J Neural Transm (2007) 114: 829–833
DOI 10.1007/s00702-007-0671-2
Printed in the Netherlands

Journal of Neural Transmission

Semicarbazide-sensitive amine oxidase substrates fail to induce insulin-like effects in fat cells from AOC3 knockout mice

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Received: September 29, 2006 / Accepted: November 15, 2006 / Published online: April 4, 2007
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Summary Substrates of semicarbazide-sensitive amine oxidases (SSAO) stimulate glucose transport in adipocytes. To definitively demonstrate the involvement of SSAO in this insulin-like effect, glucose transport has been studied in fat cells from mice with a targeted deletion of AOC3, a gene encoding a SSAO called vascular adhesion protein-1. SSAO activity was present in white adipose tissues of wild type (WT) but was absent in AOC3KO mice. The SSAO-substrates benzylamine and methylamine were unable to stimulate hexose transport in adipocytes isolated from AOC3KO mice while they were active in WT adipocytes, especially in combination with vanadate. Impairment of amine-dependent glucose uptake was also observed with tyramine while there was no change in insulin responsiveness. These observations prove that the effects of exogenous or biogenic amines on glucose transport are not receptor-mediated but are oxidation-dependent. They also confirm that the major SSAO form expressed in mouse adipocytes is encoded by the AOC3 gene.

Keywords: Insulin, glucose transport, adipose tissue, amine oxidase

Abbreviations

AOC2	second gene encoding for amine oxidase, copper-containing
AOC3	third gene for amine oxidase, copper-containing
INWAT	intrabdominal white adipose tissues
KO	knock-out
MAO	monoamine oxidase
SCWAT	subcutaneous white adipose tissues
SSAO/VAP-1	semicarbazide-sensitive amine oxidase, vascular adhesion protein-1
WT	wild-type
2-DG	2-[1,2-^{3}H]deoxyglucose

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Introduction

The semicarbazide-sensitive amine oxidase called vascular adhesion protein-1 (SSAO/VAP-1) is encoded by the AOC3 gene (Jalkanen and Salmi, 2001) (amine oxidase, copper-containing) and is mainly expressed in vessels (Smith et al., 1998), and fat deposits (Heniquez et al., 2003; Ochiai et al., 2005). The vascular SSAO/VAP-1 located in the endothelial cells has been demonstrated to mediate leukocyte adhesion (Salmi et al., 2000) while that present in smooth muscle cells influences extracellular matrix maturation (Sibon et al., 2004). The SSAO/VAP-1 found at the surface of adipocytes has been reported to mimic several short-term effects of insulin since its substrates can stimulate glucose transport and inhibit lipolysis (Morin et al., 2001). It has also been observed that AOC3 gene expression increases during adipogenesis (Moldes et al., 1999; Subra et al., 2003) and that chronic administration of SSAO substrates can improve lipid accumulation in cultured preadipocytes (Fontana et al., 2001; Mercier et al., 2001; Carpéné et al., 2006). Moreover, a portion of the SSAO/VAP-1 activity present in fat cells can be released in their environment (Stolen et al., 2004; Garcia-Vicente et al., 2005). AOC3KO mice have been recently generated to delineate the role of endothelial SSAO/VAP-1 in leukocyte adhesion (Stolen et al., 2005). The reduced lymphocyte extravasation to inflammatory sites found in AOC3KO mice (Stolen et al., 2005) has definitively established that the product of AOC3 gene is a key component for immune responses (Salmi and Jalkanen, 2005). The complete disappearance of SSAO activity in many tissues

of AOC3KO mice has also confirmed that the AOC2 gene is not able to compensate for the AOC3 invalidation.

Since the SSAO/VAP-1 found in adipose tissue is almost exclusively expressed by mature adipocytes, and since it has been reported that substrates of amine oxidases stimulate glucose uptake in these fat cells (Morin et al., 2001), our aim was to investigate the influence of the lack of SSAO on this pivotal step of adipocyte metabolism. In fact, stimulation of glucose uptake by 0.01–1 mM of exogenous or biogenic amines such as benzylamine, methylamine or tyramine has been described to occur in fat cells from rat (Enrique-Tarancon et al., 1998; Yu et al., 2004), mouse (Iglesias-Osma et al., 2005), rabbit (Iglesias-Osma et al., 2004) and man (Morin et al., 2001; Carpéné et al., 2005a), and to be prevented by SSAO- and MAO-inhibitors or antioxidants. Moreover, hydrogen peroxide, one of the end-products of amine oxidation, appears to be involved in the observed insulin-like actions, as suggested by its insulin-like properties, the inhibition of amine action by catalase, and the synergism found between amines or hydrogen peroxide and vanadate (Enrique-Tarancon et al., 2000). The present *ex vivo* explorations therefore consisted of comparisons of the glucose transport in response to insulin and to benzylamine, methylamine or tyramine, with or without vanadate in adipocytes isolated from wild-type (WT) or AOC3KO mice.

