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Semicarbazide-Sensitive Amine Oxidase: Biochemical and Physiological Properties

[Semikarbazid-Duyarlı Amin Oksiadaz: Biyokimyasal ve Fizyolojik Özellikleri]

Gülberk Uçar

Department of Biochemistry, Faculty of Pharmacy, Hacettepe University, 06100 Ankara, TURKEY

Yazışma Adresi
[Correspondence Address]

Hacettepe University, Faculty of Pharmacy,
Department of Biochemistry,
06100, Ankara, Turkey
Tel : +90-312-3118701
Fax : +90-312-3114777.
E-mail: gulberk@hacettepe.edu.tr

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ABSTRACT

The semicarbazide-sensitive amine oxidase (SSAO) is an enzyme widely distributed in many organs of mammals. The functional role of SSAO is not yet quite clear, but it is suggested that it plays roles in protection against exogenous amines, glucose transport, apoptosis, atherogenesis, cell adhesion, local generation of hydrogen peroxide as signal molecule, cross-linking of proteins and leucocyte trafficking. Plasma SSAO is reported to be elevated in diabetes mellitus, congestive heart failure, Alzheimer's disease and some inflammatory diseases. SSAO-mediated deamination of substrates produces formaldehyde and methylglyoxal, which have been proposed to be cytotoxic to the various tissues and might be involved in the pathogenesis of some disesases such as atherosclerosis, aging, cancer and skin disorders. Although SSAO has been known for years, its physiological and pathological implications are just beginning to be recognized. This review summarizes the molecular, functional and pathological properties of SSAO.

Key Words: Semicarbazide-sensitive amine oxidase (SSAO), oxidative deamination, xenobiotics, substrate, inhibitor.

ÖZET

Semikarbazid-duyarlı amin oksidaz (SSAO), memeli organlarında yaygın olarak bulunan bir enzimdir. SSAO'ın fizyolojik görevi henüz kesin olarak bilinmemekte, ancak enzimin dış kaynaklı aminlere karşı korunmada, glukoz taşınımında, apoptosiste, aterojenezde, hücre tutunmasında, bir sinyal molekülü olarak hidrojen peroksidin lokal oluşumunda, proteinlerin çapraz bağlanmasında ve lökosit trafiğinde rol oynadığı öne sürülmektedir. Plazma SSAO düzeyinin diyabette, doğuştan kalp yetmezliğinde, Alzheimer hastalığında ve bazı inflamatuar hastalıklarda yükseldiği bildirilmiştir. Bazı substratların SSAO-katalizli deaminasyonu sonucu oluşan formaldehit ve metilglioksal'ın sitotoksik etki gösterdiği ve ateroskleroz, yaşlanma, kanser ve deri bozukluklarının patojenezine katkıda bulunduğu ileri sürülmüştür. SSAO uzun yıllardan beri bilinmekle birlikte, enzimin fizyolojik ve patolojik etkinlikleri henüz tanınmaya başlanmıştır. Bu derleme, SSAO'ın moleküler, işlevsel ve patolojik özelliklerini özetlemektedir.

Anahtar Kelimeler: Semikarbazid-duyarlı amin oksidaz, oksidatif deaminasyon, ksenobiyotikler, substrat, inhibitör.

CONTENTS

1. INTRODUCTION

The oxidative deamination of endogenous and exogenous amines in mammals is catalyzed by a number of oxidases (1,2). Semicarbazide-sensitive amine oxidases (EC 1.4.3.6: amine:oxygen oxidoreductase (deaminating), SSAOs) are a group of enzymes containing copper and quinone and sensitive to semicarbazide (3,4). SSAO activity is found in a great variety of species from prokaryotes to eukaryotes, including human. The enzyme is shown to be present in cell membranes as tissue-bound form or located in the vascular system and in adipocytes as soluble form (5). Their physiological functions are yet not clear, but it has been postulated that SSAO may be involved in detoxifying xenobiotics, regulating glucose uptake, and effecting cell adhesion, leukocyte trafficking and angiogenesis (6-11). Increased plasma SSAO activities were reported in patients with diabetes, alcoholics, Alzheimer's disease, heart and vascular diseases (12-16). Although SSAO has been mostly regarded as being involved in the detoxification of amines, the products of the reaction are more toxic than the amine substrates themselves (17,18). Hydrogen peroxide (H_2O_2), formaldehyde and methylglyoxal, simultaneously formed during deamination of the substrates, such as methylamine and aminoaceton by SSAO, were reported to lead to increased oxidative stress, protein cross-linkage and cytotoxicity (16-20). Thus, SSAO may be responsible for vascular damage, atherosclerosis, diabetic complications, Alzheimer's disease and aging via these mechanisms.

