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Asymmetric dimethylarginine (ADMA) as a target for pharmacotherapy

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Abstract:

Asymmetric dimethylarginine (ADMA) is synthesized during the methylation of protein arginine residues by protein arginine methyltransferases (PRMT) and is released during proteolysis. ADMA is a competitive inhibitor of nitric oxide synthase and may decrease NO availability. ADMA is eliminated by renal excretion or is metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to citrulline and dimethylamine. Two other endogenous methylarginines are also synthesized by PRMT: N-monomethyl-L-arginine (L-NMMA) and symmetric dimethylarginine (SDMA). L-NMMA inhibits NO synthase but its concentrations in circulation are much lower than ADMA whereas SDMA is inactive. Plasma concentration of ADMA is markedly increased in patients with chronic renal failure and moderately increased in patients with many other diseases including hyperlipidemia, diabetes mellitus, arterial hypertension, hyperhomocysteinemia and heart failure. The increased concentration of ADMA is positively correlated with markers of atherosclerosis, such as carotid artery intima-media thickness and has a predictive value for acute cardiovascular events in prospective studies. Angiotensin-converting enzyme inhibitors, angiotensin AT₁ receptor antagonists, vitamin E and, according to some studies, estrogens used in hormonal replacement therapy reduce plasma ADMA concentration, which may contribute to their beneficial effect on NO synthesis and endothelial function. However, in some states associated with excess of NO, such as septic shock or excitotoxic neuronal injury ADMA may be protective by limiting toxic effect of high concentrations of NO. This article reviews the effect of pharmacotherapy on ADMA metabolism and its possible clinical implications.

Key words:

nitric oxide, nitric oxide synthase, asymmetric dimethylarginine, dimethylarginine dimethylaminohydrolase
