Functional changes in the ageing kidney: is there a role for asymmetric dimethylarginine?

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Age-related changes of renal haemodynamics

Normal human ageing occurs with morphological and functional changes in nearly all organ systems, and the kidney is no exception to this rule. Even in individuals without primary renal disease, kidney structure and function deteriorate with senescence to some extent. Recent studies have revealed, however, that age-related renal changes are accelerated by co-morbid conditions such as hypertension, atherosclerosis and heart failure [1–5].

Results from the seminal ‘Baltimore Longitudinal Study on Aging’ and from several cross-sectional studies have shown that the decrease of glomerular filtration rate (GFR) in healthy elderly subjects is less than was thought previously [1,3,6,7]. In some elderly individuals, even no change of GFR was documented over a time span of at least 25 years [6]. Thus, in a reasonable number of healthy elderly subjects, the GFR remains within the (lower) normal range. In contrast,
effective renal plasma flow (ERPF) decreases proportionally more than GFR, and this finding may explain in part the observed increase of filtration fraction (FF) in elderly individuals, i.e., the ratio between GFR and ERPF [3,7]. Furthermore, the decrease of ERPF out of proportion to the blood pressure in the healthy elderly implies that the renovascular resistance (RVR) must be elevated. Indeed, we and others have shown that RVR is significantly increased in normotensive elderly individuals without cardiovascular disease [3,8]. Renal vasoconstriction is even more pronounced in the elderly with co-morbidity such as hypertension or heart failure [3,7,9]. Thus, the hallmark of renal ageing is increased basal renovascular tone accompanied by reduced perfusion, and these age-related changes are accentuated in patients with cardiovascular co-morbidity. In addition, the ability of (post-glomerular) vessels to dilate in response to stimuli such as acetylcholine, amino acids or nitric oxide (NO) is also reduced in the elderly [10–12]. It is still unresolved whether these age-related changes in renal hemodynamics are caused by structural abnormalities, or whether there also exists a functional abnormality, i.e., reduced capacity of renal vessels to dilate as a consequence of reduced availability of (or responsiveness to) vasodilator substances. Experimental studies and studies in humans support the latter concept [10–13]. In this context, it has to be pointed out that the renal microvasculature is particularly sensitive to NO synthase (NOS) inhibition; this has been demonstrated in animal experiments as well as in human studies [14–16]. The observation points to an important role for NO in the regulation of (basal) medullary blood flow, and in the control of the pressure-natriuresis [16].

**Ageing and asymmetric dimethylarginine**

In a cross-sectional study of a random population sample, a significant positive correlation was found between age, blood pressure and plasma levels of asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of NOS [17]. ADMA is released from proteins that have been post-translationally methylated and subsequently hydrolysed. These proteins are found largely in the nucleolus and appear to be involved in RNA processing and transcriptional control. Two types of enzymes methylate arginine residues: type I protein arginine methyltransferase forms ADMA, whereas type II forms symmetric dimethylarginine, i.e., the biologically inactive stereoisomer of ADMA. ADMA is excreted by the kidneys to some extent, but the predominant degradation pathway is by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), which hydrolyses ADMA to dimethylamine and L-citrulline (Figure 1) [18,19]. Co-localization of DDAH and NOS in various cell types including renal tubular cells supports the hypothesis that the intracellular concentration of ADMA is regulated actively and cell specifically in NO-generating cells [20]. Further evidence for this hypothesis comes from results of a recently published experimental study showing an inhibitory effect of NO on DDAH activity, thus regulating its own (local) concentration via the metabolism of ADMA [21] (Figure 1). Several experimental and clinical studies have documented that DDAH activity is reduced in the presence of hypercholesterolaemia and insulin resistance [19,22], i.e., conditions that have a high prevalence among elderly subjects. Direct measurements

![Fig. 1. Biochemical pathways for generation and degradation of the endogenous nitric oxide synthase inhibitor ADMA (for explanation, also see text).](https://academic.oup.com/ndt/article-abstract/18/7/1245/1809782/45x70)
Asymmetric dimethylarginine and renal ageing

Whatever the cause(s) of increased ADMA blood levels in the elderly, they may reduce NO availability by NOS inhibition and thus contribute to endothelial dysfunction and arteriosclerosis, and finally lead to increased renovascular resistance and hypertension [19,23]. This hypothesis is supported by the finding of significantly increased plasma ADMA concentrations even in non-smoking healthy normotensive elderly subjects, in parallel with significantly reduced renal perfusion (Table 1) [24]. Furthermore, in logistic regression analysis, the plasma ADMA level was the only significant predictor of reduced ERPF and increased RVR, explaining a large part of their relationship between plasma ADMA and the level of blood pressure [24].

In summary, recent studies provide evidence for a significant relationship between increased blood levels of the endogenous NOS inhibitor ADMA, and reduced renal perfusion and high blood pressure in senescence. The role of ADMA in the pathophysiology of age-related endothelial dysfunction, resulting in increased renovascular tone and blood pressure, has to be elucidated further.

References