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Semicarbazide-sensitive amine oxidase (SSAO) and its possible contribution to vascular damage in Alzheimer's disease

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Summary One of the key pathological features of the progressive neurodegenerative disorder Alzheimer's disease (AD) is cerebral amyloid angiopathy (CAA). CAA is present in most cases of AD, and it is characterized by the deposition of β-amyloid (Aβ) in brain vessels, inducing the degeneration of vascular smooth muscle cells and endothelial cells. Herein we report that semicarbazide-sensitive amine oxidase (SSAO) is overexpressed in cerebrovascular tissue of patients with AD-CAA, and that it colocalizes with β-amyloid deposits. This over-expression correlates with high SSAO activity in plasma of severe AD patients. In addition, we have observed that the catalytic activity of SSAO is able to induce apoptosis in smooth muscle cells *in vitro*. Taken together, these results allow us to postulate that SSAO may contribute to the vascular damage associated to AD.

Keywords: β-Amyloid, Alzheimer's disease, cerebral amyloid angiopathy, formaldehyde, hydrogen peroxide, methylamine, semicarbazide-sensitive amine oxidase

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
AGE	advanced-glycation end products
CAA	cerebral amyloid angiopathy
SSAO	semicarbazide-sensitive amine oxidase
VAP-1	vascular-adhesion protein 1

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system, associated to cognitive impairment and dementia. β-Amyloid (Aβ) accumulation produces the senile plaques in the brain parenchyma characteristic of AD and the vascular deposits of cerebral amyloid angiopathy (CAA). CAA is present in most cases of AD and it is characterized by the deposition of Aβ in the tunica media and adventitia of leptomeningeal vessels and intracortical microvessels, thus producing the degeneration of vascular smooth muscle cells and endothelial cells (Vinters et al., 1988). The fact that AD and cerebrovascular diseases share risk factors supports the common view that there is a link between vascular degeneration and AD. It has been suggested that the accumulation of Aβ in the vessel wall causes the functional deterioration of the blood brain barrier, which is essential for the correct transport and clearance of Aβ from parenchyma (Deane et al., 2004; Zlokovic, 2005).

Semicarbazide-sensitive amine oxidase [E.C.1.4.3.6, amine:oxygen oxidoreductase (deaminating) (copper-containing), SSAO], also known as vascular adhesion protein-1 (VAP-1) (Salmi and Jalkanen, 1992), constitutes a large family of enzymes present in almost all mammalian species studied. SSAO is associated with cell membranes, and it is also present as a soluble form in blood plasma (Precious and Lyles, 1988; Lyles, 1996). The physiological role of SSAO is still far from clear. It is considered as a multifunctional enzyme whose function varies depending on the tissue where it is expressed (O'Sullivan et al., 2004). In adipocytes, SSAO activity stimulates glucose transport, mimicking the effects of insulin (Enrique-Tarancon et al.,

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1998), while in endothelial cells it is involved in lymphocyte trafficking (Smith et al., 1998).

SSAO catalyses the oxidative deamination of primary aromatic and aliphatic amines, producing ammonia, hydrogen peroxide (H_2O_2) and the corresponding aldehyde. Aminoacetone and methylamine are considered the physiological SSAO substrates (Precious et al., 1988), and their oxidation generates and methylglioxal formaldehyde, respectively (Dar et al., 1985). The products generated by SSAO have been considered a potential risk factor for stress-related angiopathy (Yu et al., 1997, 2003; Yu, 2001), due to their capacity to induce lipid peroxidation and the formation of advanced-glycation end products (AGE), as well as to increase the oxidative stress. The combined effect of these products could be important as risk factors in diseases related to vascular degeneration. In this context, it would be relevant to elucidate the role of human cerebrovascular SSAO in both physiological and pathological conditions.