The aim of the present review is to briefly overview the biochemical properties and physiological functions of SSAO and to discuss its possible role in certain diseases.

2. MOLECULAR PROPERTIES OF SSAO

Amine oxidases are key enzymes which are widely distributed in nature and play important roles in the metabolism of biogenic amines (21). Monoamine oxidase (MAO), a FAD-dependent amine oxidase, which plays an essential role in the oxidative deamination of biogenic amines such as serotonin, dopamine, adrenaline and also catalyzes the oxidation of xenobiotic amines has been extensively characterized (22), whereas, little is known about the structure and function of SSAO, copper-containing amine oxidase (Table 1). These two enzymes are distinct from each other with respect to their substrate specificities and inhibitor sensitivities (17,23).

In mammals, SSAO is located in many organs and tissues, most prominently in vascular smooth muscle, adipocyte, cartilage, gut, lung, liver, retina, kidney, placenta, pancreas and plasma. It is absent from the nerves and glial cells of brain, but present in the microvessels of brain and thus may contribute to the blood-brain barrier (24). However, it has been suggested that it may be associated with the nerves of dental pulp (25). The enzyme exists in tissue-bound and soluble forms, but there are wide species and tissue differences in SSAO activities (24). Tissue-bound SSAO contains a short intracellular domain, a single transmembrane domain and a long extracellular domain which includes the catalytic site (26). Plasma SSAO is accepted to be originated from the cleavage of membrane-bound form. The sources of plasma SSAO is still unclear, but it is suggested that it may be derived from liver, retina, placenta and bone tissues (24,27,28).

The mammalian SSAO (180,000 Da) is a dimeric, glycosylated protein which containes 1 mol of copper per subunit. Cu (II) in SSAO was reported to be essential for the double hydroxylation of a tyrosine residue of SSAO with an autocatalytical reaction that yields the 6-hydroxydopa (TOPA) cofactor and also for providing a positive charge in the active site (26,28). It was shown that mammals contain two genes encoding SSAO, plus a pseudo-gene. One gene encodes the tissue-bound SSAO, the other encodes only one form exists in retina (29).

3. SUBSTRATE SPECIFICITY OF SSAO

The physiological substrates of SSAO include aminoacetone, methylamine, 2-phenylethylamine (PEA),

Table 1. Amine oxidases

Amine oxidase superfamily	Enzyme	Some substrates
FAD-dependent	Monoamine oxidase A	Dopamine, noradrenaline, serotonin
	Monoamine oxidase B	Dopamine, phenylethylamine
	Polyamine oxidase	Spermine, spermidine
Cu-dependent	Plasma SSAO	Aminoaceton,methylamine, tyramine, benzylamine
	Tissue SSAO	Aminoaceton, methylamine, tyramine, benzylamine
	Diamine oxidase	Histamine, putrescine
	Lysyl oxidase	Peptide-bound lysine residues

tyramine and dopamine whereas benzylamine is a good non-physiological substrate for the mammalian SSAO (19,29). Although plasma SSAO usually has been termed as *"benzylamine oxidase"*, the physiological substrates of SSAO are accepted as aminoaceton, methylamine, 2-phenylethylamine, tyramine and dopamine (28-31). Most of the SSAO substrates are also oxidatively deaminated by MAO, but aminoacetone and methylamine are not MAO substrates (32). Serotonin (5-HT) is reported to be a good substrate for pig and human dental pulp SSAOs (25). SSAO also catalyses the oxidative deamination of a number of xenobiotics such as mescaline and anti-malarial drug, primaquine (33). Since the active site of SSAO is located in the extracellular domain (26,28), it seems that the enzme is involved in the inactivation of potentially toxic amines in both tissues and blood. In contrast, monoamine oxidases are intracellular enzymes located in the mitochondrial outer membrane (34) and they are responsible for regulation and metabolism of major monoamine neurotransmitters such as serotonin, adrenaline, nor-adrenaline and dopamine (2) (Figure 1).

