Consequently, the fat cells of obese Zucker rats have more binding sites related to these enzymes than the lean ones, especially in adipose tissue. This difference was seen without any prior pharmacological treatment. Thorough examination of the published literature, whether performed/studied in the lean rats or the obese, revealed that the antilipolytic action of tyramine, or any other MAO/SSAO substrate, was involved in a greater mobilization of fat stores, and therefore in the slimming effect of MAO and SSAO in rodents. We therefore compared the amine oxidase activity in the adipose depots of obese and lean Zucker rats. While the obese rats are homozygotous for the recessive mutation of a gene impairing leptin signalling and rendering the animals tremendously hyperphagic, their heterozygotous littermates remain lean and without insulin resistance. We therefore compared the obese and lean littermates of this useful animal model of genetic obesity, and we reported in the present manuscript that we found a greater MAO activity in the adipose depots of the obese rats than in the age-matched lean controls. This spontaneous difference was seen without any prior pharmacological treatment. In the present study, the in vivo treatment is not performed with pharmacological amine oxidase inhibitors as in our previous study, since it is the substrate tyramine that was administered to obese and lean rats and reduced the hyperglycemia and hypertriglyceridemia of the obese only. This treatment was applied to additional rats than those used for phenotyping the obese vs the lean littermates, regarding insulin responsiveness, and amine oxidase expression. Thus, even if we used the same animal model for both studies, the "innovation" of this submitted work is that the genetically obese littermates spontaneously express larger amount/activity of MAO and of binding sites related to these enzymes than the lean ones, especially in adipose tissue. Consequently, the fat cells of obese Zucker rats are likely more prone to exhibit biological...
responses to MAO and SS Rao substrates and inhibitors. Moreover, the amine oxidases appeared to be linked with glucose consumption in fat cells from both lean and obese rats. Indeed, in the adipocytes, the substrates of MAO and SS Rao were able to activate glucose consumption and its incorporation into lipids, which can be considered as an insulin-like anabolic effect. The enclosed revised manuscript allow us proposing that such larger MAO abundance in adipose tissue might contribute to the larger fat deposition found in the obese and insulin-resistant rats, and has to be added to the long list of phenotypic differences between lean and obese Zucker rats.

The confusion of the reviewer has been taken into account. It was probably induced by the terms "increase / increased" regarding amine oxidation. During revision, in several occurrences, we have changed the word "increase" or "increased" when comparing between lean and obese littermates the MAO expression, the oxidase activities, or the substrate effects on glucose utilization, by "larger, higher or greater"(e.g in legend of fig. 6). Currently, we don't know/prove where/when is the increase; we just observed that the MAO activity is larger in obese than in age-matched lean rats. Anyhow, this might prompt investigators to ask whether a similar difference exists between non-obese and obese individuals, and might constitute a relevant target for combatting obesity.


The reviewer is absolutely right. We have already reported that here is high expression of SS Rao and MAO in fully differentiated adipocytes from patients with Simpson-Golabi-Behmel syndrome. However, again, the reported comparison was performed between non-differentiated and fully-differentiated adipocytes, and nothing was described about putative difference between non-obese and obese humans, an issue that was out the scope of the present study, but which deserves future investigations. Regarding gene expression, the tools we have developed were suitable for humans and for mice but not totally validated for rat genome, and we encountered some difficulties as already mentioned in the fourth paragraph of the Discussion. Consequently, we cannot add during the revision of this Ms any additional relevant data about Maoa, Maob or Aoc3 rat genes. According to the reviewer's suggestion, it is sure that such data, at least in adipose tissue, would have supported further the larger MAO protein and oxidase activity found in obese when compared to lean rats, as displayed in figures 3, 4 and 5.


This suggestion has been taken into account, and for answering also to concerns raised by editors, the 4 following auto-citations have been removed and replaced by more recent:


SCIENCE EDITOR:
1 Scientific quality / The manuscript describes a Basic Study of the Increased amine oxidation in adipocytes of obese rats. The topic is within the scope of the WJBC. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: Perhaps a number of issues should be clarified to improve the overall quality of this manuscript. The questions raised by the reviewers should be answered. (3) Format: There are 2 tables and 9 figures; (4) References: A total of 73 references are cited, including 8 references published in the last 3 years; (5) Self-cited references: There are 8 self-cited references, The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations.

These editor remarks are entirely justified. We have removed 4 self-citations and total number of references is now of 72, as the moved quotes were replaced for the sake of clarity by the following ones:
doi 10.4331/wjbc.v11.i3.76
doi 10.4331/wjbc.v2.i10.215
doi 10.4239/wjd.v10.i1.23

2/ Language evaluation and 3/ Academic norms and rules and 4 Supplementary comments: no concern raised
OK.

5/ Issues raised:
(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

As it is difficult to encounter a single accounting document that justifies the recurrent fundings of a National institute like INSERM that are distributed yearly to Research Units, then dispatched monthly within research teams, the authors cannot provide a certificate corresponding to the duration of the studies. The approval document provided by the authors has been uploaded for the Institutional Review Board Approval. Whether this document is not considered at BPG, the editorial staff can delete if necessary the supportive foundations that were summarized as 'Supported by Institut National de la Santé et de la Recherche Médicale to INSERM Unit 1048, France.' in the revised Ms.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

These editor remarks are answered by providing the required .pptx files.

OK, thanks.

COMPANY EDITOR-IN-CHIEF: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Biological Chemistry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.
All required changes have been done by adding in red font only a minimal number of sentences, and by removing the less useful self-citations, to keep Ms as concise as possible. Please, note that for R1 version of the Ms, the corrections made during revision are indicated in red.