Characterization of human cerebrovascular SSAO/VAP-1 in physiological and pathological conditions related to cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD)

The presence of SSAO in microvascular tissue and cerebral parenchyma has been a controversial issue (Andree and Clarke, 1981; Dostert et al., 1989; Zuo and Yu, 1994). We have found by biochemical and immunohistochemical approaches that SSAO is present in human microvessels and meningeal vessels, whereas it is absent in neurons and glia (Castillo et al., 1999). The SSAO detected in human microvessels and meningeal vessels, by immunoblotting with polyclonal anti-bovine SSAO antibodies corresponded to a single 100 kDa band, similar to that described for bovine lung membrane-bound SSAO (Lizcano et al., 1998). In addition, we showed immunohistochemically that SSAO is localized in the tunica media and tunica intima of meningeal membranes (Castillo et al., 1998).

The expression of SSAO in human cerebrovascular tissue under physiological conditions suggests that the enzyme could contribute, by its own catalytic action, to the oxidative stress and vascular damage associated to some pathologies. Because oxidative stress has been linked to AD (Behl et al., 1994), we proceeded to characterize the expression of SSAO in microvessels and meningeal vessels from patients afflicted with the disease.

Human brain samples were obtained from the Banc de Teixits Neurològics de l'Hospital Clínic de Barcelona, and meningeal vessels and microvessels were prepared as previously described (Mrsulja et al., 1976). The kinetic behavior of SSAO, performed radiochemically towards

Table 1. *Kinetic constants of SSAO in microvessels and meningeal vessels from AD-CAA patients and controls. SSAO activity was determined radiochemically using benzylamine as a substrate (0, 5, 10, 50 and 100 μM).* $^{**}p < 0.01$*; statistically significant differences, and (NS); not statistically significant differences* ($p > 0.05$) *(one-way ANOVA test followed by the Newman-Keuls multiple comparison test)*

	K_m (μM)	V_{max} (pmol/min · mg)
Microvessels control ($n = 4$)	11.41 ± 0.53	11.20 ± 2.04
Microvessels AD ($n = 4$)	13.86 ± 2.18 (NS)	18.59 ± 2.04**
Meningeal vessels control ($n = 2$)	16.55 ± 1.16	452.65 ± 85.75
Meningeal vessels AD ($n = 4$)	19.25 ± 5.89 (NS)	391.68 ± 87.85 (NS)

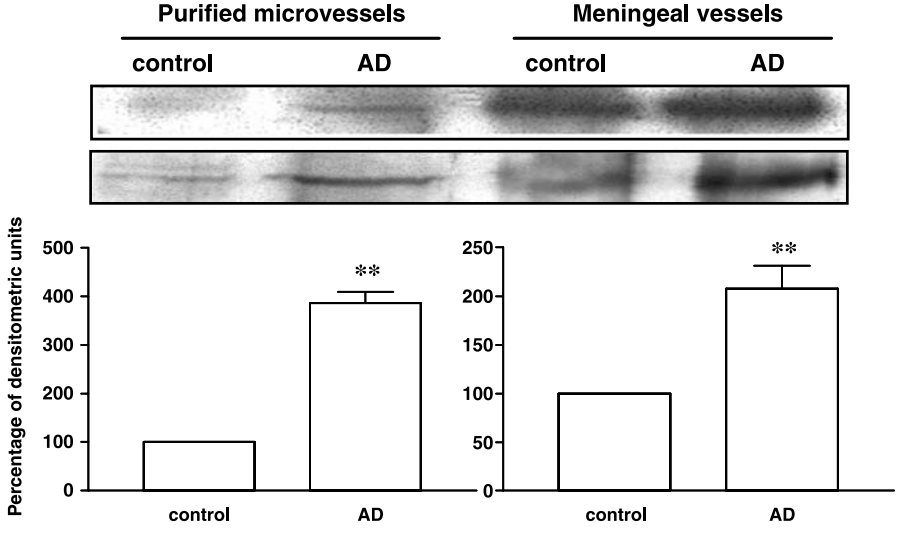

Fig. 1. Western-blot analysis of SSAO in microvessels and meningeal vessels from AD-CAA patients ($n = 2$) and controls ($n = 2$). SSAO contents are expressed as the percentage respect to controls evaluated by a densitometric analysis