It is diffucult to establish the substrate overlap between MAO and SSAO since tissue-bound SSAO activity posses wide species differences in specificities and amount of enzyme present (17,28,30) (Figure 2). The levels of tissue-bound and plasma forms of SSAO vary widely between species and there are also differences in substrate specificities between SSAOs from different mammalian sources (12,24). For instance, mescaline is oxidised more efficiently than benzylamine by pig plasma SSAO while human SSAO does not show any activity towards this substrate (35). Stereospecificity also is important for the substrate affinity of the SSAO forms: oxidation of benzylamine by plasma SSAO from ox, horse, porcine, rabbit and sheep involves abstraction of the pro-S hydrogen whereas SSAO from human aorta and plasma shows no stereospecificity in this respect (36,37). It has been suggested that the structure of the copper-containing active site of different SSAOs detect the substrate specificity (38). Variations in glycosylation of SSAO, which differ between tissues and species, also effect the substrate specificity of SSAO (39).

4. SSAO-CATALYZED OXIDATIVE DEAMINATION

As shown in below, SSAO catalyze the oxidative deamination of substrates containing an amine moiety linked to an unsubstituted methylene group, which may be aliphatic or aromatic in nature. These substrates include dopamine, b-phenylethylamine, benzylamine, kynuramine, tryptamine, methylamine, allylamine and aminoacetone (3,17). An aldehyde metabolite, hydrogen peroxide and ammonia are produced by the deamination of RCH_2NH_2 substrate.

$$RCH_2NH_2 + O_2 + H_2O \xrightarrow{\text{SSAO}} RCHO + H_2O_2 + NH_3$$

This reaction is a "ping-pong" reaction and can be divided into two separate half reactions as one reductive and one oxidative. In the first half reaction, the amine group

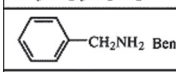
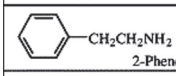
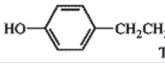
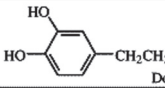
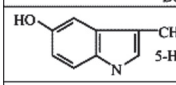
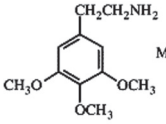
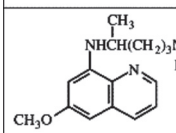
SUBSTRATES	COMMENTS
CH_3NH_2 Methylamine	Endogenous and xenobiotic. Not a substrate for MAO
$CH_2{=}CHCH_2NH_2$ Allylamine	Xenobiotic. Not a substrate for MAO. Highly toxic product
$CH_3{-}\overset{O}{\overset{\|}{C}}{-}CH_2NH_2$ Aminoacetone	Endogenous. Not a substrate for MAO
$CH_3(CH_2)_3CH_2NH_2$ *n*-Pentylamine	Xenobiotic. Also MAO-B substrate
 CH_2NH_2 Benzylamine	Xenobiotic Also MAO-B substrate
 $CH_2CH_2NH_2$ 2-Phenethylamine	Trace amine Also MAO-B substrate
 HO $CH_2CH_2NH_2$ Tyramine	Endogenous & xenobiotic Also MAO A & B substrate
 HO HO $CH_2CH_2NH_2$ Dopamine	Endogenous Also MAO A & B substrate
 HO $CH_2CH_2NH_2$ 5-Hydroxytryptamine	Substrate in dental pulp. MAO-A substrate
 $CH_2CH_2NH_2$ Mescaline CH_3O OCH_3 OCH_3	Xenobiotic. Also MAO substrate
 CH_3 $NHCH(CH_2)_3NH_2$ Primaquine CH_3O	Xenobiotic. Also MAO substrate

Fig. 1. Some known SSAO substrates (19, 25-34)

