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Influence of prolonged fasting on monoamine oxidase and semicarbazide-sensitive amine oxidase activities in rat white adipose tissue

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Monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO) activities are very high in white adipose tissue (WAT). SSAO, also known as Vascular Adhesion Protein-1 in vessels, is present at the surface of fat cells and independent approaches have evidenced its impressive increase during adipogenesis. However, the factors that might regulate the expression SSAO and MAO in adipose tissue are still poorly defined. Here, we report the influence of fasting on MAO and SSAO activities in adipose depots. A decrease of MAO activity occurred after three days of starvation in the intra-abdominal adipose tissue (INWAT) of male Wistar rats, regardless of their initial adiposity or fat loss. The reduced fat stores of seven-week old rats, loosing 59 % of INWAT mass during fasting, contained only one half of the MAO activity found in fed control. The same reduction of MAO was observed after prolonged fasting in older rats which lose only 26 % of their INWAT during the same starvation duration, leading to a fat mass comparable to that of younger fed control rats. It was therefore the endocrine and metabolic changes occurring during fasting that were responsible for the reduced MAO activity and not the amount of INWAT. Surprisingly, SSAO activity remained unchanged during starvation. In subcutaneous WAT, the changes in MAO and SSAO activities exhibited the same tendencies than those found in INWAT. Taken together, these data show that both MAO and SSAO activities increase in INWAT with age-dependent fattening, and indicate that only MAO diminishes during fasting.

Key words: Monoamine oxidase, Semicarbazide-sensitive Amine oxidase, Adipocyte, Fasting, Lipolysis, Insulin.

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Adipose tissue exhibits large variations of its mass, from massive development in morbid obesity to total depletion after prolonged starvation, and generally enlarges moderately with age-dependent fattening. In fat depots, adipocytes are not only involved in the metabolic functions regulating lipid storage, namely lipolysis and lipogenesis, but are also known to accomplish paracrine and endocrine functions that participate in body weight regulation, lipid handling or even glucose homeostasis, mainly by the secretion of adipokines and diverse other factors.

Semicarbazide-sensitive amine oxidase (SSAO) is a membrane-bound protein present at the surface of adipocytes that can be considered to belong to the family of such secreted factors (10). The amine oxidase activity of this enzyme is inhibited by hydrazine derivatives (*e.g.* semicarbazide) while it is resistant to most monoamine oxidases (MAO) inhibitors (*e.g.* pargyline). This adipocyte protein SSAO is identical to the Vascular Adhesion Protein-1 (SSAO/VAP-1) found in vessels (20). It has been recently demonstrated that the SSAO/VAP-1 found in human adipose depots is mainly stored in the adipocytes and only a minor part is found in the stroma-vascular fraction (6). A soluble, truncated, form of SSAO/VAP-1 is present in blood and it has been proposed that white adipose tissue (WAT) may constitute a source for this circulating form (10), especially under diabetic conditions in which plasma SSAO/VAP-1 levels are increased (1, 5, 21). Alongside its shedding and putative action on other targets than WAT, SSAO/VAP-1 has been involved in the regulation of adipocyte metabolism (2). Indeed, SSAO/VAP-1, like MAO, generates hydrogen peroxide when oxidizing biogenic or exogenous amines. Since hydrogen peroxide exerts insulin-like actions on adipocytes, it has been demonstrated that substrates of MAO and SSAO activate glucose uptake and inhibit lipolysis in adipocytes (3, 18), even in the absence of insulin (2). Although MAO and SSAO/VAP-1 are highly expressed in adipose tissue, especially in man (18), the factors regulating their expression are far from being well defined, the only recognized regulation being the strong increase of SSAO that occurs during adipocyte differentiation (6, 17), which is somewhat an insulin-dependent process.

It was therefore expected that insulin was promoting SSAO/VAP-1 expression in fat cells. Scarce observations made on type I diabetic rats were in accordance with this hypothesis since a decrease in SSAO activity (24) or a reduction of its affinity towards the nonphysiologial substrate benzylamine were observed in the WAT of streptozotocin-induced diabetic rats (7). The descriptions of an increase of SSAO and MAO activity in adipose depot from obese and insulin-resistant dogs (27) or a decrease of MAO without SSAO alteration in subcutaneous fat of obese subjects (25), have not clarified the nature of the possible link between SSAO expression and insulin resistance. However, it has been reported that TNFα can down-regulate SSAO expression in preadipocyte cell lineages (15), and that SSAO mRNAs are lowered in the WAT of obese Zucker rats (17). In this context, the present work aimed at further studying the variations of MAO and SSAO/VAP-1 activities in WAT under prolonged fasting, a condition that provokes large changes in the amount of stored lipids and that corresponds to decreased insulin levels.

