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Asymmetric dimethylarginine (ADMA) and cardiovascular disease

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Asymmetric dimethylarginine (ADMA) is an endogenously produced inhibitor of nitric oxide synthase that may impair endothelial function and accelerate atherosclerosis. ADMA is generated during proteolysis of posttranslationally methylated proteins. Especially the liver and kidneys serve as sinks for ADMA, by clearing large amounts of ADMA from the circulation. Failure of one these organs leads to elevated plasma levels of ADMA, which, by impairing the function of other organs, ultimately may lead to multiple organ failure. Prospective studies have shown that ADMA, independent of traditional risk factors, predicts cardiovascular events in high risk patients groups as well as in the general population.

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Endothelium-derived nitric oxide (NO), which is synthesized from arginine by NO synthase (NOS), is an important regulator of vascular homeostasis. In addition to being a powerful vasodilator, NO inhibits the adhesion of inflammatory cells to the vascular wall, the aggregation of platelets and the proliferation of smooth muscle cells (1). Inactivation and/or reduced synthesis of NO is seen in conjunction with risk factors for cardiovascular disease (CVD) and may promote endothelial dysfunction, hypertension, thrombus formation and atherogenesis (2). Asymmetric dimethylarginine (ADMA), a byproduct of cellular protein turnover, is an endogenous competitive inhibitor of NOS (3). Consequently, elevated ADMA levels may initiate and accelerate atherosclerosis and precipitate cardiovascular events.

In the following sections we describe the metabolism of ADMA, discuss some analytical aspects and review the epidemiological evidence for ADMA as a cardiovascular risk factor.

Metabolism and clearance of ADMA

The structure of ADMA and its metabolic origin and fate are shown in figures 1 and 2, respectively. The plasma concentration of ADMA is the resultant of many processes at the cellular and whole body level (4). Posttranslational methylation of the terminal guanidino-group of arginine residues in proteins is catalyzed by a family of protein arginine methyltransferases (PRMTs), comprising two classes (5). Both classes catalyze the monomethylation of arginine, but upon attachment of a second methyl group to monomethylarginine, the reaction product is PRMT-dependent. Type 1 PRMTs catalyze the formation of ADMA, whereas type 2 PRMTs produce symmetric dimethylarginine (SDMA). Arginine methylation plays a crucial role in expanding the functional repertoire of the cellular proteome (6). Most methylated proteins interact with nucleic acids and are involved in processes like transcription, RNA splicing, DNA repair, and epigenetic regulation of gene expression (7). With a few exceptions, protein methylation is irreversible and methylated arginine residues remain an integral part of the protein until it is degraded by proteolysis (6). Free ADMA, formed during proteolysis, is hydrolyzed by the intracellular enzyme dimethylarginine dimethylaminohydrolase (DDAH), of which two isoforms exist

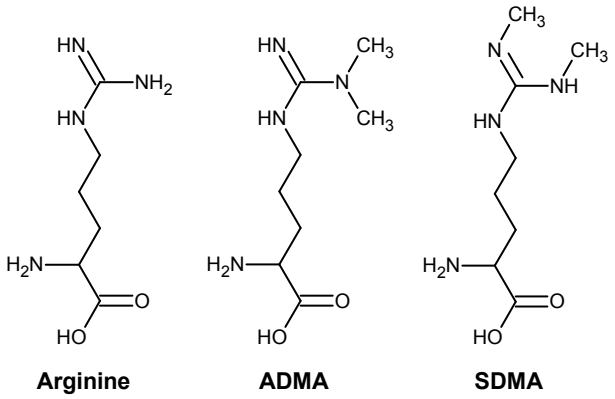

Figure 1. Structures of arginine, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA). Arginine is the substrate of nitric oxide synthase (NOS). ADMA, but not its structural isomer SDMA, inhibits NOS activity.