Material and methods

Mice breeding, tissue sampling and adipocyte isolation

Mice deficient in SSAO/VAP-1 have been produced on a pure 129 background by replacing a portion of the first exon of the mouse AOC3 gene with a neomycin-resistance cassette (Stolen et al., 2005). These AOC3KO mice were backcrossed to a C57BL/6 background. Control (WT, pure C57BL/6 background) or AOC3KO mice (mice homozygous for the null mutation in the same background) of both sexes were handled in accordance with the European Communities Council Directives for experimental animal care. They were housed with constant temperature (20–22°C), humidity (50–60%) and with a 12-h light-dark cycle. All mice had free access to food and water and, after weaning, were housed at a density of three animals per cage during seven months.

Twenty eight week-old mice were sacrificed by cervical dislocation after overnight fasting. Epididymal, perirenal and retroperitoneal white adipose tissues (INWAT) were weighed, minced and digested in Krebs-Ringer buffer containing 35 mg/ml albumin and 2 mM pyruvate plus 60 μg/ml liberase (Blendzyme3, Roche Diagnostics, Mannheim, Germany) during approx. 45 min at 37°C under shaking. Isolated adipocytes were immediately used for measurement of deoxyglucose uptake as already described (Iglesias-Osma et al., 2005). Tissue samples were immediately frozen in liquid nitrogen and stored at −80°C until amine oxidase assay.

Deoxyglucose transport in isolated adipocytes

Adipocytes were diluted 10-fold in Krebs-Ringer buffer and 400 μl of cell suspension were distributed in vials containing the tested agents and incubated for 45 min at 37°C. Then, an isotopic dilution of 2-[1,2-^{3}H]Deoxyglucose (2-DG, 26.5 Ci/mmol, PerkinElmer Life Sci., Boston, MA) was added to reach a final concentration of 0.1 mM (0.6 μCi/100 μl) for an additional 10 min. Assays were stopped by 100 μl of 100 μM cytochalasin B and aliquots were centrifuged in microtubes containing dinonyl-phthalate to separate adipocytes from buffer by flotation. Intracellular radioactive 2-DG was counted as previously described (Morin et al., 2002).

Amine oxidase activity

Oxidase activity was measured using [^{14}C]benzylamine (54 mCi/mmol, Amersham Biosciences, Little Chalfont, UK) or [^{14}C]tyramine (7.5 mCi/mmol, Sigma, St Louis, MI) according to the radiochemical method previously described (Morin et al., 2002). Briefly, adipose tissues were homogenized in 200 mM phosphate buffer containing antiprotease cocktail, and incubated for 30 min at 37°C in the presence of isotopic dilution of benzylamine (0.1 mM, approx. 220,000 dpm/assay) or tyramine (0.5 mM, approx. 150,000 dpm/assay) after a 15-min preincubation without (total oxidation) or with 0.5 mM pargyline or 1 mM semicarbazide to inhibit MAO or SSAO activities respectively.

Statistical analysis

Results are given as mean ± SEM. Statistical significance was assessed by use of Student's *t*-test (NS: nonsignificant).

Results

On normal chow diet, AOC3KO mice gained more weight than WT mice: at seven months of age, body mass of males was 39.5 ± 1.0 vs. 34.3 ± 1.0 g ($n = 11$, $p < 0.001$). The fat deposition appeared to be significantly higher in AOC3KO mice than in WT. The percentage of body mass represented by the dissected white adipose depots (INWAT plus SCWAT) reached 11.3 ± 0.7% in AOC3KO males while it was equivalent to 8.6 ± 0.8% in WT ($p < 0.02$).

