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## Letters

### Low dose L-arginine reduces blood pressure and endothelin-1 production in hypertensive uraemic rats

Sir,

The paper by Dumont *et al.* [1] indicates that improvement of nitric oxide (NO) release with low dose of L-arginine in drinking water (0.1%) significantly attenuates development of hypertension and progression of renal insufficiency in rats with reduced renal mass. The data for such interpretation seem to be clear from the evidence presented. However, we are concerned with the authors' conclusion that this effect was not present in rats receiving high dose of L-arginine (1%).

Uraemic rats and their matches receiving high dose L-arginine seemed to be different from the series of experimental uraemic animals treated, or not treated, with low L-arginine dose, with regards to blood pressure (BP) and degree of uraemia. Systolic BP (SBP) was not different between *treated* (high dose) and *untreated* rats, but SBP in the uraemic low-dose group ( $171 \pm 9$  mmHg) did not seem to be different from the *untreated* uraemic group used for comparison with the high-dose rats ( $175 \pm 11$  mmHg). Also, rats in the high-dose study were not as uraemic as those in the low-dose groups: serum creatinines were lower and creatinine clearances were 57% and 71% higher. It is conceivable that the effects described for low dose require higher BP and/or greater renal dysfunction.

Data for NO metabolites were not presented for the high-dose group, so conclusions on NO release are not supported.

Different behaviour in response to low and high L-arginine doses, is an interesting phenomenon. One would

expect increased response of NO production, lower BP, and less progression of renal insufficiency with high dose. The authors discuss several possible reasons for their results. Different outcome in *untreated* uraemic *vs* uraemic rats receiving L-arginine may be related to abnormal membrane transport properties occurring in renal failure [2–5]. L-arginine is mainly transported *via* cationic aminoacid transporter systems [6]. Abnormal transport for L-lysine [3] and L-arginine [5,7] has been described in uraemia. Increased endogenous NO synthase (NOS) inhibitors have been described in renal failure [5], which are transported *via*  $y^+$  and  $y^+L$  systems, too [6]. The existence of such endogenous L-arginine analogues have been used to explain the so called 'L-arginine paradox' [8]. Up-regulation of  $y^+L$  activity could explain the paradoxical finding of increased NO production by uraemic platelets with decreased L-arginine, and elevated N<sup>G</sup>-monomethyl-L-arginine [17]. Reduced oxygen-derived free radical formation by addition of L-arginine to cardioplegic solutions significantly improves myocardial protection. However, these beneficial effects are dose-limited, as higher concentrations of L-arginine increase free radical production, resulting in vascular and myocardial dysfunction [9].

The existence of a caveolar complex between CAT1 and endothelial NOS (eNOS) has been documented, suggesting a mechanism for a directed delivery of arginine to eNOS. Direct transfer of extracellular arginine to membrane-bound eNOS accounts for the 'arginine paradox', explaining why caveolar location of eNOS is required for optimal endothelial NO production [10].

The abnormalities described by Dumont *et al.* [1] may be related to changes in membrane properties occurring in uraemia.

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