(8). Some ADMA escapes degradation and leaves the cell via cationic amino acid transporters (CAT) that also mediate uptake of ADMA by neighboring cells or distant organs, thereby facilitating an active interorgan transport (9, 10). Clearance of ADMA from the plasma occurs for a small part by urinary excretion, but the bulk of ADMA is degraded by DDAH, after uptake from the circulation (11). Using a rat model,

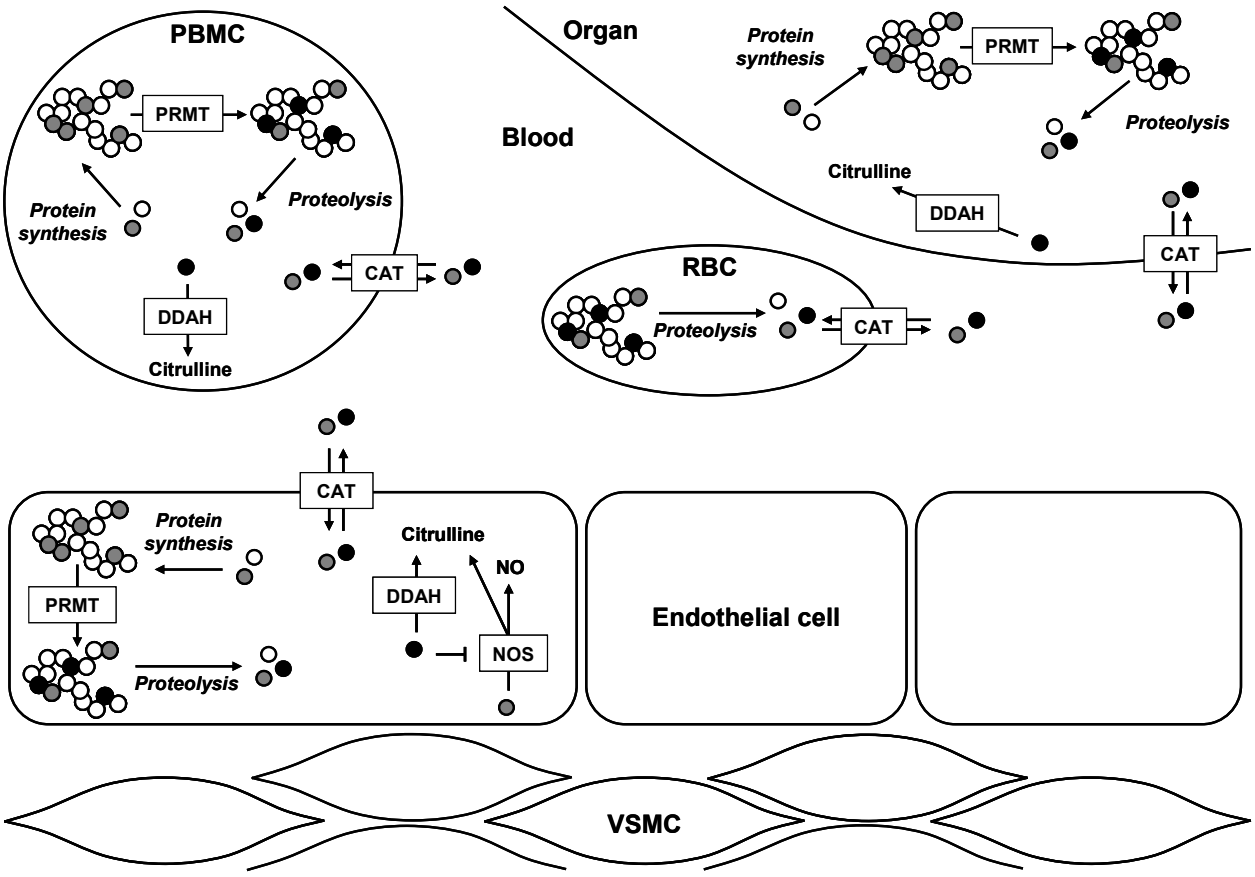

Figure 2. Schematic overview of the metabolism and clearance of asymmetric dimethylarginine (ADMA) at the cellular and whole body levels. Arginine residues of proteins are methylated by protein arginine methyltransferases (PRMT) and free ADMA is formed upon proteolysis of these proteins. ADMA is hydrolyzed by intracellular dimethylarginine dimethylaminohydrolase (DDAH) or exported from the cell by cationic amino acid transporters (CAT). Leukocytes and erythrocytes may also release ADMA into the circulation. Clearance of ADMA from the circulation occurs again by CAT-mediated uptake followed by degradation, especially by organs with a high DDAH activity, such as kidney and liver. ○ = Amino acid; ● = Arginine; ● = ADMA

