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**CARDIOVASCULAR TESTS: USE & LIMITS OF BIOCHEMICAL
MARKERS - THERAPEUTIC MEASUREMENTS OF ADMA
INVOLVED IN CARDIOVASCULAR DISORDERS.**

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Introduction

Asymmetric dimethylarginine (ADMA) is an endogenously occurring methylarginine that inhibits nitric oxide synthesis. Plasma levels of methylarginines increase in renal failure and certain cardiovascular pathologies, and in patients with end stage renal failure the level of ADMA predicts the risk of cardiovascular events and overall mortality. The object of this review is to describe the mechanisms of ADMA synthesis, metabolism and uptake and to outline techniques for measuring ADMA and the pathological states in which ADMA levels are altered.

NO inhibition

Nitric oxide (NO) is a signalling molecule which plays an important role in maintaining vascular tone, preventing platelet aggregation [1] and regulating blood pressure [2]. Nitric oxide synthases (NOS) produce NO and citrulline from arginine in a five-electron oxidation of the guanidine nitrogen of oxygen requiring NADPH and tetrahydrobiopterin as cofactors (Figure 1A). Some of the earliest inhibitors of NOS were targeted to the arginine binding site and included in this class of guanidine-substituted arginine analogues was L-N^Gmonomethylarginine (L-NMMA- Figure 1B; Fig 2 [A]) [3,4]. The inhibition constants for L-NMMA have been measured in iNOS, nNOS and eNOS to be 6.2 μ M, 0.18 and 0.94 respectively [5,6,7,8] and the K_m for arginine ranges from 7-19 μ M. There has been speculation about the mechanism of NOS inhibition by methylarginines and, at low concentrations of arginine, ADMA might bind to elicit uncoupled oxidation of NOS and generate superoxide [9,10].

Several years before the identification of nitric oxide as endothelium dependent relaxing factor [11], molecules similar to L-NMMA namely N^GN^Gdimethylarginine (ADMA- Fig 1B) and N^GN^{G'} dimethylarginine (SDMA- Fig 1B) had been detected in urine [12]. In 1992 Vallance *et al* proposed that the naturally occurring L-NMMA and ADMA might regulate nitric oxide production [12, 13]. It was subsequently shown that both L-NMMA and ADMA inhibited endothelium dependent contractions of aortic rings and altered vascular tone in humans *in vivo* [12, 13]. ADMA was found to inhibit NOS isoforms at equivalent doses as L-NMMA but SDMA did not inhibit NOS activity [15].

ADMA synthesis

One of the first proteins observed to have methylated arginine residues was myelin basic protein [16]. This process of basic amino acid methylation became well documented [17] and it was recognised that arginine methylation occurred shortly after protein synthesis. Incorporation of radiolabelled methyl groups onto the arginine residues of myelin basic protein revealed that once methylated the reaction appeared to be irreversible and the arginine-methylated protein took weeks to degrade [18, 19]. Originally methylation was divided into histone and non-histone arginine protein methylation. More recent studies have suggested that up to 200 proteins may be methylated including proteins involved in translation, transcription, membrane transporters, and cell cycle regulation [20].

Arginine residues on proteins are methylated *in vivo* by the action of protein arginine methyltransferases (PRMT); S-adenosylmethionine (SAM) donates the methyl group for the reaction and S-adenosylhomocysteine (SAH) is a reaction by-product. Both SAH and SAM affect the rate of arginine methylation, SAM promotes the reaction whilst SAH appears to be a weak inhibitor of PRMT activity [21].

Arginine residues can be asymmetrically methylated by Type 1 PRMTs or symmetrically methylated by Type 2 PRMTs; monomethylation of arginine residues appears to be an intermediate step in either the Type 1 or Type 2 PRMT reactions. Free methylarginines are released as proteins undergo proteolysis (Figure 2 [B]). Type 1 PRMTs are found in the heart, smooth muscle cells & endothelial cells, at the time of writing four Type 1 PRMT isoforms have been identified: PRMT1, PRMT3; PRMT4 (CARM1) and PRMT6 (Table 1). PRMT1 is found in brain, liver & testis

[22]. PRMT3 is found in adrenal, heart, small intestine, lung, kidney, ovary, testis, thyroid, brainstem, cerebellum, cortex, hippocampus and pituitary, with PRMT1 having a similar pattern of expression but is found at higher levels in lung [23]. PRMT3, in contrast to PRMT1, exists as a monomer and is found throughout the cytoplasm [23]. The peptide sequences recognised by the Type 1 PRMTs are thought to contain arginine flanked by glycine residues [24].