The present results show that prolonged fasting provokes a reduction of MAO expression (per mg protein or per entire WAT), especially in the intra-abdominal white adipose tissues (INWAT) of rats irrespective of their initial body weight. On the opposite, adipocyte SSAO activity appears to be spared during starvation.

Material and Methods

Chemicals.– [^{14}C]-benzylamine (57 mCi/mmol) came from Amersham Biosciences (Buckinghamshire, UK). [^{14}C]-tyramine (7.5 mCi/mmol), semicarbazide, pargyline, collagenase and other reagents were obtained from Sigma-Aldrich (Saint Quentin Fallavier, France)

Animals and treatments.– Wistar rats were handled in accordance with the principles and guidelines established by the French National Institute of Medical Research (INSERM): they were housed in animal room with constant temperature (20-22 °C), with a 12/12 h light/dark cycle and with free access to water. Two groups of male rats were constituted according to their age: 7 or 10 weeks. They were sacrificed under fed condition or after 1 to 4 days of calorie starvation. Not one of the rats used for this study died during prolonged starvation.

Tissue sampling and amine oxidase activity determination.– At the time of sacrifice, epididymal, perirenal and retroperitoneal fat depots were removed, weighed and pooled as intra-abdominal adipose tissue (INWAT). A portion of INWAT was used for adipocyte preparation by collagenase digestion while the remaining was immediately frozen, as it was the case for inguinal subcutaneous fat depots (SCWAT). Determination of amine oxidase activity was performed on homogenates of thawed samples using a previously described radiochemical method (27). For [^{14}C]-benzylamine and [^{14}C]-tyramine, the concentrations that allowed the determination of maximal amine oxidase activity were 0.1 mM and 0.5 mM, respectively (27). MAO-dependent oxidation was defined as sensitive to inhibition by pargyline 0.5 mM and resistant to 30-min preincubation with 1 mM semicarbazide (13), while SSAO-dependent oxidation was inhibited by 1 mM semicarbazide and resistant to 0.5 mM pargyline (18). Protein content was determined using the Bio-Rad reagents for DC protein assay (Hercules, CA, USA). Lipid content was gravimetrically determined after extraction in organic solvant as previously reported (16)

Lipolytic activity of isolated adipocytes and glucose uptake into fat tissue pieces.– Freshly isolated white adipocytes were used for the determination of lipolytic activity, by assessing the glycerol release in incubation medium containing 3.5 % bovine albumin, as previously described (4). The results were expressed as percentage of responses to 10 nM isoprenaline, which is independent of fat cell size and basal triglyceride breakdown (9). The previously described technique used for the determination of 2-deoxyglucose uptake into adipocytes (8) was adapted to small pieces of adipose tissues, incubated without previous collagenase digestion, and separation between internalized hexose from extracellular was performed by successive washings as for muscle (19) instead of the centrifugation through dynonylphtalate layer used for buoyant fat cells (8).

Statistical analysis.– Results are given as means ± S.E.M. Statistical significance was assessed by use of Student's *t*-test. NS means no significant difference between the compared samples.

Results

Influence of fasting duration on body mass, blood glucose, intra-abdominal adipose tissue mass and amine oxidase activity.– Fasting exerted slimming and glucose lowering effects that were statistically significant after the first day of starvation. As expected, longer fasting periods provoked a continuous fall in body and adipose mass while blood glucose level remained stable. Under these conditions, no change in SSAO was observed in the INWAT of male rats, while a decrease in MAO activity was detected after 72 hours of complete calorie restriction (Fig. 1).