we were able to show that organs with high DDAH activity, notably the kidneys and the liver, are mainly responsible for clearance of ADMA (12-14). Blood flow through the organs was measured by injection of radiolabeled microspheres and ADMA concentrations were determined in the aorta and in the renal, hepatic and portal veins. From these measurements fractional extraction (i.e. the percentage that is cleared from the plasma) and organ fluxes were calculated. Fractional extraction of ADMA was slightly higher in the kidney than in the liver. However, because blood flow through the liver is higher than through the kidneys, the liver clears more ADMA from the circulation than the kidney. In humans, measurement of arteriovenous concentration differences also revealed net renal and hepatic extraction of ADMA (15, 16). The essential role of the liver in the elimination of ADMA in humans was confirmed in several clinical studies by our group and other investigators [reviewed in (17)]. Liver cirrhosis and alcoholic hepatitis were found to be associated with elevated plasma levels of ADMA (18, 19). In patients undergoing major liver resection, ADMA levels were significantly elevated in a subgroup with prolonged postoperative hepatic injury (20), and in patients undergoing liver transplantation, the preoperative ADMA concentrations were elevated and dropped very rapidly after transplantation (21).

Taken together, these results show that deterioration of organ function, by diminished clearance, may lead to increased plasma levels of ADMA. Conversely, high plasma levels of ADMA may exacerbate organ dysfunction. In a study among critically ill patients, plasma ADMA concentration was independently related to the presence of hepatic and renal failure. In a logistic regression model, plasma ADMA ranked as the first and strongest predictor for outcome, with a 17-fold increased risk for ICU death in patients who were in the highest quartile of ADMA (22). Possibly, extensive interorgan transport of ADMA is causally involved in the cascade of failing organs in patients with multiple organ failure (23).

Analytical aspects

Reliable quantification of low plasma concentrations of ADMA and SDMA, in the presence of many other amino acids that are present in far higher concentrations, is an analytical challenge. A large number of analytical approaches has been described, most of which are based on high performance liquid chromatography (HPLC) with fluorescence detection (24). Considering the very narrow distribution of ADMA concentrations in healthy subjects (24-26), the importance of low imprecision of the analytical procedure cannot be overemphasized. We have developed an HPLC method for the simultaneous quantification of arginine, ADMA, and SDMA, with an inter-assay coefficient of variation <3% for ADMA (27). To increase throughput, we later adapted the method by performing separation on a monolithic column, that allows operation at high flow rates without loss of separation efficiency (28). Liquid chromatography with mass spectrometric detection, usually in tandem mode, is increasingly used for determination of ADMA and related analytes (29, 30), but accurate and precise quantification requires the use of stable isotope labeled internal standards. Furthermore, an ELISA for the determination of ADMA in plasma is commercially available (31). This technique allows relatively rapid analysis of large numbers of samples, but seems less selective, accurate, and precise than chromatographic techniques (32).

Regarding measurement of ADMA in plasma, we have observed no significant differences in concentrations of arginine, ADMA, and SDMA between EDTA- and heparin-plasma samples (24), but citrate-plasma should not be used because the rather large volume of citrate solution in the blood collection tubes leads to a considerable and variable dilution. Serum is also suitable for the analysis of ADMA and SDMA, but arginine concentrations are 60% higher in serum compared to plasma. Storage conditions are not very critical. Plasma can be stored indefinitely at -70°C or below, and at least several years at -20°C, without alteration in analyte concentrations, and repeated freeze/thaw cycles have no effect.

ADMA and cardiovascular disease

Because ADMA reduces NO production by competitive inhibition of NOS, elevation of ADMA is considered a risk factor for endothelial dysfunction and CVD. Many other risk factors for CVD, such as hypertension, diabetes mellitus, hypercholesterolemia and hyperhomocysteinemia, are also associated with reduced availability of NO and endothelial dysfunction, and it has been suggested that ADMA is the ultimate mediator of the adverse effect of these risk factors on the vascular endothelium (33).

