$_2$O$_2$ formation during the oxidative deamination of tyramine, blockade of hydrogen peroxide generation in glia by MAO-B inhibition was suggested as a means to diminish toxicity due to endogenous free radicals. The course of events from that time until the more recent developments in the field have been ably reviewed by Youdim and Riederer (2004).

Blaschko (1952) described at some length covalent bonding of reactive aldehydes formed from deamination of amines. A dozen years later, Holtz et al. (1964) reported that dopamine and the aldehyde derived from its deamination could covalently link to yield tetrahydropapaveroline and later Sandler et al. (1973) found this compound in the urine of parkinsonian patients being treated with DOPA. More recently, covalent bondage of aldehydes formed from the deamination of dopamine, norepinephrine (NE) and epinephrine (EPI) have received increasing attention. Burke et al. (2004) recently reviewed the evidence that reactions of these metabolites with cellular components may be etiological factors in the neurodegenerative processes culminating in death of catecholaminergic neurons in degenerative neurological disorders such as Parkinson’s disease.

Ammonia, although a third potential toxin from this source, is formed primarily from transamination of amino acids. It diffuses rapidly and is efficiently converted to urea by the liver. Only under unusual conditions of liver failure has endogenous ammonia formation been considered a hazard.

2. Early indications of in vivo catecholamine deamination

As indicated above, as late as 1950, although the catecholamines had been shown to be substrates for MAO, the role of this enzyme in their metabolism in intact animals had not been convincingly demonstrated. The introduction of radioisotopes and the discovery of an inhibitor of MAO were seminal events that enabled further investigations of the role of MAO in the disposition of catecholamines. Schayer and Smiley (1951) showed that only about one half of the radioactivity in methyl-$^{14}$C-dl-EPI could be recovered in the urine of rats that had received the labeled compound intravenously or subcutaneously, whereas all the administered radioactivity was recovered from $\beta$-$^{14}$C-dl-EPI. In a second study, Schayer et al. (1952) showed that this was not due to a difference in the metabolism of the d- and l-isomers of the catecholamine, indicating that the metabolism of both isomers of EPI involved formation of a breakdown product that lacked the N-methyl group, presumably as a result of deamination. This suggestion was proven correct during the following year (Schayer et al., 1953) when it became possible to inhibit MAO (see below).

At that time, Blaschko (1952) described three possible means of inactivation of NE and EPI: oxidative deamination, oxidation to adrenochrome, and conjugation. In that review, he also introduced the concept of “directly” acting sympathomimetic amines, which activated receptors, and “indirectly” acting sympathomimetic amines, which “preserved sympathin in the region of the receptors.” He was close to being right, but could not predict the other mechanisms that would be discovered in the next few years, e.g., active neuronal reuptake of the released transmitter as a means of “preserving” the neurotransmitter in the region of the receptor (how cocaine acts) or the release of NE (how tyramine produces its effects) as mechanisms for the adrenergic responses to “indirectly” acting sympathomimetic amines.

3. Discovery of MAO inhibitors

The fortuitous discovery by Chorine (1945) that nicotinamide had a bacteriostatic effect on the tuberculous bacillus led to the investigation of cogeners that might be used for the treatment of tuberculosis. In the course of the next few years, isonicotinylhydrazine (isoniazid) and its isopropyl
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4. The antidepressant effects of MAO inhibitors

In the mid 1950s, the biochemical effects of MAO inhibition were studied independently of clinical studies. By the end of the fifties, however, the discovery of antidepressant activity of MAO inhibitors marked a veritable therapeutic revolution in the world of neuropsychiatry. Iproniazid, the isopropyl derivative of isoniazid, had been introduced into clinical trials seeking a better drug with which to treat tuberculosis (e.g., Bloch et al., 1954; Liechtenstein and Mitzenberg, 1954). It was noted that some of the patients treated with iproniazid felt too good. Their general behavior belied the lack of improvement of their x-rays; they overexerted themselves, generally ignored appropriate medical safeguards, and were inappropriately elated. Some patients became clearly manic. These mental effects, which were reported increasingly by clinicians treating tuberculosis, suggested that iproniazid might be useful in the treatment of depression. In further support of this view, there were reports that the striking sedative effects in animals of reserpine, which had recently been introduced as a treatment for hypertension, were reversed by pretreatment with iproniazid. These observations together with the affective changes in tubercular patients, prompted the initiation of studies of iproniazid in psychiatric patients. The usefulness of iproniazid as a “psychic energizer” in the treatment of depression was first reported by Loomer et al. (1957). The potential market for an effective antidepressant and need for an alternative drug necessitated by the hepatotoxic and other side effects of iproniazid fueled the search for more specific and less toxic MAOIs. During the next few years, over 100 hundred other compounds were reported to inhibit MAO (see, e.g., the papers in a symposium edited by Zeller, 1963) and iproniazid was replaced by other MAOIs.