Further experiments were performed to compare groups of young and older

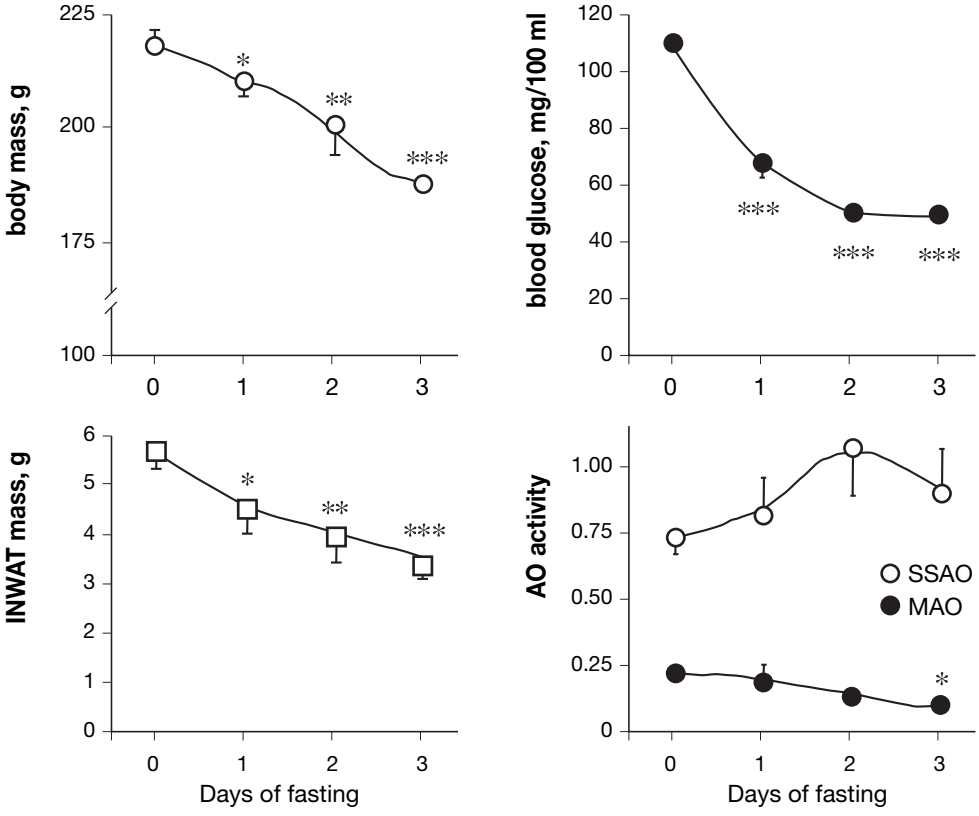

Fig. 1. *Influence of fasting duration on body mass, blood glucose, mass of intra-abdominal white adipose tissues (INWAT), and amine oxidase activities in INWAT).*

Seven-week old rats were sacrificed under fed state (day 0) or after the indicated days of fasting. Amine oxidase activities were determined on crude INWAT homogenates and are expressed as oxidized product formed in nmol/mg protein /min. Mean ± SEM of 6 animals in fed state (day 0) and of 3 for each fasting duration. Statistically different from fed control at: *p < 0.05; **p < 0.01; ***p < 0.001.

rats under fed condition and after a 4-day fasting period, in order to separate the influence of adaptation to fasting from the influence of changes in adipose tissue mass *per se*. A first comparison was made between young rats emaciated after prolonged fasting to their age-matched fed control, while a second was made in older and fatter rats, expecting that their fat depots were "normalized" by starvation to levels equivalent to those of younger fed rats.

Influence of a 4-day fasting on body mass and visceral adiposity in 7- and 10-week old rats.– The decrease in body mass and in several parameters of intra-abdominal white adipose tissue observed after prolonged fasting are shown in Fig. 2. As expected, the amount of lipids stored in INWAT was the highest in older fed rats. Although it significantly decreased during starvation in older rats, the decrease in younger rats was even more pronounced. It can be noted than in the older rats, there was no alteration in the protein content of the visceral adipose depots induced by age or by fasting. These results indicated that the fat accretion occurring from 7 to 10 weeks of age was hypertrophic (replenishment of existing adipocytes), since increase of INWAT mass was due to lipid storage but not to protein anabolism. While protein content was spared in the older rats during prolonged fasting, a dramatic lipid mobilization occurred, leading to reduction of fat cell size without reduction of fat cell number (not shown). On the opposite, the lean 7-week old rats submitted to starvation entered in a phase of protein catabolism and could not spare all their proteins, but the decrease in total protein content of INWAT did not reach statistical significance in these animals

