Semicarbazide-sensitive amine oxidase and mortality in chronic heart failure

See page 1859 for the article to which this Editorial refers

A 5-year follow-up clinical investigation, as reported in this issue, has shown that mortality in patients with chronic heart failure is significantly increased in the subgroup of patients with higher serum semicarbazide-sensitive amine oxidase (SSAO) activity than in those with low SSAO activity[1]. This intriguing finding not only suggests that serum SSAO could become an independent prognostic marker for chronic heart failure, but it also raises the interesting notion of a potential involvement of SSAO-catalyzed deamination in the pathogenic process related to the morbidity and mortality of patients suffering with cardiovascular disorders.

SSAO is an enzyme, or group of enzymes, residing predominantly in the plasma membrane of endothelial, vascular smooth muscle and adipose cells[3]. The enzyme contains copper and 6-hydroxydopa quinone (TOPA) as cofactors. Therefore, hydrazine compounds, such as semicarbazide, are generally potent at inhibiting SSAO activity. This is distinctly different from the well-known monoamine oxidases, which are mitochondrial flavine-containing enzymes. SSAO was initially found capable of deaminating benzylamine and was thus called benzylamine oxidase. However, benzylamine is not present endogenously. Methylamine and aminoacetone have now been established as the endogenous substrates for SSAO. This discovery has stimulated vigorous research of the enzyme.

The physiological function of SSAO was initially thought to be simply to detoxify xenobiotic amines. Recently, SSAO-mediated deamination has been shown to be co-localized with GLUT-4 transporter in adipocytes. The hydrogen peroxide generated from SSAO-mediated deamination was found to be involved in the regulation of glucose transport[3]. It was also suggested that SSAO might play a role in connective tissue matrix development and maintenance and specifically the development of normal elastin in vascular smooth muscle cells[4]. Interestingly, totally independent research has revealed that the primary structure of a protein called VAP-1 (vascular adhesion protein-1) is identical to that of SSAO[5]. VAP-1 is also capable of deaminating amines. VAP-1, which contains polysialic acid, induces cell adhesion and regulates lymphocyte trafficking. It would be intriguing to know whether or not the dual functions of this protein act in a concerted fashion. VAP-1 level is up-regulated during certain types of chronic inflammation[6]. Formaldehyde is a well-known potent inflammatory agent, and yet it is a deaminated product of methylamine as catalyzed by SSAO.

The first observation of the association of SSAO with damage to the heart followed from studies of a cardiovascular toxin, allylamine. Allylamine is an industrial chemical and is known to cause extensive and progressive vascular and myocardial lesions in several mammalian species. Allylamine (CH\textsubscript{2}=CHCH\textsubscript{2}NH\textsubscript{2}) is actually converted by vascular SSAO to acrolein (CH\textsubscript{2}=CHCHO), an extremely toxic agent[7]. This vascular toxicity of allylamine could, therefore, be completely prevented by selective SSAO inhibitors as shown in experimental animals.

Unlike allylamine, methylamine and aminoacetone are present endogenously. Deamination of methylamine and aminoacetone leads to the production of...
formaldehyde and methylglyoxal, respectively, along with $\text{H}_2\text{O}_2$ and ammonia:

$$\text{CH}_3\text{NH}_2+\text{O}_2+\text{H}_2\text{O} \xrightarrow{\text{SSAO}} \text{HCHO}+\text{H}_2\text{O}_2+\text{NH}_3$$

$$\text{CH}_3\text{CO}\text{CH}_2\text{NH}_2+\text{O}_2+\text{H}_2\text{O} \xrightarrow{\text{SSAO}} \text{CH}_3\text{COCHO}+\text{H}_2\text{O}_2+\text{NH}_3$$

All of these metabolic products are well known to be very reactive and toxic.