Null mutation of AOC3 was verified by previously described genotyping (Stolen et al., 2005). It resulted in a total loss of AOC3 mRNAs and of semicarbazide-sensitive oxidation of benzylamine in various tissues (not shown). In SCWAT homogenates from WT mice, SSAO/VAP-1 activity was able to oxidize 1.83 ± 0.12 nmol benzylamine/mg protein/min while it was at the limit of detection in AOC3KO mice (0.003 ± 0.001 nmol benzylamine/mg protein/min, $n = 11$, $p < 0.001$). When 0.5 mM tyramine was incubated with SCWAT homogenates and in the absence of any inhibitor, 0.37 ± 0.03 and 0.20 ± 0.02 nmol tyramine/mg protein/min were oxidized in WT and AOC3KO, respectively ($p < 0.001$). The MAO-dependent part of this oxidation (sensitive to pargyline inhibition) was similar in both genotypes (0.15 ± 0.02 and 0.16 ± 0.01 nmol tyramine/mg protein/min, NS) while the SSAO-dependent oxidation was 0.20 ± 0.01 nmol tyramine/mg protein/min in WT and was undetectable in AOC3KO.

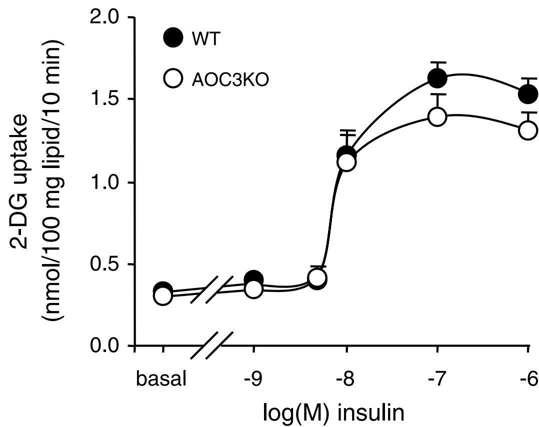

Fig. 1. Dose-dependent insulin stimulation of hexose transport in adipocytes from WT and AOC3KO mice. Adipocytes isolated from intra-abdominal fat depots were incubated for 45 min without (basal) or with insulin before 2-DG uptake, assayed on additional 10 min. Mean ± SEM of 8 WT (closed symbols) and 8 AOC3KO (open symbols) males

Basal glucose transport was not different in adipocytes from INWAT of WT or AOC3KO mice: in males the mean values were 0.33 ± 0.03 and 0.31 ± 0.04 nmol 2-DG/100 mg lipid/10 min, respectively ($n = 8$, NS). Insulin responsiveness was also comparable as shown by the superimposable dose-response curves for males of both genotypes (Fig. 1). 100 nM insulin elicited a 4–5 fold increase over basal glucose in adipocytes from WT or AOC3KO, in males as well as in females.

Benzylamine and methylamine dose-dependently enhanced glucose uptake into adipocytes of WT whereas they did not stimulate glucose uptake in AOC3KO mice. In males, 0.1 and 1 mM benzylamine slightly stimulated the uptake in WT (stimulation was equivalent to 14 ± 3 and $20 \pm 3\%$ of maximal insulin-dependent stimulation) but not in AOC3KO (5 ± 3 and $-1 \pm 1\%$ of insulin stimulation, $n = 8$, $p < 0.05$). Similarly, 0.1 mM methylamine weakly activated transport in WT only (13 ± 3 vs. $-1 \pm 3\%$ of insulin stimulation, $n = 8$, $p < 0.01$). In females, benzylamine and methylamine were even more efficient on the adipocytes from WT mice while they did not activate uptake into AOC3KO fat cells (Fig. 2).

As already reported in diverse models (Enrique-Tarancon et al., 1998, 2000), the combination of amines and 0.1 mM vanadate exhibited a powerful insulin-mimicking effect. In adipocytes from WT male mice, the presence of vanadate at 0.1 mM did not modify basal or insulin-stimulated hexose uptake but allowed 1 mM benzylamine or methylamine to activate glucose uptake to the same extent as insulin (i.e. five-fold stimulation over basal level) (Fig. 3). Of note, the glucose uptake induced by these amines plus vanadate was almost abolished in adipocytes from AOC3KO mice (Fig. 3). This supports the idea that activation of glucose transport by amines plus vanadate is mediated by SSAO-dependent oxidation.