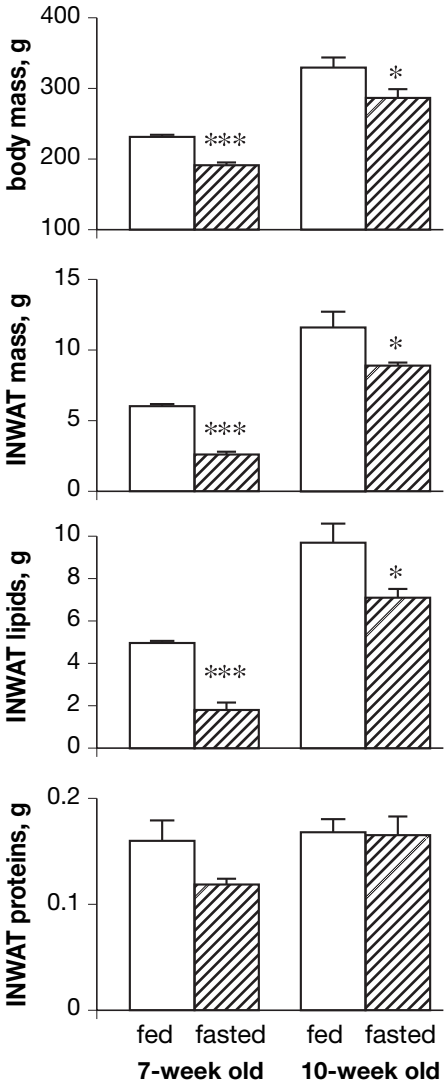

Fig. 2. *Influence of a 4-day fasting on body mass and visceral adiposity in 7- or 10- week old rats.* Wistar rats of different age (7- and 10-week old, on left and right columns, respectively) were sacrificed in fed conditions (open columns) or after 4 days of starvation (shaded columns). Adipose tissues were dissected, weighed, and lipid or protein contents were determined in crude homogenates used for amine oxidase activity determination. Mean ± SEM of 6 (7-week old) or 3 (10-week old) animals. *p <0.05; ***p<0.001 *vs.* corresponding fed condition.

intensively mobilizing their lipid stores. Thus, the starvation-induced loss of INWAT mass was largely mediated by reduction of lipid storage (Fig. 2) and a subsequent decline in mean fat cell diameter, while no decrease in fat cell number could be evidenced, regardless of the age (not shown).

Influence of a 4-day fasting on the richness of amine oxidase activity in adipose tissues: role of anatomical location and of fat store extent.– Tyramine oxidation was due to both MAO and SSAO activities in equivalent proportions in intra-abdominal fat depots, as demonstrated by the similar amount of amine oxidized in a manner that was sensitive to pargyline or semicarbazide, respectively (Fig. 3, upper panel). While MAO and SSAO activities shared the same magnitude of tyramine oxidation in INWAT of fed rats, the oxidation levels found in 10-week old males were around two fold greater than that found in younger and less fat animals. Whatever the age, prolonged fasting

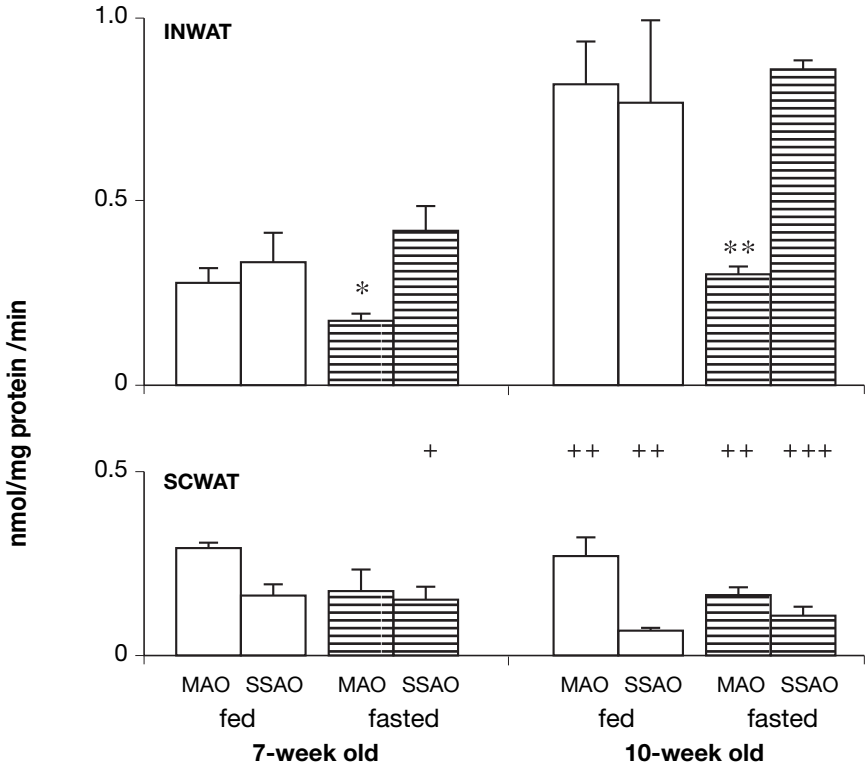

Fig. 3. *Influence of a 4-day fasting on amine oxidase activity (nmol/mg protein/min): role of fat depot anatomical location and lipid store extension.*
Tyramine was incubated for 30 min at 37 °C in tubes (final volume of 200 µl) containing 131 to 469 µg protein, depending on the rat age, or the anatomical location of adipose tissue: intra-abdominal (upper panel) or subcutaneous (lower panel). MAO and SSAO activities were expressed as nmol/mg protein/min. Mean ± SEM of 3 animals. Different from corresponding fed condition at: *$p < 0.05$; **$p < 0.01$. Difference between INWAT and SCWAT significant at: $^{+}p < 0.05$; $^{++}p < 0.01$, $^{+++}p < 0.001$.