5. Metabolic products formed from catecholamines

At about the time that iproniazid was introduced as an antidepressant, Armstrong et al. (1957) reported that 3-methoxy-4-hydroxy-D-mandelic acid (vanillylmandelic acid, VMA) was a major urinary metabolite of NE; large amounts of VMA were found in the urine of patients with phaeochromocytoma, a catecholamine-producing tumor, usually of the adrenal medulla. They assumed that VMA was formed from 3,4-dihydroxymandelic acid derived from the deamination of the catecholamine. However, Axelrod and Tomchick (1958) discovered an enzyme that O-methylates EPI and other catechols, catechol-O-methyltransferase (COMT). Axelrod then showed that O-methylation appeared to be the major initial route of metabolic transformation of administered EPI and NE in rats (1958a and 1958b). Quantitative assessment of the relative magnitude of O-methylation of administered EPI in humans showed that about 2/3 of administered EPI was converted to metanephrine before being further metabolized (Copin, 1960). Although in humans VMA is the major urinary catecholamine metabolite, in rats, administration of $^3$H-EPI or $^3$H-NE resulted in the excretion of a compound that was clearly different from the known metabolites of these catecholamines. The new compound was identified as 3-methoxy-4-hydroxy-phenylglycol (MHPG), excreted as its sulfate conjugate (Axelrod et al., 1959a). Shortly thereafter, we (Copin and Axelrod, 1960) found that 3,4-dihydroxyphenylglycol (DHPG) was formed from $^3$H-EPI administered to rats that had been pretreated with pyrogallol, an inhibitor of COMT (Axelrod and Laroche, 1959). At that
time we thought (incorrectly) that the difference between the major urinary metabolites in humans and rats was the result of a species difference in the oxidation versus reduction of the aldehyde formed when NE or EPI was deaminated. Studies carried out over 20 years later showed that VMA was formed mainly from oxidation of plasma MHPG (Blombery et al., 1980; Mardh et al., 1981) and the species difference is in the fate of MHPG; oxidation to VMA vs conjugation with sulfate.

6. MAO vs COMT in terminating the action of catecholamines

Pyrogallol and other catechols had been reported to potentiate the effects of administered EPI and sympathetic nerve stimulation (Bacq, 1936). Although initially Bacq thought to be due to the antioxidant properties of catechols, the demonstration that pyrogallol was a potent inhibitor of COMT (Bacq et al., 1959; Axelrod and Laroche, 1959) strongly suggested that O-methylation was the primary means of inactivation of NE. This view was supported by reports that MAO inhibition with iproniazid prolonged the actions of neither released (Brown and Gillespie, 1957) nor administered catecholamines (Greisemer et al., 1957; Corne and Graham, 1957). The opposite view for the inactivation of NE in brain was based on the effects of MAO inhibition on the effects of reserpine. Shore et al. (1957) thought that MAO was mainly responsible for the physiological inactivation of both serotonin and NE in brain because iproniazid was found to elevate the tissue levels of these amines and to prevent reserpine-induced decline in their levels. Iproniazid also increased cardiac NE levels (Pletscher, 1958). However, Crout (1961) reported that inhibition of both COMT and MAO failed to significantly affect the cardiovascular effects of NE, indicating that alternatives to metabolic inactivation must be sought. The relationships of MAO and COMT to sites of NE metabolism did not become apparent until more information about the storage and release of NE became available.