benzylamine as substrate, revealed that the V_{max} value for SSAO was about 40 times higher in human meningeal vessels than in pure microvessels preparations, whereas the K_m values were similar (Table 1). The catalytic efficacy, expressed as the V_{max}/K_m ratio, was higher in meningeal vessels than in microvessels, pointing to the possibility of two different forms of SSAO in the human cerebrovascular system. In meningeal vessel preparations, neither SSAO K_m nor V_{max} values were statistically different in AD-CAA patients and controls. In contrast, the V_{max} in microvessel preparations was higher in AD-CAA samples (18.590 ± 2.043 pmol/min · mg protein, $n = 4$) than in controls (11.198 ± 2.043 pmol/min · mg protein, $n = 4$), although the K_m values did not differ (Table 1). SSAO expression in brain vascular preparations was also studied by Western-blotting using polyclonal anti-SSAO antibodies (see Fig. 1). Results, from 2 AD-CAA samples and 2 controls, showed that SSAO was overexpressed in both human meningeal vessels (a 2-fold increase) and microvessels (a 4-fold increase) in AD-CAA patients.

In order to confirm these results, we assessed the expression of SSAO immunohistochemically in 10 *post-mortem* samples from AD patients and 8 control samples (Banc de Teixits Neurològics de l'Hospital Clínic de Barcelona). A moderate to strong selective increase in SSAO immunoreactivity was seen in the AD samples between the intima and the muscular layer of arteries containing amyloid deposits (Ferrer et al., 2002). Double labeling for SSAO and βA4 confirmed the co-localization of the increased SSAO immunoreactivity and the abnormal amyloid deposition, the latter being distributed at the periphery of SSAO deposits. Increased Cu/Zn superoxide dismutase 1 (SOD1) immunoreactivity was also observed, indicating the presence of oxidative stress. Because a strong link between βA4 amyloid, oxidative stress and neurodegeneration has been proposed in AD (Hensley et al., 1995), the results obtained by Western-Blot analysis allow us to suggest that the overexpression of SSAO could contribute to the oxidative stress and the vascular damage related with AD-CAA.

Alteration of human plasma SSAO activity in AD

Soluble SSAO activity is altered in several pathological conditions. Plasma SSAO is increased in patients suffering from diabetes type I and II (Boomsma et al., 1995), congestive heart failure (Boomsma et al., 1997), non-diabetic obesity (Meszaros et al., 1999), and it has been implicated in atherosclerosis (Gronvall-Nordquist et al., 2001; Karadi et al., 2002). Serum SSAO activity is also altered in inflammatory liver diseases (Garpenstrand et al., 1999; Kurkijarvi et al., 2000). Here we studied whether the overexpression of SSAO detected in cerebrovascular tissue of AD-CAA patients (Ferrer et al., 2002) was correlated with altered SSAO in plasma. Previous results reported by our group showed a clear increase of plasma SSAO activity in moderate-severe and severe AD patients (del Mar et al., 2005). The study presented here was performed in a larger number of patients and confirmed the results obtained previously.

Human plasma samples were provided by the Fundació ACE, Institut Català de Neurociències Aplicades (Barcelona, Spain), and SSAO activity was determined radiochemically towards benzylamine as substrate. Controls and AD patients ($n = 164$) did not have any chronic metabolic disease or congestive heart failure, and their ages ranged from 65 to 94 years. All patients were suffering from sporadic Alzheimer dementia, according to NINCDS-ADRA criteria (McKhann et al., 1984). They were distributed in 5 groups based on the Global Deterioration Scale (GDS) (Reisberg et al., 1982): Age-matched control cases ($n = 29$), who were free of neurological disease, mild-D ($n = 52$, GDS = 3–4), moderate ($n = 41$, GDS = 5), moderate-severe ($n = 24$, GDS = 6) and severe dementia ($n = 18$, GDS = 7).