resulted in an impressive fall in MAO activity without alteration of SSAO activity. A half-reduction of MAO activity occurred in fasted rats, independently of their final adiposity: very reduced in emaciated young males, or normalized in the older and fatter ones.

During fasting, the energy requirement for survival does not mobilize lipids only from visceral fat depots but also from subcutaneous stores. The latter anatomical location was therefore studied in parallel. In the younger rats, SCWAT exhibited less changes during fasting than INWAT: regarding mass reduction, SCWAT undergoes 31 % loss *vs* 59 % for INWAT. However, in the older and fatter rats, both anatomical locations participated equally to fat mobilisation since their respective weight loss represented 26 % and 32 % reduction. In SCWAT, the MAO-dependent oxidation of tyramine was greater than the SSAO-dependent component (Fig. 3, lower panel). However, age and/or fattening was surprisingly not accompanied with an increased richness in amine oxidase activity of SCWAT. After prolonged fasting, the decrease in MAO activity resembled that observed in INWAT, but did not reach statistical significance, whatever the age studied. As described above for INWAT, prolonged fasting did not induce any alteration of SSAO activity in SCWAT. Moreover, SSAO activity was lower in SCWAT than in INWAT in almost all the conditions tested.

Overall capacity of intra-abdominal white adipose tissues to oxidize tyramine or benzylamine: influence of fattening and of prolonged fasting.– The simple measurement of an enzymatic activity on a "per mg protein" basis is biochemically satisfactory to describe a richness in a given tissue but could lead to erroneous interpretations on physiological regulations when comparing conditions in which this tissue varies dramatically in size, as it is the case for INWAT during fasting. To better compare the total SSAO and MAO activities restrained in INWAT, we have expressed amine oxidation on a "per entire adipose depot" basis. Fig. 4 shows that the overall MAO- and SSAO-dependent oxidations of tyramine found in the INWAT of young rats under fed state, increased together with INWAT mass during rat growth. After prolonged fasting, the resulting INWAT exhibited a robust limitation of its overall capacity to oxidize tyramine in a MAO-dependent manner, while its SSAO component was unaltered.

When benzylamine was subjected to oxidation by INWAT homogenates, a very limited MAO activity was hardly detectable, but a strong SSAO activity was revealed, especially in 10-week old rats. This observation is in perfect agreement with the widely recognized SSAO-substrate nature of benzylamine and with its lower ability to be oxidized by MAO-B. Therefore, no significant change in MAO activity could be detected with benzylamine in response to ageing or fasting. However, the overall SSAO-dependent oxidation of benzylamine endowed in INWAT was unaltered by prolonged fasting, irrespective of fat mass loss or age of the rats. Moreover, the expression benzylamine oxidation per total amount of WAT confirmed that the SSAO activity present in INWAT was increasing with age and/or fattening (Fig. 4, lower panel), as already observed with tyramine.

Influence of prolonged fasting on antilipolytic responses to insulin, vana-

dium, tyramine and benzylamine.– Adipocytes isolated from INWAT were incubated for 90 min with 10 nM isoprenaline to reach a submaximal stimulation of lipolysis, then it was verified whether antilipolytic responses to insulin or other antilipolytic agents were modified by fasting. When present at 100 nM, insulin impaired the isoprenaline lipolytic action in a similar partial manner in young and older rats (Fig. 5). Such antilipolytic effect was not altered by fasting and was slightly enhanced in the presence of vanadate 0.1 mM, which was practically ineffective on its own. The insulin antilipolytic effect could be mimicked by tyramine or benzylamine plus vanadium in all the tested ages or nutritional conditions. However, tyramine, at 1 mM and in the presence of vanadate, was able to totally counteract the lipolytic effect of isoprenaline in fed animals but was clearly less antilipolytic in fasted conditions.