7. Uptake and storage of NE

After intravenous administration of $^3$H-EPI or $^3$H-NE to animals, a major portion of the administered compounds was retained in the tissues and not metabolized (Axelrod et al., 1959b; Whitby et al., 1961). When it was shown that the binding of tritiated catecholamines was markedly diminished after chronic sympathetic denervation, it became evident that presynaptic neuronal reuptake was the major means of terminating the actions of the released neurotransmitter (Hertting et al., 1961). Cocaine potentiation of the actions of EPI, first described by Fröhlich and Loewi (1910), had been attributed to inhibition of oxidation of the catecholamine (Philpot, 1940). Blaschko (1952) found this explanation unsatisfactory because it “is surprising that the action of tyramine is blocked by cocaine.” An alternative to Philpot’s explanation was provided when it was shown that cocaine inhibited uptake of $^3$H-NE (Whitby et al., 1960). Since uptake of tyramine is required for its release of NE, this also explained why cocaine blocked the effects of tyramine. Many other drugs (e.g., imipramine, tyramine, amphetamine, phenoxybenzamine, etc.) were found to inhibit NE uptake and its retention in the tissues (Axelrod et al., 1961, 1962). Determination of the site in the nerve terminals at which the $^3$H-NE was retained then attracted attention. Because Hillarp (1958) had shown that in the adrenal medulla, catecholamines were stored in granules, a similar site for storage of the catecholamine in sympathetic neurons was suspected. This possibility was examined by combined electron microscopy and autoradiography of sympathetic nerves of the pineal gland of rats that had received $^3$H-NE (Wolfe et al., 1962). They found a striking localization of photographic grains overlying non-myelinated axons that contained granulated vesicles. The vesicular sequestration of the catecholamine protected it from metabolism by MAO.

The discovery that reserpine, which had recently been introduced as an antihypertensive agent and antipsychotic, depleted tissue levels of serotonin (Pletscher et al., 1955) and NE (Bertler et al., 1956; Holtzbauer and Vogt, 1956) not only spawned hypotheses about the physiological role of these amines, but provided a valuable new pharmacological tool. As indicated earlier, until Blaschko (1952) introduced the concept of “directly” and “indirectly” acting amines, it had been assumed that all sympathomimetic drugs produced their effects by acting on the same receptors as the endogenous catecholamines. When it was shown that pretreatment with reserpine prevented the actions of some sympathomimetic drugs, such as tyramine, it was proposed that such amines acted by releasing NE form the sympathetic nerves (e.g., Burn and Rand, 1958). During reserpine-induced depletion of tissue amines, however, there were no indications that the amines were released at sites at which they normally elicited physiological responses.

The role of MAO in the metabolism of NE became better understood when it was found that the metabolites excreted within 3 hours after intravenously administered $^3$H-NE and of $^3$H-NE released by tyramine 10 hours after administration of the labeled catecholamine reflected metabolism
primarily by O-methylation, whereas the metabolites of the $^3$H-NE that had been retained for 10 hours or of stored $^3$H-NE depleted by the action of reserpine reflected metabolism by MAO (Kopin and Gordon, 1963). NE that is released outside the nerve and escapes reuptake is metabolized by COMT; MAO metabolizes NE released from storage sites into the neuronal cytoplasm. This explains the absence of sympathetic response during reserpine-induced depletion of catecholamines stores. Blocking the vesicular storage of NE exposes the amine to destruction by MAO. Thus, the mechanism for reversal of the effects of reserpine by pretreatment of animals with a MAOI becomes apparent. If vesicular storage is prevented by reserpine and MAO is also blocked, then the catecholamine released into the cytoplasm cannot be deaminated and escapes into the extraneuronal space to activate receptors. In addition to tyramine causing release of NE into the extracellular space, but it also competes with reuptake of the released NE (Axelrod et al., 1962), which is then exposed to metabolism by COMT.

Much later it was shown that VMA is formed mainly in the liver from oxidation of plasma MHPG (Blombery et al., 1980; Marde et al., 1981), further studies showed that intraneuronal NE is deaminated and reduced to form 3,4-dihydroxyphenylglycol (DHPG). Eisenhofer et al. (2004) recently reviewed the bases for changes our concepts of the storage and metabolism of NE and some of the misconceptions that have persisted. Vesicular NE stores are not inert but are rather in dynamic equilibrium with the cytoplasmic catecholamine. The avid vesicular amine transporter captures most of the free cytoplasmic catecholamine. Although only a small portion of the cytoplasmic NE is metabolized to DHPG, it is the main source of metabolites of NE. DHPG is readily diffusible, escaping to the plasma or extraneuronal tissues after which it is O-methylated to form MHPG. DHPG and MHPG in plasma are rapidly converted to VMA or MHPG conjugates in the liver. When reserpine blocks the vesicular amine transporter, NE depletion results from deamination to DHPG of the cytoplasmic NE that has been rapidly “leaking” out of the vesicle. Under normal circumstances, more NE is metabolized intraneuronally than is released by exocytosis.