PRMT5 is the only known Type2 PRMT and it appears to be localised to the cytosol, symmetrically methylated arginine residues have been found in the nucleoplasm of HeLa cells [25]. PRMT5, like PRMT3, is sensitive to agents that modify cysteine sulphhydryl groups [26]. Several single nucleotide polymorphisms (SNP) have been identified for the PRMT isoforms and published in the SNP database (Table 1) with PRMT3 having significantly more SNP than other isoforms.

The information available about the regulation of PRMT expression and regulation is incomplete. Both oxidised and normal low-density lipoprotein (LDL) increase the expression of PRMT1, PRMT2 and PRMT3 [27]. Increased activity of PRMT1 has been demonstrated following moderate levels of shear stress, which can be attenuated by I κ B kinase A or the PPAR γ activator, troglitazone [28]. The action of shear stress upon PRMT1 is attributed to the action of NF γ B response element, and following shear stress increased levels of methylarginines have been measured [28]. Similar levels of shear stress have been shown to activate eNOS through AKT-phosphorylation [29, 30].

PRMT type	Class	Arginine methylation	Localisation	Chromosome	SNP	Reference
Type 1	PRMT1	MMA, ADMA	Nucleus	19q13	22	[22; 31]
	PRMT3	MMA, ADMA	Cytosol	11p15.1	240	[23; 26]
	CARM1/PRMT4	MMA, ADMA	Nucleus	12p13.32	48	[32]
	PRMT6	MMA, ADMA	Nucleus	1p13.3	16	[26]
	PRMT2	No apparent Arginine methylation	Nucleus	21q22.3	87	[33]
Type 2	PRMT5	MMA, SDMA	Cytoplasm	14q11.2	22	[25, 26, 34]

Table 1: Summary of Type 1 and Type 2 PRMT isoforms, chromosomal localisation as published by the Wellcome Trust Sanger Centre: http://www.ensembl.org/Homo_sapiens/ and single nucleotide polymorphism (SNP) data from <http://www.ncbi.nlm.nih.gov/SNP/>.

ADMA metabolism

A route for ADMA metabolism was proposed following observations in *in vivo* studies that excretion of radiolabelled ADMA and L-NMMA levels were lower than those measured in urine for SDMA [35]. An enzyme was identified from rat kidney lysate which could metabolise ADMA to citrulline and dimethylamine respectively [36]. This enzyme was subsequently purified from rat tissue and became known as N^G,N^G-dimethylarginine dimethylaminohydrolase - DDAH (Figure 2-[C]; [37]); it was found later in human tissue [38]. DDAH also metabolises L-NMMA to citrulline and methylamine but it has no activity towards SDMA [15]. The activity of DDAH

alters the concentration of methylarginines within cells and the levels of NO produced by the cells (Figure 2-[A]; [39]).

A second DDAH isoform (DDAHII) was identified with 62% homology to DDAHI [40]. DDAHII is expressed in highly vascularised tissues and in immune tissues whereas the distributions of DDAH1 correlates with those described for nNOS [41]. Interestingly DDAHII levels are highly expressed in foetal tissues. Both DDAHI and II were found to have a cytosolic localisation suggesting that they maintain low ADMA levels throughout the cell [42, 43]. The DDAH1 gene maps to chromosome 1p22 and DDAHII maps to the MHC III region of chromosome 6p21.3 [41].

Whilst DDAH plays an important role in metabolising endogenously occurring NOS inhibitors, high levels of NO appear to feedback to influence the activity of DDAH. Leiper *et al* demonstrated that DDAH could be nitrosylated [43]. The crystal structure showed that the DDAH active site contained a catalytic triad Cys-His-Glu [44] and mutation of this active site Cys249 abolished nitrosylation. Furthermore NO released from cytokine stimulated endothelial cells elicited DDAH nitrosylation and reduced DDAH activity, indicating that following iNOS induction DDAH activity may be reduced leading to an accumulation of methylarginines [43]. It has been suggested that zinc might regulate DDAHI activity through interactions with active site cysteine residues [45], although no zinc was identified from the crystal structure of DDAH.

Based upon measurements of urinary dimethylamine as an indicator of ADMA metabolism, it seems that a healthy adult generates about 300 μM of ADMA per day of which 250 μM is metabolised by DDAH [46].

Manipulation of DDAH expression

Treatment of endothelial cells with all-*trans*-Retinoic acid (atRA) decreases levels of secreted ADMA and increases the levels of NO_x generated by the cells [47]. DDAHII expression is upregulated by all-*trans*-Retinoic acid, possibly acting through a PPAR/RXR site in the DDAHII promoter.

