DDAH Says NO to ADMA

John P. Cooke, Yohannes T. Ghebremariam

Endothelium-derived nitric oxide (NO) is vasoprotective, as it enhances endothelial cell survival and proliferation, inhibits the excessive proliferation of vascular smooth muscle cells, and suppresses the adhesion of platelets and inflammatory cells to the vessel wall.1 Substantial evidence from preclinical studies and human research indicates that impairment of the endothelial NO synthase (NOS) pathway accelerates vascular disease and increases the risk for major adverse cardiovascular events.2–5 Impairment of the NOS pathway is multifactorial, but it is increasingly apparent that circulating inhibitors of NOS play an important role. Asymmetric dimethylarginine (ADMA) and monomethyl-L-arginine (MMA)6 are endogenous competitive inhibitors of NOS. Most human studies have focused on ADMA, as it is the more prevalent species in human plasma. Plasma ADMA is elevated in patients with cardiovascular disease or with risk factors, and it contributes to vascular resistance and stiffness.7,8 Notably, several large studies have shown that plasma ADMA is an independent biomarker for cardiovascular morbidity and total mortality.4,5,9 Accordingly, endogenous mechanisms that regulate ADMA are deserving of further scientific attention.

Synthesis and Metabolism of ADMA
Protein-arginine methyltransferases methylate arginine residues on histone and other nuclear proteins.10–12 When these proteins are hydrolyzed, free methylarginines are released, including ADMA, MMA, and symmetrical dimethylarginine (this last methylarginine does not inhibit NOS) (Figure). These may be expelled from the cell by the cationic transporter to be secreted in the urine, which is the primary route for symmetrical dimethylarginine clearance. However, the majority of ADMA and MMA (≈80%) is degraded within the cell by dimethylarginine dimethylaminohydrolase (DDAH).13–16 The activity of DDAH is reduced by oxidative stress that is associated with cardiovascular disease,17–19 causing ADMA levels to become elevated in these conditions.13,20 By contrast, global overexpression of DDAH1 in transgenic mice reduces ADMA levels and increases NO production.21–23 These DDAH1-overexpressing mice manifest reduced vascular resistance, increased insulin sensitivity, and enhanced endothelial regeneration,21–23 and they are resistant to vascular lesion formation induced by endothelial denudation, vascular inflammation, or hypercholesterolemia.22,24,25 These observations are consistent with an essential role of DDAH1 in maintaining vascular homeostasis.

Global DDAH1 Deletion: Accumulation of ADMA and Loss of Homeostasis
In this issue of ATVB, Hu et al26 provide strong evidence that of the 2 DDAH isoforms (DDAH1 and DDAH2), DDAH1 is largely responsible for the degradation of ADMA. They generated a murine model of global DDAH1 knockout (DDAH1−/−) by targeting exon 4 of the DDAH1 gene. The DDAH1−/− mice displayed normal developmental features while showing negligible tissue DDAH activity in several tissues. The abrogation of DDAH enzymatic activity (assessed using isotope-labeled ADMA or MMA) was surprising, because expression of the DDAH2 isoenzyme was unaffected. The expression of endothelial NOS, protein arginine methyltransferases 1 and 3, and cationic transporter were also unaffected. With the loss of DDAH activity there were significant elevations in tissue and plasma ADMA and MMA.

Isolated aortic rings from the DDAH1−/− mice manifested impaired endothelium-dependent vasodilation in response to acetylcholine, consistent with ADMA-induced suppression of NOS. These animals also exhibited a significant increase in blood pressure, reminiscent of the hemodynamic abnormality in endothelial NOS knockout mice.27 The elevation in blood pressure was reversed by infusion of L-arginine, consistent with the competitive inhibition of NOS by ADMA.

This study confirms the importance of DDAH in regulating NO synthesis by its degradation of the endogenous NOS inhibitors ADMA and MMA. Furthermore, this study suggests that a specific isoenzyme, DDAH1, is primarily responsible for metabolism of the methylarginines and that DDAH2 cannot compensate for the loss of DDAH1.

Future Directions
Although the study of Hu et al26 complements previous studies using the endothelial-specific DDAH1 knockout and heterozygous DDAH1-deficient mice,28,29 it also raises some interesting questions. First, there is a discrepancy between this study and a previous one that suggested that the global DDAH1 knockout was lethal.29 It is possible that in the previous study (in which exon 1 of DDAH was targeted), the deletion might have adversely affected another genomic region necessary for embryogenesis. If DDAH2 does not compensate for the loss of DDAH1, what may be its function? The literature is mixed regarding the importance of DDAH2 in the metabolism of ADMA.6,30–32 Overexpression of DDAH2 improves endothelium-dependent vasorelaxation and increases NO synthesis, whereas small interfering RNA knockdown of DDAH2 reduces NO synthe-
Figure. The role of DDAH1 in the metabolism of the NOS antagonists ADMA and MMA. DDAH1 is a key enzyme that converts methylarginines to L-arginine. This metabolic pathway is critical for maintaining endothelial function and cardiovascular health.

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Disclosures

None.

References


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