The decline in MAO activity found in INWAT was also accompanied by another impairment of insulin-like action of tyramine: activation of glucose uptake into pieces of INWAT incubated in the presence of 0.1 mM vanadium. In control 7-week old rats, 0.5 mM tyramine reproduced 87 ± 14 % of the 100 nM insulin effect, while this percentage fell down to 45 ± 12 % in 4-day fasted rats ($p < 0.05$, not shown).

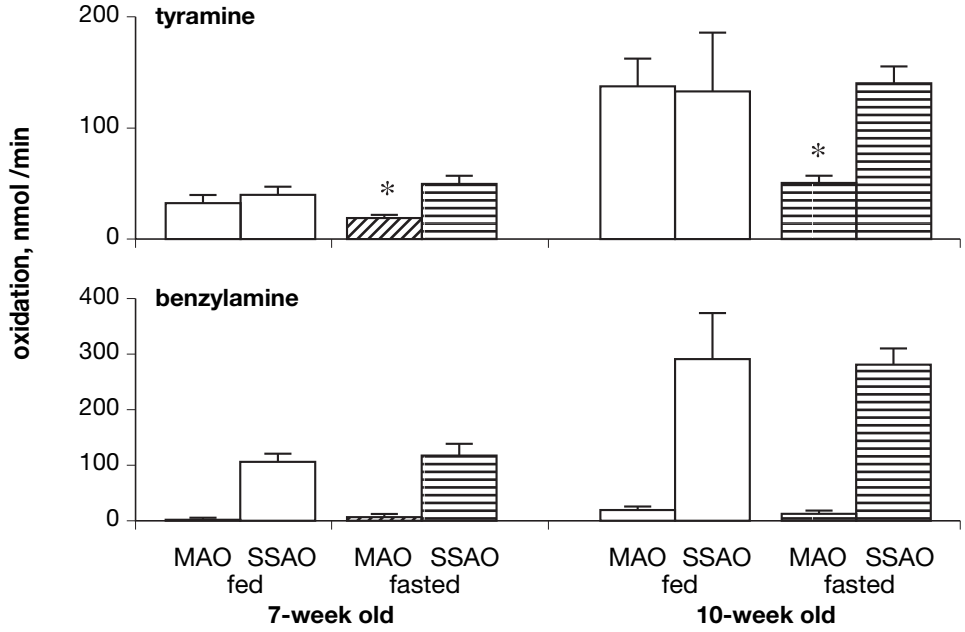

Fig. 4. *Influence of a 4-day fasting on the capacity of intra-abdominal white adipose tissue to oxidize tyramine or benzylamine*

In each group of rats, the global capacity of INWAT to oxidize 0.5 mM [^{14}C]-tyramine (upper panel) or 0.1 mM [^{14}C]-benzylamine (lower panel) oxidation was expressed as nmol of amine oxidized per total fat tissue per min. Mean ± SEM of 6 (7-week old) or 3 (10-week old) animals. Different from respective fed state at *$p < 0.05$.