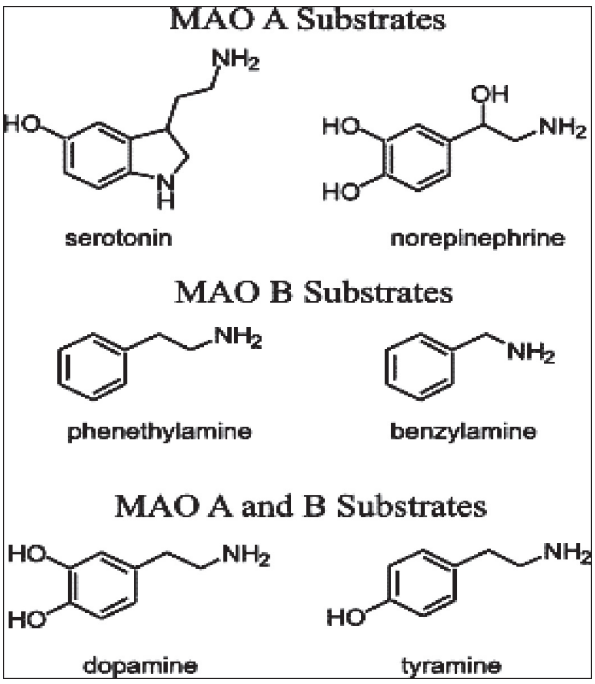


Fig. 2. Some known MAO substrates (17, 28, 30)

interacts with topa quinone co-factor (TPQ) in the active site and a Schiff base is produced. In the second half-reaction, the reduced TPQ is reoxidized by Cu^{2+} and O_2 under the H_2O_2 and NH_3 production (5):

$$E\text{-}CHO + RCH_2NH_2 \longrightarrow E\text{-}CH_2NH_2 + RCHO$$
$$E\text{-}CH_2NH_2 + O_2 + H_2O \longrightarrow E\text{-}CHO + H_2O_2 + NH_3$$

The membrane-bound SSAO is often characterized by its high affinity towards non-physiological amine, benzylamine, which is also a good substrate for MAO-B (40), indicating that SSAO and MAO overlap to some extent. However, SSAO is distinguished from MAOs by its insensitivity towards selective MAO inhibitors such as clorgyline, l-deprenyl and pargyline (41). It has been recently shown that there is a sequence designated as –Asn-X-Asp-Tyr-Tyr- around TPQ, where X corresponds to SSAO, plays a vital role in SSAO-catalyzed deamination of substrates (39). TPQ co-factor was belieived to be pyrroloquinoline quinone.

Methylamine and aminoaceton are readly deaminated by SSAO to yield methylglyoxal, formaldehyde, H_2O_2 and ammonia, both in vitro and in vivo (18,19,31,42).

$$CH_3NH_2 + O_2 + H_2O \xrightarrow{SSAO} HCHO + H_2O_2 + NH_3$$
Methylamine — Formaldehyde

$$CH_3COCH_2NH_2 + O_2 + H_2O \longrightarrow CH_3COCHO + H_2O_2 + NH_3$$
Aminoacetone — Methylglyoxal

$$CH_2{=}CHCH_2NH_2 + O_2 + H_2O \longrightarrow CH_2{=}CHCHO + H_2O_2 + NH_3$$
Allylamine — Acrolein

Methylamine was found in blood, urine and tissues of humans (20,43) and can be derived from deamination of adrenaline, creatine and creatinine (44).

Aminoaceton is endogenously derived from glycine or threonine (2,20). The aldehyde products of the SSAO reaction have attention in terms of their potential toxicity. These aldehydes may be oxidised to the corresponding carboxylic acid by aldehyde dehydrogenase or aldehyde oxidase or reduced to the corresponding alcohols by aldehyde reductases or alcohol dehydrogenase. However, formaldehyde produced by the oxidative deamination of methylamine is potentially toxic (43, 44). Since the formaldehyde produced would have to be transported into cells, such as erythrocytes for metabolism, this causes formaldehyde-induced toxicity in blood vessels (44).

Metabolism of xenobiotic allylamine by SSAO produces acrolein, which leads to vascular toxicity. It has been demonstrated that SSAO inhibition can prevent the SSAO-mediated vascular damage (45). It appears that this toxicity may result from the synergistic action of acrolein and H_2O_2, since the presence of catalase reduced the extent of the damage caused by allylamine oxidation (46).

Methylglyoxal cytotoxicity is resulted from its ability to cross-link of proteins and increased cross-linkage has been recognized to be involved in the aging process, which seems to be related to chronic vascular diseases (47).

H_2O_2 is a major reactive oxygen species, which is also generated in SSAO-catalyzed deaminations. H_2O_2 can be converted to toxic hydroxyl radical via the Fenton reaction and has been implicated in several diseases (48). Free radicals can be generated from formaldehyde in the presence of H_2O_2 under alkaline conditions, but it has been shown that in the presence of free amino group with formaldehyde and H_2O_2, however, excited formaldehyde and singlet oxygen are generated even under physiological conditions (49). It seems possible that SSAO-mediated oxidative stress may cause the oxidation of LDL and glycoxidation of proteins.