8. Hypotensive effects of MAO inhibition

Orthostatic hypotension was a major side effect of iproniazid treatment. This was unexpected because of the earlier studies that showed that catecholamines were substrates for MAO and that deamination was clearly involved in the metabolism of catecholamines. Furthermore, as indicated above, tissue levels of the amines are generally increased when MAO is inhibited (Shore et al., 1957; Pletscher, 1958). Although the mechanism of the sympatholytic effects was unknown, it was thought that iproniazid might be beneficial for treating hypertension and anginal pain. When Kakimoto and Armstrong (1962) found that octopamine, the β-hydroxylated derivative of tyramine, appeared in the urine of patients and animals treated with iproniazid and was markedly increased in the tissues of animals treated with the MAOI, they suggested that “the beneficial effects of monoamine oxidase inhibitors in the treatment of angina1 pain might result from the accumulation of octopamine”. Subsequently it was shown that the octopamine that accumulated in the tissue was in sympathetic nerves where it is a “false neurotransmitter” (Kopin et al., 1964). The slow (over several days) accumulation of octopamine is the result of combined failure of MAO in the gastrointestinal tract and the liver to remove the small quantities of tyramine formed by bacterial fermentation in the intestine. This relatively small amount of tyramine reaches the systemic circulation and is taken up into the sympathetic neurons without releasing significant amounts of NE. Because the MAO in the neuron is also inhibited, the tyramine is transported into the synaptic vesicles. The dopamine-β-hydroxylase in the vesicles converts the tyramine to octopamine, which slowly replaces a portion of the NE and is released instead of a portion of the NE. Since octopamine is almost inactive as a transmitter, the effects of nerve stimulation are markedly reduced. Octopamine is among a number of compounds that can serve as false adrenergic neurotransmitters (Kopin, 1968) but is the major amine accumulated in the sympathetic neurons when MAO is inhibited. Although other mechanisms for MOAI-induced orthostatic hypotension have been suggested, e.g., an effect mediated by central nervous system or ganglionic amines, they do not explain the reduced effects of direct stimulation of sympathetic nerves in organ preparations such as the perfused spleen of cats chronically pretreated with a MAO inhibitor.

9. Hypertensive crises from MAO inhibitors

As indicated above, tyramine was identified as the major pressor substance in putrified meat (Dale and Dixon, 1909). Over 60 years later, when hypertensive crises were reported in patients who were being treated with MAO inhibitors (e.g., Blackwell, 1963), the cause of the pressor effect was found to be dietary; as in putrifying meat, tyramine is formed by bacterial decarboxylation of tyrosine during the process of manufacture of cheese, wine, etc., and is present in high concentrations in the ingested products (Horwitz, 1919).
et al., 1964; Blackwell and Mabbitt, 1965). When such foods are ingested, if MAO is inhibited, the concentration of tyramine in the systemic circulation increases rapidly and attains levels that release large quantities of NE. This causes a marked rise in systemic blood pressure, similar to the effects of the tyramine in putrified meat described in 1909 by Dale and Dixon. When MAO in inhibited, but the ingested foods produce only small quantities of tyramine, there are prolonged, relatively low elevations in plasma tyramine concentrations slow displacement of NE stores by octopamine that diminishes sympathetic responsivity, as described above. Avoidance of the hypertensive response to high levels of ingested tyramine became feasible when subtypes of MAO and drugs that selectively inhibit MAO-B were discovered (see Youdim and Finberg, 1987).

10. Multiple forms of MAO

Entirely new perspectives about MAO arose after the demonstration that there are two types of MAO. Although a few previously published evidence suggested that MAO was complex, the first definitive evidence for two different enzymes was present by Johnston (1968). During examination of the kinetics of inhibition of MAO by new potential MAO inhibitors, he noted that one of the compounds being tested, clorgyline (at that time designated as M&B 9302), was strikingly different from most others. Using tyramine as a substrate, graphing of percentage inhibition of MAO activity in a rat brain mitochondrial preparation revealed a pair of sigmoid curves. The midpoints of these curves were separated by over three orders of magnitude. He interpreted this difference as indicating that there were two forms of MAO. The first, MAO-A, was very sensitive to inhibition by clorgyline, whereas the second, MAO-B was relatively resistant to the inhibitor. However, tyramine was an equally good substrate for MAO-A and MAO-B. When tryptamine was used as substrate, only MAO-A activity was apparent, indicating that tryptamine is a poor substrate for MAO-B.

