Reviewer’s report

Title: From arginine methylation to ADMA: A novel mechanism with therapeutic potential in chronic lung diseases

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Reviewer: Rainer H Boger

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Major compulsory revisions:

1. There are also metabolites of enzymatic degradation of SDMA described, although little is known about the specific enzymes involved in this metabolism (Ogawa T et al. Arch Biochem Biophys. 1987 252:526-37). The authors should hint to the possibility that enzymatic degradation may also occur for SDMA.

2. Data from transgenic animal models in which DDAH1 is overexpressed cannot support a role for endogenous expression of DDAH1 in ADMA homeostasis, as suggested by the authors. In overexpression models, the activity of the transgene is largely dependent on the promoter to which it is linked in the overexpression vector. Therefore, these studies cannot rule out the possibility that under wild-type conditions, DDAH2 may be more important than DDAH1.

3. Cytokines and growth factors mentioned in the article should be given by their full names, abbreviations may be given in brackets but sole mentioning of abbreviations is not acceptable (e.g. page 6, Wnt = ?).

4. The discussion of the relevance of plasma ADMA levels needs some amendment. In the study by Cardounel, a relationship between extracellular ADMA and NOS activity was constructed by adding ADMA from the extracellular side. By contrast, whenever endogenous plasma levels of methylarginines are measured, this ADMA stems from “spillover” from intracellular protein breakdown, as correctly described by the authors. Therefore, this is a completely different situation: When ADMA is added from the outside, it needs to be taken up by y+ transporters into the cells – knowing that ADMA does not have a terribly high affinity to the y+ transporters this means that only a minute proportion of any dosage applied to the outside of cells is actually responsible for any biological effect that takes place in the cytoplasm. Quite in contrast, any small change in plasma ADMA under conditions of a clinical study may indicate a much greater change in intracellular ADMA, considering that enzymatic breakdown of ADMA in the cytoplasm is the major pathway of ADMA inactivation, and only part of the intracellular ADMA flux is passed to the extracellular fluid. The authors should apply more caution in discussing the possible relationship between changes plasma ADMA and disease pathology, taking into consideration the above mentioned thoughts. Maybe some of the prospective clinical trials in which the association between minute differences in ADMA and total mortality or
cardiovascular event rates in patients with cardiovascular diseases should be cited here.

Minor essential revisions:
5. In order to better illustrate the complex metabolism of methylarginines, a scheme drawing would be very helpful. Also, the authors might want to devise a graph in which the possible molecular relationships between ADMA biosynthesis and metabolism and lung pathology are depicted.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I hold patents related to assays for ADMA.