Reviewer's report

Title: Genetic deletion in uncoupling protein 3 augments 18F-fluorodeoxyglucose cardiac uptake in the ischemic heart

Version: 2 Date: 31 May 2014

Reviewer: Gianmario Sambuceti

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The study investigates whether deletion of gene encoding for the uncoupling protein 3 (UCP3) and its effect on glucose metabolism and functional response to myocardial infarction can be identified by FDG cardiac uptake and echocardiography. Selected model asked for a permanent coronary artery ligation in UCP3 knockout (UCP3-/-) and wildtype (WT) mice. Imaging was performed one week after induction of myocardial infarction or sham procedure. Under control condition UCP3 deletion did not modify LV volumes nor FDG uptake measured as SUV. By contrast, LV response to myocardial infarction diverged as UCP3-/- deletion was associated with a greater LV enlargement and a higher increase in FDG uptake with respect to WT mice.

Based on these data, the authors conclude that “… in a mice model of permanent coronary occlusion, UCP3 deficiency results in a metabolic shift that favored glycolytic metabolism and increased FDG uptake.”

Extending recent literature related to the role of UCP3 in both in skeletal muscle and myocardium, these data document a role for this protein in tissue response to prolonged ischemia in the absence of reperfusion.

1. Major comments

1.1 Pathophysiological aspects:

Actually, the paper does not provide any mechanistic explanation of the role of UCP3 protein in cardiac protection from ischemic injury. At least some comments might be added in the discussion to address this point. Actually, most classical literature considers an increased glycolytic rate as direct metabolic response to ischemia able to restore NAD+ pool and thus allowing a residual ATP production by anaerobic glycolysis with lactate release in venous efflux.

By contrast, the present data indicate that increased glucose consumption was associated with a larger infarct size and a more severe impairment in systolic function. The novel – paradoxical – nature of these findings and their (apparent) disagreement with the current model of metabolic response to ischemia should be discussed in more detail.

1.2 Methodological issue

The definition of tracer uptake index should be better defined: As far as I understand, (and I might be wrong, obviously) it seems to me that average SUV
of whole left ventricular myocardium was considered. Should this be true, I would strongly recommend providing a separate analysis of FDG uptake in infarcted and remote areas which is possible using the adopted software. This request has two reasons:

a. a metabolic shift in remote myocardium seems a possible explanation of data. Should this be confirmed, it would provide a completely different interpretation confirming the presence of signaling mechanisms between these ischemic/necrotic and control tissue.

b. average SUV in UCP3 knockout mice was almost double with respect to control ones. Considering the used thresholding method, this would indicate that tracer uptake was similar in infarct region of knockout animals and in normal regions of control animals. Was it a true infarct?

1.3 technical aspects

Finally, since no dynamic acquisition was performed, myocardial glucose metabolism was indexed by FDG SUV. Though largely used, this approach might have been hampered by the systemic effect of UCP3 deletion on glycolytic flux in the whole body tissues: In other words, the authors might wish reassure the readership that both serum glucose level and (more importantly) blood tracer availability for myocardial uptake were not altered in knockout mice. I am well aware that this consideration does not fit with the data in sham operated models. Yet, the hemodynamic consequences of infarction might have influenced overall metabolism.

Accordingly, the authors might wish to analyze:

a. was there any difference in serum glucose levels in the four groups at imaging?

b. was FDG SUV in non cardiac tissues (e.g. liver and muscles) independent from UCP deletion and myocardial infarction?

1. Minor comment (typo)

At line 172, the sentence: “Moreover, and UCP3-/- mice displayed a significant worsening in cardiac function after coronary artery ligation compared with WT.” is unclear.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I do not have any conflict of interest in this revision.