Estrogen also appears to reduce ADMA levels and increase DDAH activity, this attenuation in ADMA increased NO levels [48]. In contrast the anti-cancer drug tamoxifen increased ADMA levels and reduced levels of NO [48]. Following estrogen replacement, in post-menopausal women, levels of plasma ADMA were reported to fall, consistent with the observations of estrogen on DDAH activity [49].

There may also be other factors which regulate DDAH: Interleukin 1 β has been reported to increase both DDAH and iNOS expression in rat smooth muscle cells with a corresponding fall in ADMA levels [50]. ADMA levels were observed to rise in the presence of either oxidised LDL or tumour necrosis factor- α , which was accompanied by a fall in DDAH activity [51]. DDAHI expression was increased in an *in vivo* model correlating with area of low blood flow in the heart [52], shear stress has been demonstrated to effect PRMT activity [28].

Genetic variants of DDAH

Polymorphisms have now been identified for DDAHII, one of which involves a 6G/7G variation at -871 of the DDAHII promoter occurring in approximately 1% of

the population, this polymorphism tested in promoter reporter assays indicated that it might lead to increased basal DDAHII activity [53]. A mutation in human DDAHI has also been published [54].

At the time of writing there were 13 published single nucleotide polymorphisms (SNP) on the NCBI SNP database (<http://www.ncbi.nlm.nih.gov/SNP/>) for DDAHII and 338 reports of SNP for DDAH1. It remains to be seen whether these polymorphisms correlate with raised ADMA levels in cardiovascular disorders or can be used to predict cardiovascular morbidity.

DDAH regulation of angiogenesis

ADMA has been shown to affect angiogenic processes in an *in vivo* model [55] and atRA, which has been shown to increase DDAH activity [47] has been implicated in the regulation of angiogenesis as well as modulating endothelial cell growth and differentiation. In DDAHII overexpressing endothelial cells, levels of VEGF were increased and there was increased tube formation in an *in vitro* model [56]. Levels of DDAHII are abundant in the placenta, a highly vascularised tissue [40]. DDAH overexpression in tumour cells has also been shown to increase VEGF expression and leads to increased neovascularisation [57].

Effects of systemic ADMA

There are numerous reports documenting changes in ADMA levels correlating with various cardiovascular disorders. In a randomised double-blinded trial administration of ADMA to healthy subjects decreased heart rate, increased cardiac output and

caused a rise in blood pressure [46]. Another interesting finding from this study was the effect that systemic ADMA had on the vasculature in response to exercise; cardiac output doubled in response to exercise, but after ADMA there was a significantly depressed cardiac response to exercise.

Arginine Transport

The arginine paradox

Arginine is transported through the cationic amino acid transporters (CAT) of system y⁺, which are sodium independent. In endothelial cells up to 2mM arginine has been measured [58] which is significantly higher than the K_m for NOS of 7-19 μM [5, 6, 7, 8], therefore arginine should never be rate limiting for NOS and the NOS enzymes should be saturated by substrate arginine. However, in numerous *in vitro* and *in vivo* studies endothelial NO production has been augmented by arginine supplementation (recent review [59]). This has led to unexplained “arginine paradox” where despite high intracellular arginine concentrations, arginine can be rate limiting for NOS.

Effects of methylarginines on arginine transport

The methylarginines ADMA, L-NMMA and SDMA have all been shown to compete with arginine for the y⁺ transporter (Figure 2 [D]) and this has been demonstrated in macrophages, microvascular and endothelial cells [60; 61; 62]. Some investigators have questioned whether the concentrations of ADMA measured in plasma and other biological samples for ADMA (typically 0.5 – 1 μM) could inhibit NOS given the physiological levels of arginine. The K_m of DDAH for ADMA is high (100 μM) and

this might suggest that under certain conditions localised ADMA can reach high concentrations indeed L-NMMA appears to accumulate greater than 5-fold inside the cells [63].

Inhibition of DDAH with S-2-amino-4(3-methylguanidino)butanoic acid (4124W) leads to a significant accumulation of ADMA [39] culminating in impaired NO production [47]. In neurons Zweier & Cardounel reported that intracellular levels of ADMA were at levels sufficiently high that more than 50 % of nNOS could be expected to be inhibited at any given time [64]. Therefore there is evidence to suggest that intracellular levels of ADMA exceed circulating levels and that ADMA may be concentrated within cells at levels which can affect NOS. ADMA may also have a paracrine action and ADMA secreted from endothelial cells has been demonstrated to inhibit the NO production of cytokine stimulated macrophages [65].