5. SSAO AND PATHOLOGICAL CONDITIONS

SSAO activity is found to be altered in a number of disease states, as summarized in Table 2. Plasma SSAO activity is increased in cardiac disease and in congestive heart failure (4,5,8,12,16,20,45). Atherogenesis is a complex process in which leisons formed at the blood vessels progress via fatty streaks, followed by formation of fibrous plaques and trombus, resulted in deposition of fibrin and plateletes. Atherogenesis involves endothelial disfunction, smooth muscle proliferation and subsequ-

Table 2. Altered SSAO activity in some diseases

Disease	Increased	Decreased
Cardiac disease (plasma)	+	-
Congestive heart disease (plasma)	+	-
Diabetes typeI (human plasma)	+	-
Diabetes type II (human plasma)	+	-
Diabetes (rat kidney)	+	-
Diabetic retinopathy (plasma)	+	-
Diabetic atherosclerosis (plasma)	+	-
Diabetic nephropathy (plasma)	+	-
Hypertension (plasma)	+	-
Alzheimer's disease (cerebral blood vessels)	+	-
Burns(plasma)	-	+
Cancer (solid tumour) (tumour tissue)	-	+
Cancer (breast) (plasma)	-	+
Inflammatory liver disease (plasma)	+	-
Kidney transplant rejection (plasma)	+	-
Pre-eclampsia (plasma)	-	-
Stroke (plasma)	-	-

ently, disruption. Hypotheses regarding the mechanism of atherogenesis include oxidative stress, hypercholesterolemia, LDL, LDL receptors, Apo-E, advanced glycation, cytokines, hormones, abnormal lipid metabolism, etc. It has been suggested that SSAO-mediated deamination is involved in atherogenesis and vascular disorders and selective SSAO inhibitors can prevent such toxicity (44,46). Formaldehyde and H_2O_2, derived from SSAO-catalyzed methylamine deamination, or increased availability of substrates have been proposed to cause chronic stress; damage endothelial cells; induce protein cross-linkage of structural proteins, such as collagen; increase rigidity of blood vessels and lead to vascular dysfunction (17,46). Allylamine is reported to cause extensive and progressive vascular and myocardial lesions similar to that seen in atherosclerosis and this vascular toxicity of allylamine can be prevented by the SSAO inhibitor semicarbazide (13,46).

SSAO expression was shown to be increased in cerebral blood vessels of subjects with Alzheimer's disease (13,-30,50). Aldehydes produced by SSAO-mediated deamination of methylamine and aminoacetone were suggested to cause intra- and intermolecular protein cross-linkages and b-amyloid formation, deposition and subsequently plaque formation in the compartments adjacent to the cerebrovessels (51). Since SSAO-mediated generation of formaldehyde can also lead to cytotoxicity, which induces inflammation and release of more SSAO, it has been postulated that increased SSAO-mediated reaction may be chronically involved in the pathogenesis of vascular dementia (51).

Already in the 1960s it was demonstrated that plasma SSAO activity was elevated in patients with diabetes mellitus (4,5,8,10,14) and recently it was shown that this increase in activity is correlated to the degreee of vascular damage, nephropathy, and retinopathy (18,52,-53). Increased SSAO activity has been observed in sheep and rat plasma and rat kidney in experimental diabetic models (54). These observations have been further confirmed in both Type I and II diabetics (7,8,10,14,52). Formaldehyde and H_2O_2, derived from SSAO-mediated methylamine deamination, were found to be responsible for the diabetic complications (5,8,14,18,53). SSAO is known to be selectively located in tissues which are vulnerable to diabetic complications and it can be released into the blood stream from damaged SSAO-rich tissues. Interestingly, the sequence of another protein called VAP-1 has been found to be identical to SSAO which has been shown to be capable of deaminating amines. VAP-1 induces cell adhesion and regulates lymphocyte trafficking and it was reported that it is involved in granulocyte extravasation and inflammation (9,55). Thus, it seems possible that this protein is the same protein as SSAO and increased expression of it as a response to inflammation leads to enhanced levels of toxic aldehydes in blood, increased oxidative stress and cause vascular injury and inflammation (55).