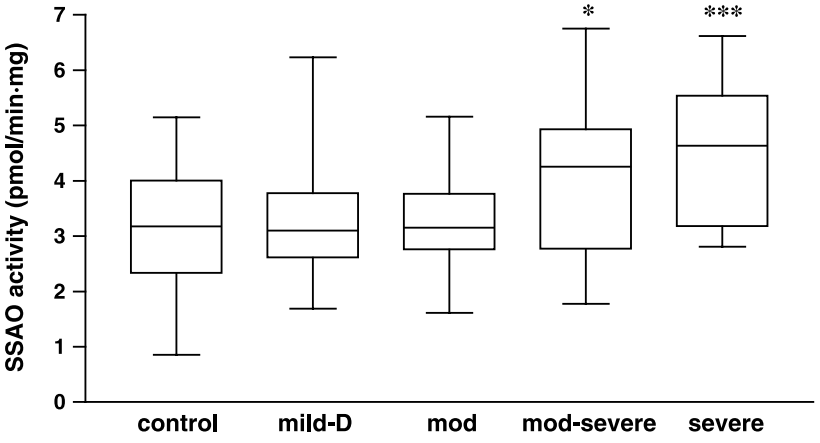

Fig. 2. SSAO activity in controls ($n = 29$) and groups with different level of AD severity classified by GDS criteria; mild-D ($n = 52$), moderate ($n = 41$), moderate-severe ($n = 24$) and severe ($n = 18$). Statistically significant differences are shown as $^{***}p < 0.001$, $^{*}p < 0.05$ (one-way ANOVA test followed by the Newman-Keuls multiple comparison test)

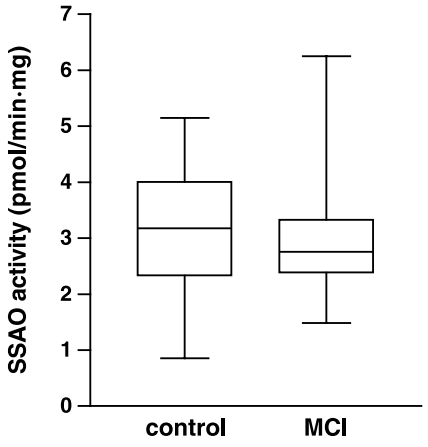

Fig. 3. SSAO activity in controls ($n = 29$) and the mild cognitive impairment group (MCI) ($n = 35$). There are no statistically significant differences between groups

Plasma SSAO specific activity from control samples showed no significant difference compared to mild or moderate patients. However, we observed a clear increase in SSAO activity in plasma from moderate-severe ($p < 0.05$) and severe AD patients ($p < 0.001$) (see Fig. 2), with patient age being an independent correlative factor (data not shown). A number of patients categorized as mild cognitive impairment (MCI) (Jack et al., 1999; Petersen and Morris, 2005) ($n = 35$) were also included in the study (see Fig. 3). MCI includes individuals who are not cognitive normal for age and yet have not evident dementia; MCI is equivalent to a GDS rating of 3. As expected, their plasma SSAO activity was not increased with respect to controls.

Altogether, our results open the possibility that the SSAO overexpression found in AD brain vessels could be the responsible for the increased plasma SSAO activity observed in severe AD patients. This increase may result from increased shedding of SSAO from the cell membrane, since it has been proposed that soluble SSAO is derived from the membrane-bound enzyme (Abella et al., 2004; Stolen et al., 2004b). It has also been reported, from studies with adipocytes, that soluble SSAO is shed from the membrane by a metalloprotease activity (Abella et al., 2004). Furthermore, transgenic mouse models expressing human VAP-1 in endothelial cells showed that VAP-1 from vascular cells can be the major source of circulating SSAO in mice (Stolen et al., 2004b). These data support a possible link between the overexpression of vascular membrane-bound SSAO and alterations of soluble protein levels in pathological conditions, such as AD associated to CAA.

Since SSAO is an adhesion protein whose expression is induced under inflammatory conditions (Arvilommi et al., 1997), an increased SSAO activity in advanced AD could be the result of vascular degeneration and inflammation. Overexpression of membrane bound SSAO by vascular cells, and its release into plasma, could amplify the oxidative stress and contribute to vascular damage in AD. However, further studies are required to elucidate the molecular mechanism that controls the shedding of the membrane-bound enzyme and the possible pathological agents involved.