To verify whether the effect of tyramine, a common substrate for MAO and SSAO, was also impaired in adipocytes from AOC3KO mice, the amine was tested at 1 mM in combination with 0.1 mM vanadate and the presence of MAO- or SSAO- inhibitors. Figure 4 shows that the residual effect of tyramine found in AOC3KO males was com-

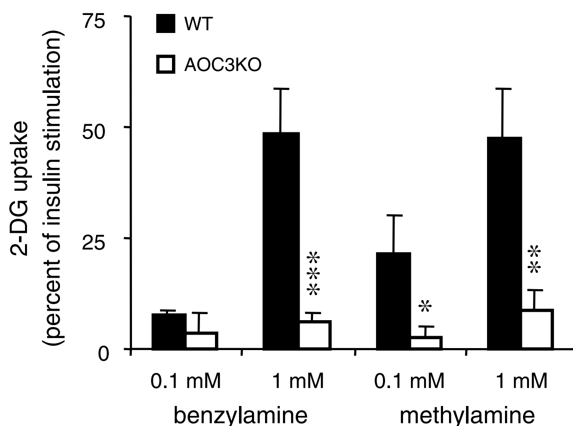

Fig. 2. Lack of activation of glucose uptake by benzylamine and methylamine in adipocytes of AOC3KO mice. INWAT Adipocytes were incubated for 45 min with the indicated agents and subjected to 2-DG uptake assay. Uptake was expressed as % stimulation, by setting 100 nM insulin at 100% and basal values at 0%. Mean ± SEM of 4 female WT and 6 female AOC3KO. Difference between WT (black symbols) and AOC3KO (open symbols) significant at: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

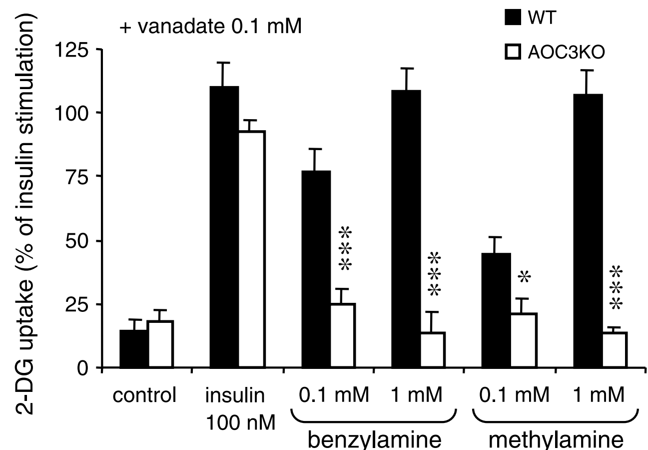

Fig. 3. Loss of insulin-like effect of benzylamine or methylamine plus vanadate in adipocytes from AOC3KO mice. Cells were incubated for 45 min with 0.1 mM vanadate and the indicated agents before 2-DG uptake. Results are expressed as % stimulation with 100 nM insulin set at 100% and basal (without vanadate) at 0%. Mean ± SEM of 8 WT and AOC3 KO adipocyte preparations from male INWAT. Different from corresponding WT at: $p < 0.05$, $^{***}p < 0.001$

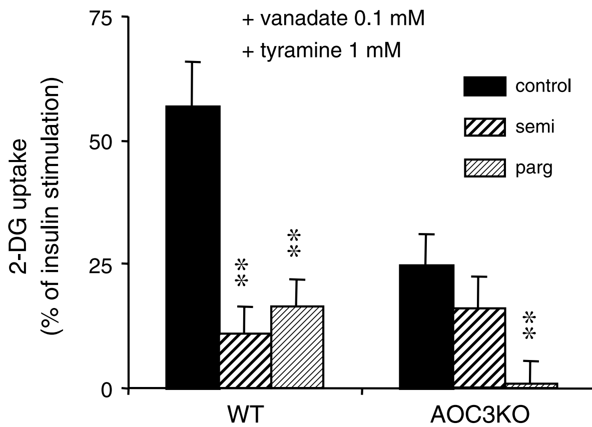

Fig. 4. SSAO- and MAO-dependent components of tyramine-induced stimulation of glucose transport in mouse adipocytes. Cells were incubated in the presence 0.1 mM vanadate plus 1 mM tyramine without or with 1 mM semicarbazide (semi) or 0.5 mM pargyline (parg). Results are expressed as % stimulation with 100 nM insulin set at 100% and basal 2-DG uptake at 0%. Mean ± SEM of 6 WT and 8 AOC3KO fat cell preparations; $^{**}p < 0.01$ from cells treated with vanadate plus tyramine

pletely inhibited by pargyline and was less altered by semicarbazide. In WT males, the tyramine-induced stimulation of hexose transport was almost equally repressed by both inhibitors. In females, the insulin-like effect of vanadate plus tyramine decreased from 91 ± 5% in WT to 40 ± 6% in AOC3KO ($n = 6$, $p < 0.001$). It therefore appeared that, in mice lacking SSAO/VAP-1 activity, the remaining activation of glucose transport by tyramine was entirely due to MAO activation since SSAO-mediated component was abolished.

