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Semicarbazide-sensitive amine oxidase (SSAO): from cell to circulation

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Summary

Semicarbazide-sensitive amine oxidase (SSAO) is a multi-functional enzyme widely present in nature. It converts primary amines into their corresponding aldehydes, while generating H_2O_2 and NH_3. In mammals, SSAO circulates in plasma, while a membrane-bound form (often referred to as vascular adhesion protein-1, VAP-1) is found in many tissues and organs, especially in adipocytes and vascular endothelial and smooth muscle cells. In recent years, evidence has been accumulating that SSAO has a role in protein cross-linking, formation of advanced glycation end-products, atherogenesis, glucose regulation and leukocyte extravasation at inflammation sites. Plasma SSAO is quite stable in healthy adults, but is elevated in diabetes mellitus (both type 1 and type 2), congestive heart failure and liver cirrhosis. The origin of circulating SSAO remains unclear, but recent evidence from clinical studies and from (transgenic) animal studies suggests that adipocytes and vascular endothelial cells may be the most important source. Studies with cell cultures show evidence that the membrane-bound SSAO can be split off from the cells, thus giving rise to the (truncated) circulating form of SSAO. In some pathological conditions the diseased organ may be the main source of the elevated plasma SSAO. Little is known as yet about the regulation of plasma SSAO. Thyroid hormone appears to play a (modest) role in this respect. Further evidence from clinical, animal and cell-culture studies, helped by the new availability of selective SSAO inhibitors, is needed to shed more light on the question of the regulation of SSAO.

key words: **semicarbazide-sensitive amine oxidase • adhesion protein • adipocytes • vascular smooth muscle cells • diabetes mellitus • congestive heart failure • liver cirrhosis • thyroid hormone**

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BACKGROUND

Semicarbazide-sensitive amine oxidase (SSAO; E.C.1.4.3.6) is a common name for a group of copper-containing amine oxidases widely present in nature in microorganisms, plants, and animals, including man [1,2]. Biochemically, SSAO converts primary amines into the corresponding aldehydes, generating at the same time hydrogen peroxide and ammonia. In man, methylamine and aminoacetone have been reported to be natural substrates, leading to formation of the toxic products formaldehyde and methylglyoxal, while exogenous compounds such as benzylamine and allylamine are ready substrates for the enzyme. Depending on the species concerned, other amines, such as serotonin, dopamine, tryptamine etc, can also be converted. SSAO has a different inhibitor pattern than the monoamine oxidases MAO-A and -B, which catalyze the same reaction, although not always with the same substrates. Methylamine and aminoacetone, for example, are not substrates for MAO-A or -B. The name SSAO was coined because semicarbazide is a good inhibitor of the enzyme, through reaction with the functional carbonyl group of SSAO, a topaquinone entity formed posttranslationally by modification of a tyrosine unit in the amino acid chain [3].

SSAO is encountered both in a circulating form in plasma, and as a membrane-bound form with a short cytoplasmic tail, a single transmembrane part, and a large, highly glycosylated, extracellular domain containing the active center. Membrane-bound SSAO has been found to be identical to the vascular adhesion protein known as VAP-1 [4].

The functional role of SSAO remains rather unclear, and is probably manifold. It may protect against the negative effects of endogenous or exogenous amines by enzymatic transformation, which, however, may sometimes lead to even more toxic products than the original amines. This is the case, for example, with allylamine, which in itself is not very toxic, while reaction with SSAO forms the highly potent cardiotoxic substance acrolein [5]. The reactive aldehydes formed by SSAO from methylamine and aminoacetone are implicated in the cross-linking of proteins, which is sometimes useful, but may also lead to advanced glycation end products [6–10]. Experimental evidence also seems to indicate a role for SSAO in apoptosis and atherogenesis [11,12]. The (local) production of hydrogen peroxide, a signaling molecule, by reaction of SSAO with a substrate, may be important in specific circumstances. This is the case, for example, in the role SSAO plays in promoting glucose transport into the cells by recruitment of the GLUT4 transporter to the cell membranes, a process that can be blocked by the hydrogen peroxide scavenger catalase [13]. The VAP-1 side of SSAO is responsible for leukocyte trafficking at inflammation sites [4].

(Patho)physiology

In humans, SSAO can be found in most organs and tissues, especially in vascular endothelial and smooth muscle cells, adipocytes and the umbilical cord. It also circulates in plasma, where its activity normally appears to be well-regulated and stable. In healthy adults, the SSAO activity remains within the range of 150–550 mU/l until about 60 years of age, when it slowly starts increasing (Figure 1). Interestingly, in children from birth to age 16, plasma SSAO activity is substantially higher (Figure 1).