SSAO has been found to be involved in the regulation of GLUT-4 in isolated rat adipose cells (7). Benzylamine, an SSAO substrate, caused a marked stimulation of glucose uptake in adipocytes and this induction was blocked by catalase and SSAO inhibitors suggesting that H_2O_2 production resulted from SSAO-mediated deamination plays a crucial regulatory role in this process (7). SSAO has been claimed to be an important role in glucose uptake in adipocytes since SSAO-mediated deamination mimics insulin-like actions such as signal transduction, lipid metabolism and differentiation of adipocytes (56).

6. ALTERNATIVE FUNCTIONS OF SSAO

Although products of SSAO-catalyzed deaminations are potentially toxic, they may have important roles in some certain physiological conditions. Hydrogen peroxide is known to mimic the effects of insulin and induces a recruitment of intracellular GLUT-4 receptors to cell surface, stimulates glucose uptake. SSAO substrates have been shown to stimulate glucose transport and SSAO inhibitors abolish completely this effect (7). Since activation of glucose transport was reversed by catalase, it was suggested that H_2O_2 plays an important role in this process (57).

SSAO activity appears to play a significant role in the development of some cell types. Methylamine and other SSAO substrates were shown to induce maturation of adipocytes in a dose-dependent manner and since this effect was prevented by SSAO inhibition and by treatment with antioxidants, it was suggested that H_2O_2 formation plays a key role (56,58).

SSAO activity also plays an important role in extracellular matrix deposition and maintenance in vascular smooth muscle and inhibition of SSAO is resulted in aberrations in collagen and elastin deposition by heart smooth muscle cells (59).

VAP-1, which possess SSAO activity, is reported to support the adhesion of lymphocytes to endothelial cells and mediates lymphocyte re-circulation and to be involved in inflammatory conditions (55). VAP-1 has been shown to support sialic-acid dependent adhesion under shear stress and to mediate tethering to the tumour endothelium in human heptacellular carcinoma of T-cells (60). In mature adipocytes, SSAO is located in caveolae with CD36 and the scavenger lipoprotein receptor as major proteins, and may be involved in lipid transport (61).

7. SSAO INHIBITORS

Today, there are no selective and potent inhibitors of human SSAO. Semicarbazide and cyanide are both

SSAO inhibitors that also inhibit some other enzymes. Some inhibitors of MAO, such as MDL 72145 ((E)-2-(3',4'-dimethoxyphenyl)-3-fluoroallylamine), originally developed as antidepressants, have been reported also to inhibit SSAO irreversibly (62). However, it is also a potent inhibitor of MAO-B and also affects MAO-A activity. Substituted b-chloroallylamines are weak inhibitors of MAO and MDL 72274 [(E)-b-phenyl-3-chloroallylamine] shows high potency and selectivity for SSAO in vitro, compared with its activity against MAO (63) (Figure 3). An inhibitor with high selectivity for pig plasma SSAO, named as B24, was synthesized as SSAO substrate, but appeared to be a highly potent SSAO inhibitor (35).

It has been shown that the primary aromatic monoamines with a single methyl substituent on a-carbon atom adjacent to amino group, are SSAO inhibitors with inhibitory properties of MAO, such as mexiletine and amphetamine (5). Amiflamine [FLA 336(+)], its enantiomer [FLA 336(-)] and its metabolites [FLA 788 (+), FLA 668 (+)] inhibit MAO-A and SSAO (64) (Figure 4). D,L-a-methylbenzylamine and its enantiomers D- and L-form of a-methylbenzylamine, are found to be SSAO and MAO-A inhibitors (65). 2-Bromoethylamine was shown to be a potent and selective SSAO inhibitor (66).

