Letters and Replies

Is the afferent arteriole the main location of nitric oxide action and synthesis in humans?

Sir,
I read with great interest the recently published paper by Delles et al. [1] on the role of nitric oxide (NO) in regulating renal haemodynamics in humans. The authors focused their attention on the changes that NO synthase inhibition with L-NAME induces on renal haemodynamics in subjects with mild to moderate hypertension and in controls. On the basis of the results obtained in basal conditions and after treatment with valsartan and amlodipine, the authors concluded that the afferent arteriole appears to be the main location of endothelium-derived NO synthesis and action in humans.

I would like to make some comments.

First of all, the study lacks a daily protein intake assessment: it is well known that protein intake influences the renal haemodynamics inducing glomerular hyperfiltration, probably NO-related [2,3]. Thus, I think that an immoderate protein intake in hypertensives, characterized by higher body mass index and body weight, might have influenced the results of the study.

Secondly, the haemodynamic pattern found by the authors during NO synthase inhibition with L-NAME is characterized by the fall of the renal plasma flow coupled with the rise of the glomerular filtration rate (GFR) and filtration fraction (FF). These changes can only exist when the increase of the tone in the efferent side of the glomerulus exceeds that of the afferent one. Indeed, other authors found that L-NAME administration increases significantly both afferent and efferent resistances in the isolated perfused kidney [4]. For these reasons, the conclusion that the results of this study suggest a prevalent effect of NO on the afferent arteriole seems speculative.

Finally, the data regarding the haemodynamic changes in response to NO synthase inhibition with L-NAME in patients taking antihypertensive medications are not normally distributed (SD greater than the average). The parametric tests (Student’s t-test in this case) are characterized by weak performances when used for the analysis of non-normally distributed data. I think that the authors should pay attention to extrapolating conclusions on the basis of their data.

However, even if I accept the results obtained during the treatment with amlodipine, I would underline the fact that GFR and FF also rose in this case. This demonstrates how the efferent side of the glomerulus is sensitive to NO synthase inhibition with L-NAME when the afferent arteriole is extremely vasodilated by means of a dihydropyridine. The block of the angiotensin-II receptor-mediated effects of valsartan in the synthesis of NO might explain the results found during the treatment with this drug.

In summary, the purpose of this study is very intriguing. However, I think that studies focused on this topic need the standardization (and evaluation) of all dietary factors influencing renal haemodynamics, the right statistical approach and a more accurate data evaluation.

Conflict of interest statement. None declared.

Sir,
We thank Luigi Vernaglione for his critical comments on our paper on the role of nitric oxide (NO) in the regulation of renal haemodynamics in humans [1]. He expresses some concern about standardization of dietary factors, data analysis and interpretation. We are fully aware of the fact that diet may have an important impact on renal haemodynamics. While we have already discussed a potential confounding role of sodium intake on the response of renal haemodynamics to NO synthase inhibition in our paper [1,2], Vernaglione highlights possible effects of uncontrolled protein intake and potential differences between normotensive and hypertensive subjects. Unfortunately, self-reported protein intake and calculation of protein intake from urine urea excretion do not accurately reflect dietary protein intake and administration of a standardized formula diet over 8 weeks to control for protein intake appears not feasible. Thus, theoretical considerations, such as detailed dietary control, cannot be put into practice reasonably. However, we asked patients not to change their dietary habits during their participation in this study, which should exclude dramatic changes in protein intake. Although we cannot rule out a difference in protein intake between normotensive and hypertensive study participants, we want to point out that the main findings of our study derive from the relatively homogenous group of hypertensive subjects and not from a comparison between normotensive and hypertensive subjects.

We also may reassure Vernaglione that parametric tests have been applied only after formal testing of our data for normal distribution. However, Vernaglione is right in that non-parametric tests may, nevertheless, be useful in the analysis of data with SDs greater than the average. We have

doi:10.1093/ndt/gfh456

Reply