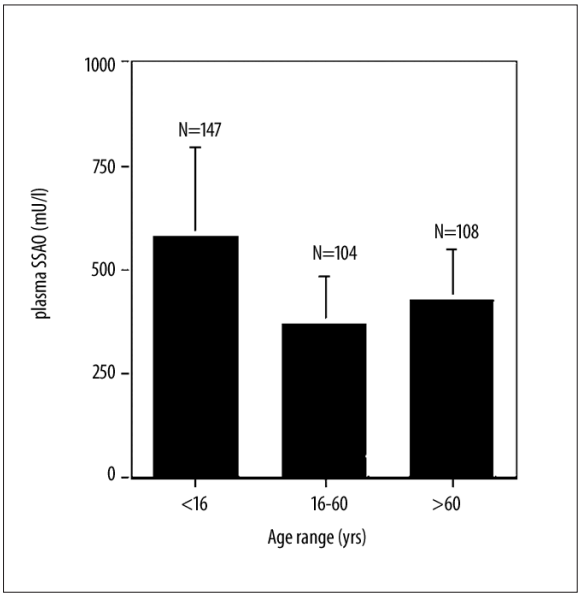

Figure 1. Normal plasma SSAO activities (mean ±SD) in different age ranges. N – number of subjects.

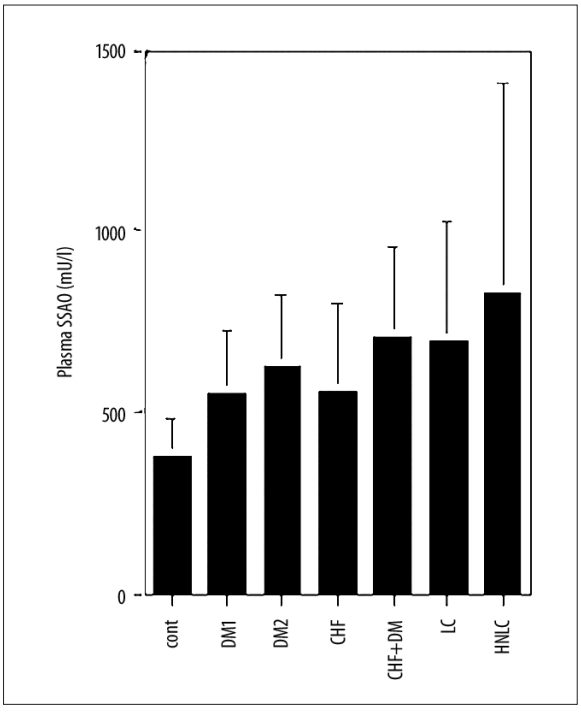

Figure 2. Plasma SSAO activities (mean ±SD) in controls and patients with various diseases. Cont.– controls; DM1 – diabetes mellitus type 1; DM2 – diabetes mellitus type 2; CHF (+DM) – congestive heartfailure (+diabetes mellitus); (HN)LC – (hyponatriemic) liver cirrhosis.

In some pathological conditions, plasma SSAO activities have been found to be significantly elevated [14–19]. This is the case in several pathologies (Figure 2):

1. diabetes mellitus, both type 1 and type 2 (DM1 and DM2);
2. congestive heart failure (CHF);
3. liver cirrhosis.

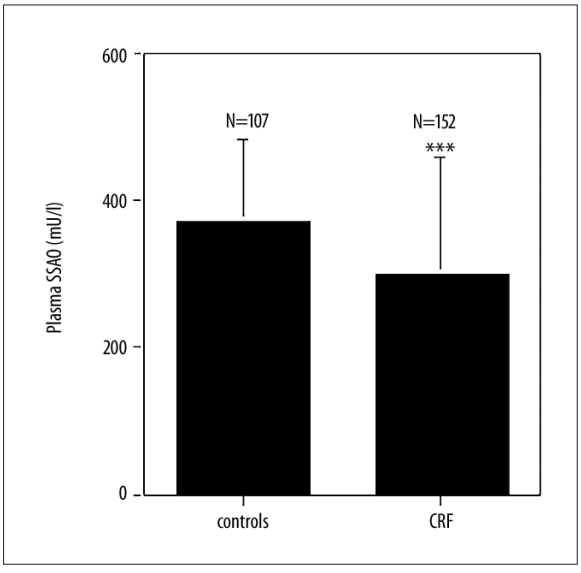

Figure 3. Plasma SSAO activities (mean ±SD) in controls vs. patients with chronic renal failure (CRF). N – number of subjects. *** p<0.0001 CRF vs. controls.

Table 1. Effects of medication on plasma SSAO activities.