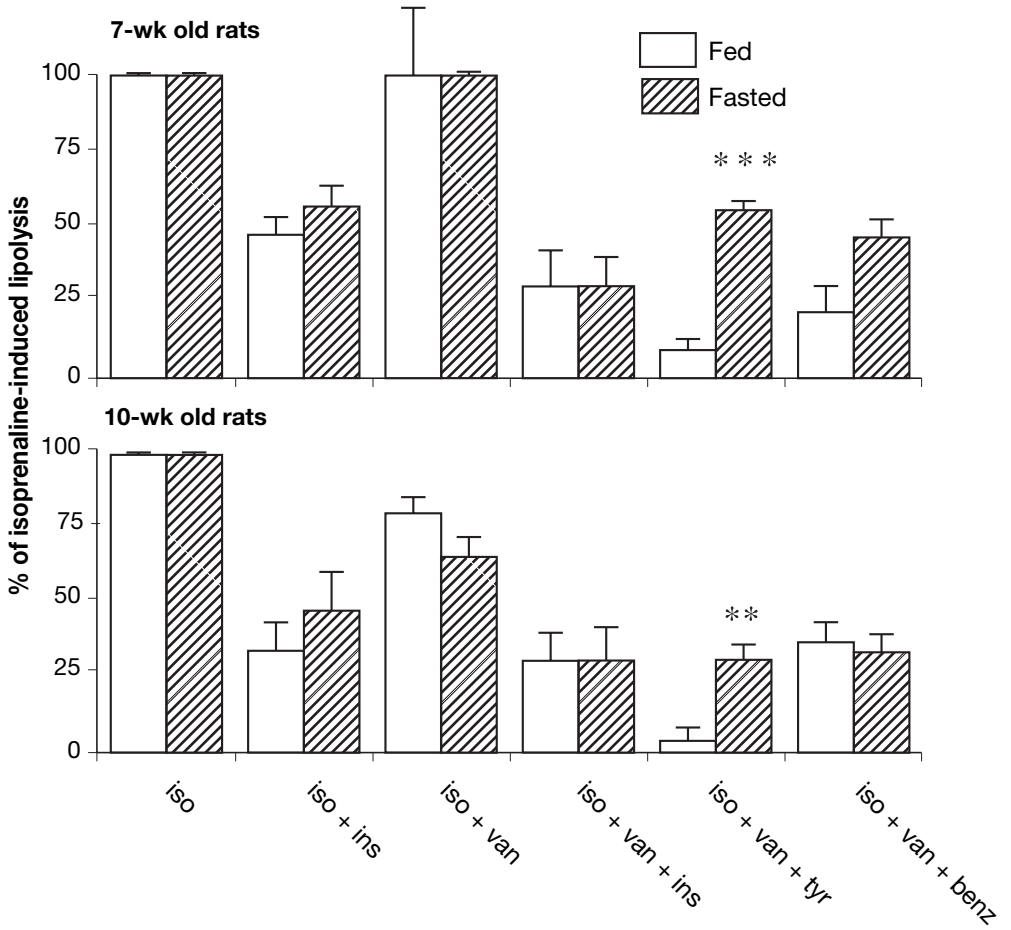

Fig. 5. *Influence of prolonged fasting on antilipolytic responses in intra-abdominal white adipose tissue of 7-week and 10-week old rats*

Adipocytes isolated from INWAT were incubated for 90 min with 10 nM isoprenaline to reach a submaximal stimulation of lipolysis equivalent to 3.2 and 2.7 fold increase above basal in fed and fasted 7-week old rats (upper panel), and to 3.7 and 3.5 fold in fed and fasted 10-week old rats (lower panel), respectively. Antilipolytic agents (insulin 100 nM, tyramine 1 mM and benzylamine 0.1 mM) were added for 90 min with isoprenaline alone (iso) or together with 0.1 mM vanadate (iso + van). Results are expressed as percentage of 10 nM isoprenaline-induced lipolysis. Mean ± SEM of 3 determinations. Different from corresponding fed condition at: $^{**}p < 0.01$; $^{***}p < 0.001$.

Discussion

The present work clearly shows that the SSAO/VAP-1 activity found in adipose depots is unaltered by fasting while MAO is deeply reduced. These observations improve our current knowledge about amine oxidase regulation in adipocytes, which was limited to the repeatedly reported increase of SSAO during adipocyte differentiation (6, 14, 17, 22).

The lack of detectable change of SSAO activity in adipose tissue during fasting

was clearly evident in both anatomical locations studied whatever the age of the rats. This preservation of SSAO capacity in fat stores during weight loss is likely the consequence of: 1) persistent and elevated SSAO expression in spite of deep endocrine and metabolic disturbances, and 2) maintained total protein content in INWAT, especially in older and fatter rats that manage a thrifty adaptation to calorie restriction. Thus, it can be definitively assessed that the fasting-induced depletion of fat cell stores is not a cause of SSAO/VAP-1 down-regulation, in spite of the decrease in insulin circulating levels.

However, SSAO activity is not completely independent from adipose tissue size since a clear increase in SSAO activity was detected in INWAT when its mass increases during growth. Such increase of SSAO activity occurred in INWAT of control rats without any increase of protein content between the two ages studied. It can be stated therefore that the richness in SSAO (expressed on a "per mg protein" basis) was increasing together with fat deposition. Such increased SSAO activity is likely due to an enhanced expression of SSAO in the mature adipocytes since they contain much more activity and express much more mRNAs of the AOC3 gene encoding for SSAO/VAP-1 than the other cell types found in the adipose tissue (6). The SSAO enrichment that occurs in hypertrophied fat cells resembles to the SSAO emergence that takes place during adipocyte differentiation (6, 14, 17, 22). Nevertheless, the relationship between fat depot extension and SSAO expression could be more complicated than it appears since SCWAT, which also enlarges with rat growth, did not exhibit SSAO increase. Similarly, an increase in SSAO activity in intra-abdominal - but not subcutaneous - fat depots has been reported in dogs fed a high-fat diet (27). Therefore, this observation could be considered as one of the numerous regional differences between fat depots. However, mice rendered obese by high-fat diet feeding did not exhibit such increase when adipose SSAO activity is expressed on a per mg protein basis: they exhibit only an increase in the overall capacity of WAT to oxidize benzylamine, when compared to lean controls (23). At this point, the need for further determinations of age- and adiposity-dependent changes in adipose SSAO becomes evident, especially for clinical investigations. Indeed, the numerous variations of plasma SSAO/VAP-1 found in patients suffering from a broad variety of metabolic diseases (5) warrant to be extended to the adipose tissue-bound form.