In 1966, Moussa Youdim, working with Ted Sourkes at McGill University in Montreal, sowed the seeds of his remarkably productive career by being the first to solubilize MAO (Youdim and Sourkes, 1966). After joining Merton Sandler in London, Moussa, working with solubilized preparations of MAO subjected to electrophoresis, separated of several isoenzymes of MAO with differing substrate specificities (Youdim et al., 1969) supporting the view that there were several forms of MAO. When a specific inhibitor of MAO-B, deprenyl (selegiline), was discovered (Knoll and Magyar, 1972), it became possible to compare the effects of each of the MAO specific inhibitors on the metabolism and responses elicited by a variety of amines. It had been recognized that the existence of multiple forms of MAO might have important physiological and pharmacological implications (Sandler and Youdim, 1972). After Birkmeyer et al. (1975) reported that deprenyl could potentiate the effects of DOPA in parkinsonian patients, it was found that this MAO inhibitor could be administered without fear of “cheese effect” (Lees et al., 1977; Sandler et al., 1978). Although deprenyl prolonged the effects of administered DOPA, it did not alter the symptoms of depression, when present, in parkinsonian patients (Lees et al., 1977). This was one of the first reports suggesting that inhibition of MAO-A was required for the antidepressant effect, as well as the “cheese effect” of non-specific MAO inhibitors. Thus, the initial use of deprenyl in parkinsonian patients was based on the potentiation of DOPA by inhibition of MAO-B. Subsequently molecular genetic approaches definitively established the existence two distinct forms of MAO (Bach et al., 1988). Studies of their tissue distribution, molecular structure, etc. have yielded volumes of new information about the enzymes, but their potentially important role in pathogenic mechanisms was a matter of infrequent speculation.

11. The relationship of MPTP toxicity to MAO

The accidental discovery that a contaminant of an illicit narcotic caused a parkinsonian syndrome in drug addicts and in chemist exposed to the toxin stimulated an entirely new approach to study of the etiology of Parkinson add. Soon after 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) was discovered as the cause of severe chronic Parkinsonism in humans (Davis et al., 1979; Langston et al., 1983) and in primates (Burns et al., 1973), the mechanism of its toxicity was found to require its conversion to 1-methyl-4-phenylpyridinium (MPP+) by the action of MAO (Chiba et al., 1984). This unleashed a flood of research seeking environmental or endogenous agents (see review by Tanner, 1989) that might mimic MPTP. Others focused on determination of how MPP+ caused cell death and how these mechanisms might explain the degeneration of striatal dopaminergic neurons in Parkinson’s disease.

12. MAO and neurotoxicity

As described above, H2O2 formation as a product of deamination was discovered over about 80 years ago, but it was assumed that the ubiquitous catalase would rapidly destroy this potentially toxic agent. This view has been questioned. The cycles of oxidative stress, free radicals
and the catalysis by iron in generating them, mitochondrial damage that has been demonstrated in Parkinson’s disease, the cascade of events that terminate in cell death, the relationship of genetic abnormalities in the a-synuclein or parkin (defects that are the bases of heritable forms of Parkinson’s disease) and the aldehydes formed from catecholamine deamination are all pieces of a puzzle that continues to challenge investigators. The mechanism(s) of neuronal degeneration remain poorly defined, but there are numerous active approaches to development of agents that target MAO (particularly the B form) and other potential participants in the events terminating in cell death (see e.g., Youdim and Riederer, 2004). The rationale for targeting multiple sites with a single drug that would prevent or retard the progression of neurodegenerative diseases has been championed by Moussa Youdim and his collaborators (see e.g., Youdim and Buccafusco, 2005).

13. Moussa Youdim and the future

Since his first paper describing solubilization of MAO, Moussa Youdim has contributed hundreds of papers dealing with many of these MAO-associated issues. He has been an imaginative scientist, inspired leader and highly valued collaborator in the pharmacological approaches to the alleviation, retardation the progress or prevention of the development of Parkinson’s and Alzheimer’s diseases. We wish him well in all his future endeavors, knowing that he will not shirk from trying to meet the new challenges.

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