Disease	Medication	SSAO-start	SSAO-end
		(mean ±SD, mU/l)	
Heart failure	Carvedilol	521±193	544±231
Atherosclerosis	Statins	466±163	459±161
Hep. C virus	Glycyrrhizine	489±175	473±125
Colitis ulcerosa	Nicorette	381±104	395±105
Hypertension	Enalapril	432±97	439±105
	+ Candesartan		453±100
Diabetes type 1	Enalapril		736±148
	+ Candesartan		743±148
Diabetes type 2	Pioglitazone	588±116	583±121
	ACE-inhibitor		697±193
	+ARB		703±186

ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blocker.

In DM, the elevation is greater, with increasing occurrence of complications; the elevation is already present in children at first diagnosis of DM1 [15]. In CHF, also, elevations in plasma SSAO reflect the severity of the disease, as shown by the association of plasma SSAO activity with survival [20]. In liver cirrhosis, the elevated activities of SSAO are probably a reflection of the increased VAP-1 expression at the site of inflammation [19]. This may be specific for liver inflammation, since other inflammatory diseases, such as colitis ulcerosa and Sjøgren's disease, are not accompanied by elevations in plasma SSAO [2].

Mainly experimental data seem to indicate possible roles for and changes in SSAO activity in various pathophysiological conditions, such as stroke and Alzheimer's disease, but no firm data from human studies are available as yet.

Decreases in plasma SSAO are less commonly found, and should be looked at with caution. Although this is not widely known, some commonly used drugs are good inhibitors of SSAO, e.g. benserazide and carbidopa (Parkinson's disease), isoniazide (tuberculosis), hydralazine (hypertension), aminoguanidine (DM), imipramine (depression) [2]. Very low activities have been reported in children born with hernia diaphragmatica, which normalizes after successful surgical correction [2]. In 152 patients with chronic renal failure on hemodialysis, plasma SSAO activity was found to be significantly lower than in 107 healthy controls (300±157 vs. 370±112 mU/l, p<0.0001, Figure 3). The actual decrease is probably even greater, since quite a few of these renal failure patients will also have DM or CHF, which would tend to increase plasma SSAO activities. This finding contrasts with the report of increased plasma SSAO (=soluble VAP-1) in patients with end-stage renal failure, which normalizes after transplantation [21].

Clues for sources

There is a great lack in knowledge about the origin of the circulating SSAO and its relation to the membrane-bound form, which severely hampers investigations into the regulation of plasma SSAO. It has been suggested that sheddases cut the membrane-bound SSAO at the extracellular stalk region, and that the circulating SSAO is thus a truncated version, a process known to occur for many membrane-bound proteins [19,22,23]. The possibility of different genes or different combinations of encoding regions, however, cannot be excluded. There is some experimental evidence that indeed metallo-proteases are able to cut off the extracellular part of membrane-bound SSAO in cultured adipocytes, since the metalloprotease inhibitor batimastat prevented release of SSAO from adipocytes [24]. We ourselves have also found that both N-ethylmaleimide, a general shedding-inducing agent, as well as phorbolesters which induce shedding via PKC, are able to stimulate release of SSAO from adipocytes. Recent experiments with transgenic and knockout mice strongly suggest that the membrane-bound VAP-1 was the only source for plasma SSAO activity in these animals [25]. Whether the same goes for other tissues and cells and other species is not yet known. Probably circulating SSAO is thus indeed the truncated form of membrane-bound SSAO, but definite proof is still lacking.

In a few instances it has been shown that elevated plasma SSAO activities can be brought down to normal levels again. This was reported to be the case in two patients with severe liver cirrhosis, whose highly elevated plasma SSAO became completely normalized after liver transplantation [2]. This would suggest that at least in these cases the (diseased) liver was the source of the elevated SSAO; however, an alternative explanation, that an unknown substance from the diseased liver induces production of SSAO elsewhere or regulates its clearance, cannot be completely ruled out. A similar case has been reported, a pregnant woman with diabetes insipidus and strongly elevated plasma SSAO throughout pregnancy [2]. After birth of the baby, the plasma SSAO activity of the mother rapidly normalized within two days, suggesting that in this case the umbilical cord

