Letter and Reply

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Endothelial and red blood cell turnover rate—factors possibly affecting circulating ADMA levels?

Sir,
The interesting reports by Desai and co-workers [1] and Billecke and associates [2] have attracted our great attention.

First, in endothelial cells supraphysiological concentrations of recombinant human erythropoietin (EPO) dose-dependently decreased asymmetric dimethyl-L-arginine (ADMA) generation and stimulated the expression of dimethylarginine dimethylaminohydrolase type II (DDAH-II), an enzyme decomposing ADMA, but not symmetric dimethyl-L-arginine (SDMA) [1]. This clearly contrasts with the opposite results by Scalera et al. [3] who had described EPO-mediated ADMA elevations and lowering of DDAH-II activity under similar conditions.

Second, as acknowledged by Desai et al. [1], their short-term (24-h) EPO effects are difficult to reconcile with serum ADMA elevations by 46% with unchanged SDMA despite concomitant upregulation of DDAH-I, the predominant DDAH isoform in the kidney and the liver, after EPO administration for 10 weeks in mice. Due to a simultaneous rise in haematocrit by 45%, red cell proteins with incorporated ADMA residues were proposed as a potential source of the EPO-induced ADMA accumulation [1]. However, this mechanism is unable to explain increased plasma ADMA in renal patients 7 days after initiation of EPO therapy, i.e. before a rise in erythrocyte counts [3].

Therefore, we would like to suggest that the recently reported EPO-induced acceleration of progenitor cell-mediated endothelial turnover [4] might contribute to EPO-dependent ADMA elevations as free ADMA is liberated during proteolysis, including that accompanying apoptosis. Importantly, the whole-body protein turnover rate determined ADMA levels in ageing and obesity [5].

Additionally, a similar mechanism might occur at accelerated erythropoiesis, usually associated with potentiated erythrocyte destruction. Furthermore, the importance of erythrocytes as a reservoir of protein-bound ADMA was suggested by Billecke et al. [2] who observed a positive correlation between proteolysis rate and gradual ADMA accumulation during 5-h incubations of lysed whole blood supernatants at 37°C.

Conflict of interest statement. None declared.

Editorial Note: Dr Billecke et al. had no further comments on this letter.

Reply

Sir,
We thank Surdacki and Wieczorek-Surdacka for highlighting several observations we discussed in our recent publication [1]. The conflicting findings from our in vitro experiments and those of Scalera et al. were addressed in our paper [1,2]. We also pointed out possible reasons for the discrepancy between our in vitro and in vivo data [1]. We would like to take this opportunity to emphasize that the study by Scalera et al. that is cited by Surdacki and Wieczorek-Surdacka as well as our publication was primarily focused on endothelial cells [2]. Scalera et al. briefly summarized the results from plasma ADMA determinations in three patients with chronic renal failure at baseline and 7 days after initiation of EPO therapy. In the discussion, the authors clearly characterized the human data as observational [2]. In the absence of any details about the patients, methods or design of this observational study, the authors only stated that in patients who had chronic renal disease and received for the first time EPO for 7 days the ADMA plasma concentrations increased by 16% [2]. Based on this information, it is unclear whether the increase in plasma


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