Discussion

It has already been demonstrated that SSAO inhibitors (e.g. semicarbazide or hydralazine) and antioxidant agents (e.g. N-acetyl-cysteine or catalase) are able to block the glucose uptake induced by relatively high concentrations of benzylamine or methylamine (Enrique-Tarancon et al., 1998; Morin et al., 2001; Carpéné et al., 2005b). To further demonstrate that the activation of hexose transport by such amines was totally dependent on the presence of a functional SSAO activity, this work compared 2-DG uptake in isolated adipocytes from WT and AOC3KO mice.

The elimination of SSAO-dependent oxidation of benzylamine in AOC3KO mice was likely responsible for the abolition of the amine-dependent stimulation of glucose uptake. The small but significant effect of millimolar doses of benzylamine totally disappeared in the adipocytes of AOC3KO mice of both sexes. The same observation, made for methylamine, definitively demonstrated that SSAO-dependent oxidation was necessary to observe an insulin-like effect of the amines. Noteworthy, the insulin responsiveness of the AOC3KO adipocytes was not altered, arguing that, although exhibiting insulin-mimicking properties, the SSAO/VAP-1 activity was not necessary for insulin action, at least when considering the stimulation of glucose transport.

When vanadate was added to the incubation medium together with doses of amines above their Km values for amine oxidases (0.01–1 mM), their combination elicited a strong stimulation of glucose transport into WT adipocytes, the magnitude of which was equivalent to maximal insulin stimulation. The role of pervanadate in this synergism has been previously documented (Abella et al., 2003; Carpéné et al., 2005b). This potent insulin mimicker which irreversibly inhibits protein tyrosin phosphatases is formed via oxidation of vanadate by the hydrogen peroxide generated during amine oxidation. In AOC3KO adipocytes, the lack of oxidation of SSAO substrates and the subsequent lack of hydrogen peroxide formation (Stolen et al., 2005) is likely responsible for the dramatic loss of insulin-like action of benzylamine or methylamine plus vanadate.

The stimulation of hexose transport obtained in the presence of vanadate plus tyramine was also impaired in AOC3KO mice, although a residual activation of uptake could be detected. However, a complete *ex vivo* blockade of the residual tyramine-induced hexose uptake was obtained with the MAO-inhibitor pargyline in adipocytes from AOC3KO, while neither pargyline nor semicarbazide were able to totally block tyramine effect in WT fat cells. Our observations can therefore be explained by the presence of a MAO-dependent activation of glucose uptake in both WT or AOC3KO mice, which can be unmasked only in the latter genotype. In line with this point are the characteristics of the residual tyramine oxidation found in the SCWAT of AOC3KO mice: first, it was exclusively pargyline-sensitive and second it was of same amplitude as the MAO-dependent oxidation of tyramine in WT mice. Therefore, both SSAO and MAO, known to be highly expressed in adipocytes, can promote glucose uptake once activated by their substrates. Moreover, regarding SSAO, the complete removal of benzylamine oxidation capacity in adipose tissue from AOC3KO mice indicated that the predominantly active form of SSAO in murine adipose tissue was encoded by the gene AOC3. This is in complete agreement with previous observations indicating that transcripts of AOC2 gene are much less abundant than those of AOC3, while AOC1 is weakly expressed in human adipocytes (Heniquez et al., 2003).

The concomitant invalidation of SSAO/VAP-1 activity and of insulin-like effects of benzylamine or methylamine

reported in this study makes this model indispensable to further test SSAO/VAP-1's role in adipose tissue biology and metabolic control. However, there is not at the present time any indication supporting the spontaneous *in vivo* occurrence or the physiological relevance of the amine-dependent insulin-like effects observed in our *in vitro* studies with exogenous amines. Further studies on the adipose tissue development and on the metabolic control of mice with null mutation of the AOC3 gene appear to be of first importance, especially because, under our conditions, this model can be considered as mildly obese.

Acknowledgements

The authors express gratitude to the "Service de Zootechnie de l'IFR31" (Toulouse, France) and Estelle Wanecq for animal care.

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