A half-reduction of MAO activity was found in INWAT after four days of starvation, irrespective of the magnitude of lipid store depletion: dramatic in young and lean, or moderate in fatter and older rats. Among the diverse adaptations to calorie deprivation, a decrease in the mitochondrial machinery could be involved in such decrease of MAO (which is a marker of mitochondrial outer membrane) and could be linked to decreased thyroid activity. Again, MAO abundance was apparently more tightly related to the extent of lipid stores in INWAT than in SCWAT. Moreover, the decrease of MAO expression observed in fasting-induced depletion could not be generalized to all the situations of lipid mobilization. For instance, visceral fat tissue of rats treated with a β3-adrenergic agonist exhibits a strong lipid mobilization (9) but also an increased mitochondriogenesis (12), and an increased MAO activity in the INWAT (8). Thus, factors playing a positive role on mitochondrial function can increase MAO activity in adipocytes,

regardless of fat cell size. Finally, the decrease of MAO activity in INWAT after prolonged fasting is probably not simply associated with mitochondrial remodelling, since changes in the substrate levels may also interfere with MAO regulation. In this view, it must be mentioned that catecholamines, that are MAO substrates, are produced by sympathetic innervation, and were reported to increase in several -but not all- fat depots of rats during prolonged fasting (11). It has been previously reported on rat adipocytes that another biogenic amine, tyramine, is oxidized by MAO, then generates hydrogen peroxide, which in turn inhibits lipolysis or activates glucose uptake (26). It is therefore coherent that fasting decreases both tyramine oxidation and tyramine insulin-like effects in INWAT. Taken together, our observations show that enlarged fat depots contain higher MAO activity than shrunk ones. Since amine oxidation may influence adipocyte functions, there is still a need to increase our knowledge on the regulation and the physiological role of amine oxidases and their substrates in adipose tissue.

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Z. IFFIÚ-SOLTÉSZ, D. PRÉVOT y C. CARPÉNÉ. *Influencia del ayuno prolongado sobre la actividad monoamino oxidasa y amino oxidasa sensible al semicarbazide en el tejido adiposo blanco de rata*. J Physiol Biochem, **65** (1), 11-24, 2009.

La actividad monoamino oxidasa (MAO) y aminooxidasa sensible al semicarbazide (SSAO) están muy elevadas en el tejido adiposo blanco (TAB). SSAO, también conocida como proteína de adhesión vascular-1, está presente en la superficie de los adipocitos maduros. Diferentes investigaciones muestran incremento de su expresión durante la adipogénesis, aunque los factores que regulan la expresión en el TAB no son bien conocidos. Este trabajo describe la influencia del ayuno sobre la actividad MAO y SSAO en TAB. Se ha observado que tras tres días de ayuno disminuye la actividad MAO en el tejido adiposo intra-abdominal (INWAT) de ratas macho Wistar, independientemente de la grasa inicial o de la pérdida de peso inducida por el ayuno. El ayuno redujo un 59 % el peso del INWAT y un 50% la actividad MAO en ratas de 7 semanas de edad comparadas con su control (ratas sin ayuno). La misma disminución de la actividad MAO se encontró en ratas de mayor edad (10 semanas) aunque solo perdieron el 26 % de su INWAT durante el mismo ayuno, igualando dicha reserva grasa a la de las ratas más jóvenes sin ayunar. Los resultados indican que serían los cambios endocrinos y metabólicos que ocurren durante el ayuno los responsables de la disminución de la actividad MAO y no la perdida de tejido adiposo en sí. Sorprendentemente, no se observó ningún cambio significativo en la actividad SSAO durante el ayuno. En el tejido adiposo subcutáneo, los cambios de actividad MAO y SSAO mostraron las mismas tendencias que en el INWAT. Los resultados muestran que la edad conlleva un aumento de la actividad de la MAO y de la SSAO en tejido adiposo blanco de rata y que el ayuno reduce la actividad de la MAO, no la de la SSAO.

Palabras clave: Amino oxidasa sensible al semicarbazide, Insulina, Lipolisis, Tejido adiposo, Monoamino oxidasa.

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