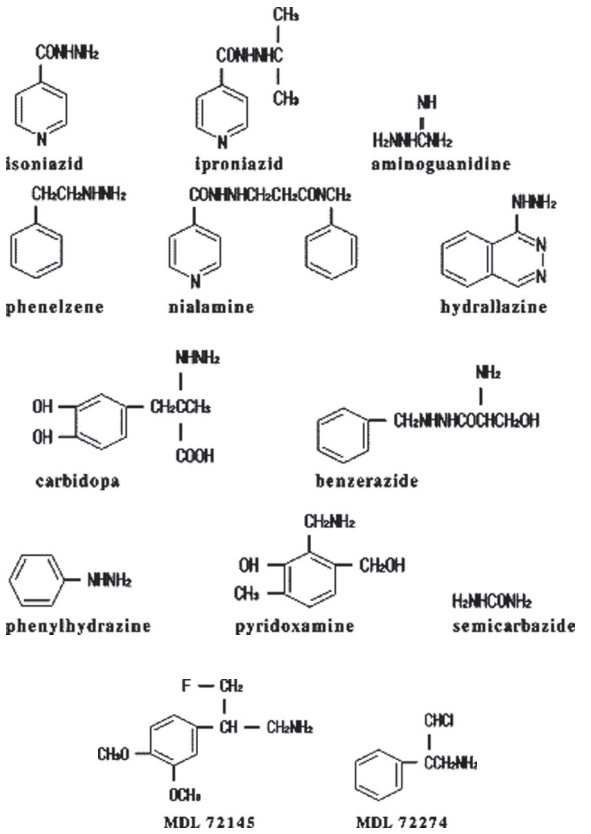


Fig. 3. Some hydrazine and halloamine derivatives presented as SSAO inhibitors.

Hydrazine derivatives are also SSAO inhibitors (Figure34). Highly selective SSAO inhibitor semicarbazide has already been introduced and detected as a useful compound for distinguishing SSAO from MAO in tissues (67). Some irreversible and non-selective MAO inhibitors, such as phenelzine, phenylhydrazine, hydrallazine, aminoguanidine, iproniazide, isoniazide, nialamide, benzerazide and carbidopa, are thought to be possible SSAO inhibitors because of their abilities to bind to FAD in MAO which is outside of the substrate binding site (Figure 3). Hydrallazine is a peripheral vasodilator used as anti-hypertensive and irreversible and and partially time-dependent inhibitor of SSAO whereas phenylhydrazine is the potent irreversible SSAO inhibitor (68); aminoguanizine is used to prevent diabetic nephropathy (69).

Procarbazide and its metabolite monomethylhydrazine also appears to be highly selective for SSAO (70).

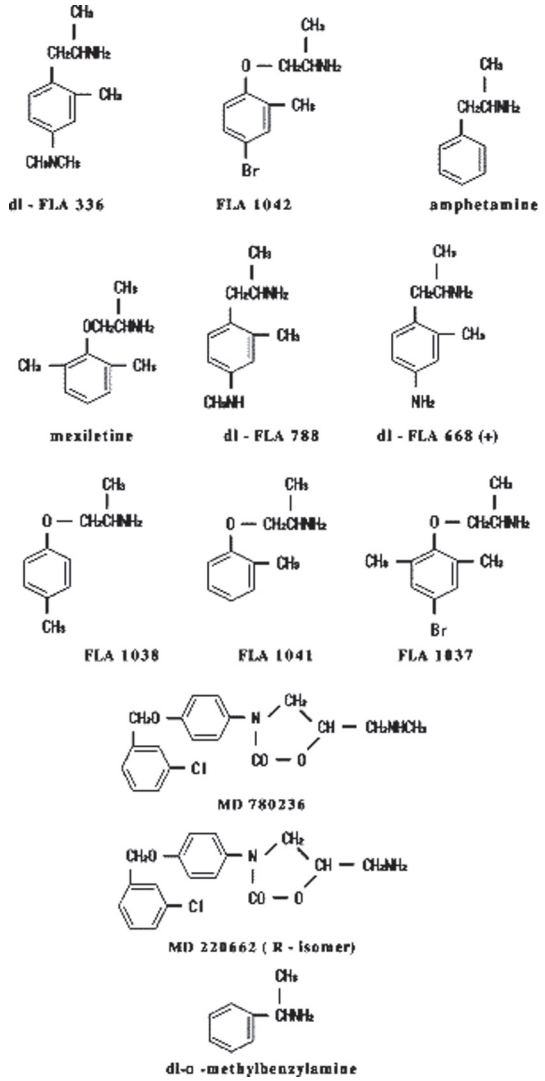


Fig. 4. Some a-methylsunstituted amines designed as SSAO inhibitors.

8. CONCLUSION

SSAO was discovered over three decades ago during investigation of MAO. Little is known about its molecular structure and exact physiological functions in mammals, but it can be assumed that it may have several and competitive functions. A considerable amount of research evidence suggest that SSAO plays a role in vascular diseases, diabetes and Alzheimer's disease. Increased knowledge regarding the structure of SSAO can facilitate the development of inhibitors with high potency and selectivity.

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