Methylamine, in the presence of SSAO, has been shown to be toxic to human endothelial cells\[8\]. Selective SSAO inhibitors can protect these endothelial cells against SSAO/methylamine induced damage. Administration of carbon-14 labelled methylamine induces the formation of long-lasting radioactively labelled residues, which have been identified as formaldehyde–protein adducts. Such a finding is not surprising, since methylamine is rapidly catabolized by SSAO, and formaldehyde is an extremely reactive chemical. It interacts with monoamines or amides to form methylene bridges and produces irreversibly covalently cross-linked complexes with proteins and with single stranded DNA. Chronic administration of methylamine increases albuminuria and fatty streaks in C57BL/6 mice fed with high cholesterol diet.

Methylglyoxal, as derived from the deamination of aminoacetone, also stimulates protein cross-linkage and causes cytotoxicity\[9\]. The methylglyoxal level has been found to be significantly higher in diabetic patients. Advanced glycation and aggregation of proteins are related to chronic vascular disorders, which are very important pathogenic factors in diabetic complications. Toxic aldehydes, such as formaldehyde and methylglyoxal, can induce protein aggregation, which could be involved in vascular disorders and accelerate the ageing process. Diabetes has been considered to be an accelerated ageing process.

It was reported four decades ago that serum SSAO activity is increased in diabetic patients\[10\]. This finding has recently been confirmed in different laboratories\[11,12\]. An elevated level of serum SSAO was detected in both type-I and type-II diabetes mellitus. SSAO is also positively correlated with the severity of diabetic retinopathy\[13\]. Increased serum and kidney SSAO activity have also been demonstrated in animal models of diabetes. It was proposed that increased SSAO-mediated production of toxic aldehydes initiates vascular damage and subsequent angiopathy, which is probably the primary cause of diabetic complications\[8\]. Recently a significant increase of serum SSAO activity was also found in association with chronic heart failure\[14\], atherosclerosis and obesity\[12\]. Mouse strains that are vulnerable to atherosclerosis exhibit significantly higher SSAO activity as well as methylamine turnover than strains resistant to atherosclerosis\[15\]. Rabbits also easily develop atherosclerotic lesions, if fed a cholesterol rich diet. They exhibit a serum SSAO and deamination rate of methylamine several folds higher than rodents and human.

Increased SSAO-mediated deamination seems, at least in part, to be involved in atherogenesis and vascular disorders. This is summarized in the scheme in Fig. 1.

Both formaldehyde and methylglyoxal are capable of inducing protein aggregations and enhancing advanced glycation. This will alter functional and structural proteins, which can initiate injury to blood vessels, subsequently leading to atherosclerosis. Hydrogen peroxide increases oxidative stress and is also well known to be related to atherogenesis. SSAO-catalyzed deamination may enhance oxidative modification of the LDL structure, which could also
be due to vascular damage. In light of the above it is reasonable to propose that a strategy to reduce SSAO-mediated reactions may reduce the risk of angiopathy.

It is unclear how serum SSAO activity is increased in diabetic, cerebral infarct or atherosclerotic patients. It could be a result of compensatory up-regulation (i.e. in response to increased substrate concentrations), or it may be a consequence of vascular damage caused by the illness, i.e. SSAO is released into the blood stream from damaged SSAO-rich tissues, such as vascular smooth muscle cells. Such an increase of SSAO-mediated deamination (i.e. of methylamine and/or aminoacetone) would increase toxic aldehyde levels in blood, enhance oxidative stress and cause more vascular injury in the blood vessels. The vascular injury could produce more SSAO leakage and so an escalating cytotoxic cycle contributing towards angiopathy would ensue. The finding of a reduced survival rate in heart patients possessing high serum SSAO activity\(^{[1]}\) seems to be consistent with this SSAO hypothesis. High serum SSAO may be a marker of damage to vasculatures as well as a factor actively involved in the deterioration of the vasculatures. Clearly, the potential involvement of SSAO-mediated deamination in cardiovascular morbidity and mortality warrants further investigation.

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**References**