The catalytic action of SSAO induces apoptosis in smooth muscle cells in culture

To investigate whether the increase of membrane-bound SSAO expression and plasma SSAO activity in AD play a role in cerebrovascular damage, we performed toxicity studies *in vitro*. Under pathological conditions, when both methylamine levels (Yu and Zuo, 1993; Hernandez et al., 2006) and SSAO activity are elevated, its own catalytic action could be an important source of toxicity through the products generated, such as H_2O_2 and formaldehyde. H_2O_2 is a major reactive oxygen species and is the principal generator of oxidative stress, which is widely implicated in several diseases. On the other hand, formaldehyde is a very reactive aliphatic aldehyde, which is considered to be a powerful inflammatory agent (d'A Heck, 1988; Yu and Deng, 1998).

We studied the cytotoxic effect of soluble SSAO, through its catalytic action, on rat aorta A7r5 smooth muscle cells, and in primary cultures of human aorta smooth muscle cells. Bovine serum, which contains high SSAO activity was used as a soluble enzyme source and different amines, methylamine, tyramine and benzylamine, were used as SSAO substrates (Hernandez et al., 2006). Our results confirmed that methylamine and tyramine oxidation by soluble SSAO catalytic action induced cytotoxicity and apoptosis in rat and human smooth muscle cells, which was prevented by SSAO inhibitors, semicarbazide and MDL-72974A. In contrast, benzylamine, a non-physiological SSAO substrate, did not show any deleterious effects. We next evaluated the effect of each of the SSAO reaction products, H_2O_2, formaldehyde and ammonia. Whereas H_2O_2 and formaldehyde were extremely cytotoxic, ammonia was not toxic at any concentration assayed, suggesting that the ammonia produced does not contribute to cell damage. It is very well known that oxidative stress is an underlying factor that contributes to the apoptotic process. Among the diverse factors capable of inducing oxidative stress, H_2O_2 plays a key role because it is generated in nearly all sources of oxidative stress and can diffuse freely in and out of cells and tissues (Barbouti et al., 2002).

However, we found that formaldehyde had a higher apoptotic effect than H_2O_2, suggesting that the formaldehyde produced during methylamine oxidation would be the main contributor to the cell death. Formaldehyde is an extremely reactive aldehyde capable of covalent interactions with macromolecules (Gubisne-Haberle et al., 2004), thus altering cellular structures. It has been previously described as a strong apoptotic inducer in other cell types (Teng et al., 2001; Tyihak et al., 2001). However, under alkaline conditions, free radicals can be generated from formaldehyde and H_2O_2, which may contribute synergistically to oxidative stress (Lichszteld, 1979) and vascular damage.

In order to confirm the cytotoxic effects of SSAO overexpression, we studied whether the methylamine oxidation was able to induce apoptosis in smooth muscle cells transfected stably with hSSAO/VAP-1 gene (Sole et al., manuscript in preparation). Our results confirm that both an increase of soluble SSAO levels and the overexpression of the membrane-bound enzyme were toxic to cells in culture. Furthermore, we observed that the transfection of SSAO produced an increase of soluble SSAO in the culture medium, confirming that in smooth muscle cells the soluble form was a product of the overexpressed protein. Our results are consistent with studies that demonstrated that the administration of methylamine to transgenic mice, overexpressing VAP-1/SSAO to produce vascular complications, increased AGE levels and modificated the progression of atherosclerosis (Stolen et al., 2004a).

In summary, the alteration of SSAO expression and the increase of its physiological substrate levels, in pathological conditions, are important factors that may amplify the vascular damage associated to certain diseases. Taken together, our results prompt us to suggest that an augmented expression and the concomitant increase in catalytic activity of SSAO isoforms observed in severe Alzheimer's disease may play an important role in the vascular damage underlying the AD-CAA disorder. Further studies must be performed in order to elucidate the mechanisms that induce such SSAO overexpression in this neurodegenerative disorder.

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