Intima-media thickness (IMT) of the carotid arteries is a surrogate marker of generalized atherosclerosis and future CVD, both in the general population and in high-risk patient groups. Both in univariate and multivariate regression analysis, the plasma concentration of ADMA was directly related to carotid IMT in healthy volunteers and in patients with renal failure (34, 35). The results of prospective clinical studies provide the most compelling evidence for a role of ADMA in the development of CVD. In one of the first prospective studies, conducted in a cohort of 225 patients with end-stage renal disease, ADMA and age were the strongest predictors of cardiovascular events and total mortality, even after adjustment for other traditional and novel risk factors (36). Since then, many other prospective studies in high-risk populations have confirmed that ADMA is an independent CVD risk factor [reviewed in (37, 38)]. In contrast, adequate information on the relevance of ADMA as a marker of morbidity and mortality in the general population is sparse (38). We have investigated this issue in the Hoorn Study, a community-based prospective cohort study among 2484 men and women, aged between 50 and 75 years (39). The main outcome measure was the combined incidence of fatal and non-fatal CVD events during 10 year follow-up. After adjusting for age, gender and established risk factors, a high plasma concentration of ADMA (i.e. highest quintile versus the four lower quintiles) was associated with a hazard ratio for CVD of 1.49 (95% confidence interval 1.16 to 1.90)

in subjects without diabetes and 0.48 (95% confidence interval 0.24 to 0.98) in subjects with diabetes. In another large community-based cohort, the Framingham Offspring Study, ADMA was significantly associated with all-cause mortality, but not with CVD incidence (40). Interestingly, in that study, effect modification by diabetes status was also observed. In patients with diabetes, there was a trend towards lower risk of total mortality with increasing quartiles of ADMA (41). The independent observation of this apparent protective effect of high ADMA levels in patients with diabetes in two large prospective studies makes it unlikely that this is a chance finding, and merits further investigation. It may reflect a true protective effect of ADMA, for instance by inhibition of uncoupled NOS that produces superoxide instead of NO, or may simply indicate that measurement of ADMA in plasma does not adequately gauge its effect on the cardiovascular system. Both generation and DDAH-mediated metabolism of ADMA as well as inhibition of NOS activity by ADMA are intracellular processes, but most studies report on plasma ADMA levels, based on the underlying assumption that the concentration of ADMA in plasma accurately reflects intracellular ADMA levels. It is tempting to speculate that there may be (patho)physiological conditions in which intracellular and circulatory ADMA are inversely associated. A situation like this may occur if CAT expression or activity is diminished, resulting in a slow cellular egress of ADMA, thereby increasing intracellular, but decreasing extracellular ADMA levels (10).

Conclusions and outstanding questions

Over the past decade it has become clear that ADMA is a risk factor for CVD in individuals at high risk, such as patients with chronic kidney disease or coronary artery disease. More recent studies have extended this observation to the general population, in which ADMA was shown to be an independent risk predictor of moderate strength. Two patient categories stand out in terms of aberrant ADMA-associated risk. In critically ill patients with failure of multiple organ systems, high plasma levels of ADMA are associated with an extremely high mortality risk. In contrast, in patients with type 2 diabetes, high ADMA is associated with a reduced cardiovascular risk.

Most clinical studies report on plasma ADMA levels, based on the underlying assumption that the concentration of ADMA in plasma reflects intracellular ADMA levels. Reports on the relation between plasma and intracellular ADMA levels in vascular and other tissues and organs are scarce, and further study in this field is urgently needed.

On a parallel note, the relation between the concentration of ADMA in plasma and in erythrocytes is an interesting field of inquiry. Increased plasma levels of ADMA have been found in diseases that are associated with elevated hemolysis, such as sickle cell disease (42, 43) and HELLP syndrome (44), and in vitro experiments have confirmed release of ADMA upon erythrocyte lysis (45). Further experiments are required to delineate the exact role of erythrocytes in the metabolism and transport of ADMA. Likewise, peripheral blood mononuclear cells (PBMC) produce and excrete ADMA (46), but whether measurement of the intracellular concentration of ADMA in PBMC or other types of leukocytes provides clinically useful information remains to be established.

Finally, homoarginine, a naturally occurring homologue of arginine that affects NO production, seems to be an interesting new player in the cardiovascular field. A recent study found low homoarginine levels to be independently associated with cardiovascular and all-cause mortality in patients referred for coronary angiography and in patients undergoing hemodialysis (47). Studies are needed to elucidate the underlying (patho)physiological mechanisms, the biochemical pathways involved in synthesis and degradation of homoarginine, and potential interactions with the metabolism of ADMA.

In conclusion, ADMA is coming of age in the field of CVD risk, but our understanding of its metabolism and role in the vascular system is still far from complete.

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