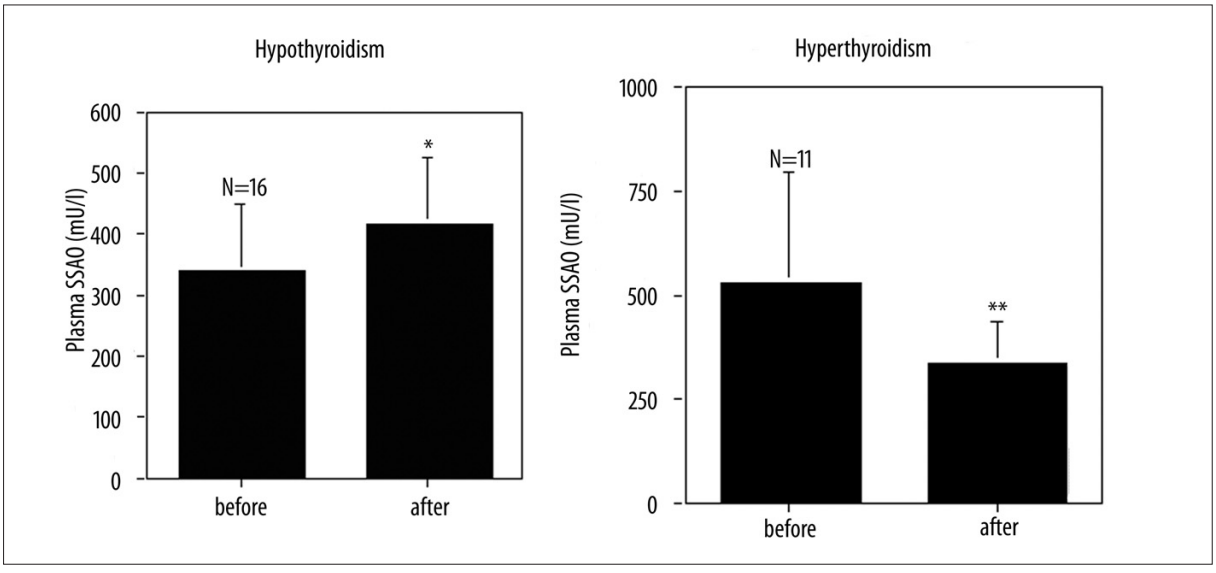

Figure 4. Plasma SSAO activities (mean ±SD) in patients with hypothyroidism and hyperthyroidism before and after treatment. N – number of subjects. * p=0.020 ** p=0.011.

and placenta were the origin of the increased SSAO (the baby had normal plasma SSAO for its age). Recent studies in mice suggest that plasma SSAO originates from both endothelial cells and adipocytes [25].

In view of the possible relation between vascular sclerotic diseases and plasma SSAO, we are presently investigating whether surgical correction of atherosclerotic lesions influences plasma SSAO activities. Preliminary data seem to indicate that, indeed, surgery for coronary artery disease can lead to a lowering of elevated plasma SSAO activities, suggesting that possibly the heart can also be a source of plasma SSAO.

Clues for regulation

An interesting question is whether drugs known to be beneficial in various syndromes, involving elevated or normal plasma SSAO, have effects on plasma SSAO. Some results from studies along these lines are given in Table 1. So far, no effects of any drug on plasma SSAO activity are proven. Once plasma SSAO is elevated, the drugs investigated do not seem to be able to reverse the increase in production, despite favorable results on progression of the disease.

Studies on associations of plasma SSAO with other systems involved in a particular disease may give clues as to common factors involved in their regulation. In preeclamptic patients no association with SSAO could be found in the known endothelial dysfunction markers von Willebrand factor and ED1 fibronectin [26]. In patients with DM1, plasma SSAO has been reported to correlate inversely with circulating insulin concentrations, suggesting that insulin regulates plasma SSAO [23]. We have recently found, also in patients with DM1, indications for associations between plasma SSAO and plasma components of the renin-angiotensin system, notably angiotensin-converting enzyme activity, which might point to a common regulatory factor. This is presently under further investigation.

Thyroid hormone is a well-known transcription factor, which is also a component of the culture medium used for maturation of pre-adipocytes into adipocytes. We have therefore investigated plasma SSAO in patients with hypothyroidism and hyperthyroidism, both when they had the disease and after appropriate treatment, when they were again euthyroid. The results (Figure 4) indicate that plasma SSAO is relatively low in patients with hypothyroidism, and increases when the euthyroid state is reached, while plasma SSAO is relatively high in patients with hyperthyroidism, and decreases when the euthyroid state is reached. This suggests that thyroid hormone does play a (moderate) role in the regulation of plasma SSAO.

The involvement of TNF-α in the regulation of SSAO has been described [24,27]. However, an important clue for the regulation of plasma SSAO, which is the fact that children under 16 years of age have much higher activities than subjects above the age of 16, has so far not been pursued.

Final remarks

Although considerable progress has been made in the past several years in unraveling the role and function of the enigmatic SSAO/VAP-1 molecule, its regulation, and its origin, much remains to be resolved. Clues obtained from clinical studies, combined with experimental work in cell cultures, may be helpful in this respect, as are animal studies with or without new molecular biological techniques. Care should be taken, however, in extrapolating results from animal studies to man, in view of the huge differences, especially in plasma SSAO activities between different species. Now that specific SSAO inhibitors are becoming available, we can expect rapid progress in the near future in our knowledge on the many facets of this interesting, so far little known enzyme/protein and its various roles in human physiology and pathophysiology.

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