Other factors which influence arginine uptake

Arginine uptake is affected the inflammatory stimuli: tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and lipopolysaccharide (LPS). LPS has been shown to increase the uptake of L-NMMA by greater than 80% [63; 67] and LPS has been shown to increase the expression of CAT mRNA [66]. Arginine transport may be influenced by changes in the membrane potential of potassium inward rectifying K⁺ channels.

The NO signalling pathway appears to directly influence arginine uptake: NO may attenuate the uptake of arginine by cells [68], and in response to arginine starvation there is an increase in the expression of the cationic amino acid transporter [69]. The transport of arginine is altered under pathophysiological conditions. Hypoxia, which

is associated with increases in proteolysis, appears to reduce the transport of arginine [70]. During hyperglycaemia there is an increase in the activation of cationic amino acid transport which may impact upon diabetes.

Methods of detecting ADMA

The original measurements of ADMA were performed using HPLC (Paik 1970; Vallance *et al* 1992) and after 30 years HPLC analysis is the predominant method used to determine ADMA levels. In recent years ADMA samples have derivatised by ortho-phthaldialdehyde reagent (OPA) and detected by fluorometry which has greatly increased the sensitivity of the method (Teerlink *et al* 2002). Refinements in the HPLC techniques and the sample extraction have reduced the amount of starting sample, for plasma less than 0.1 ml is required to determine levels of ADMA. Limitations of this method for detecting ADMA are the number of samples which can be injected and the time required to extract samples prior to HPLC analysis. Comparisons of the ratios of ADMA: SDMA and ADMA: arginine have been frequently used to describe changes in ADMA in disease states. Typically the levels of ADMA in plasma from healthy adults have been described 0.3-1 μ M (MacAllister *et al* 1996b; Teerlink *et al* 2002; Zoccali *et al* 2001) and levels of ADMA in cerebral spinal fluid 0.01-0.07 μ M (Abe *et al* 2001; Mulder *et al* 2002). Interestingly the ratio of ADMA to SDMA in CSF is 1:3 whereas in plasma from normal patients there are equal levels of ADMA: SDMA (Mulder *et al* 2002).

Several methods have now been described to measure ADMA using mass spectrometry coupled to a separation system (Vishwanathan *et al* 2000; Tsikas *et al* 2003,; Martens-Lobenhoffer & Bode-Boger 2003). These methods appear to have lowered the limits of detection and may have advantages over HPLC with higher sample throughput. Antibodies raised against ADMA are commercially available but there are no published reports of groups having successfully used these at the time of writing.

Method	Basal plasma	Limits of detection	Reference
HPLC	$0.42 \pm 0.06 \mu\text{M}$	$0.01 \mu\text{M}$	Teerlink <i>et al</i> 2002
HPLC-MS	$0.453 \pm 0.128 \mu\text{M}$	$0.2 \mu\text{M}$	Martens-Lobenhoffer <i>et al</i> 2003
Gas chromatography coupled to MS	$0.39 \pm 0.6 \mu\text{Mol}$	10 amol	Tsikas <i>et al</i> 2003
Liquid chromatography coupled to MS-MS	$25.1 \pm 9.4 \text{ ng/ml}$	1 ng/ml	Vishwanathan <i>et al</i> 2000

DDAH activity measurement

DDAH activity has been measured by the conversion of radiolabelled methylarginine to radiolabelled citrulline (MacAllister *et al* 1996). A colorimetric assay is also in use to measure the end point of the DDAH reaction (Knipp *et al* 2000), citrulline, but is limiting for use with coloured assay materials such as particularly tissue. Dimethylamine is also measured as an indicator of DDAH activity (Achan *et al* 2003).

ADMA in cardiovascular disorders

It has been recorded over the past 30 years that urinary methylarginines increase in various disease states including muscular dystrophy (Lou 1979) and liver disease including chronic active hepatitis (Carnegie *et al* 1977). Changes in ADMA in renal failure patients were later associated with impaired NO production (Vallance *et al* 1992)

In healthy individuals there appears to be a correlation between levels of ADMA and subsequent acute coronary events and the levels of ADMA appear to predict both the occurrence of cardiovascular events and mortality (Valkonen *et al* 2001). In some reports ADMA levels are increased in hypertension and high levels of salt in the diet might also increase ADMA (Osanai *et al* 2002). ADMA may contribute to left ventricular hypertrophy (Zoccali *et al* 2002) and reduce renal excretion of sodium perhaps contributing to hypertension (Matsuoka *et al* 1997).

Chronic renal failure

The risk of cardiovascular mortality is increased by 20-fold in association with chronic renal failure. In 1992 Vallance *et al* reported that levels of plasma ADMA were several fold higher in renal failure patients than in healthy controls (Vallance *et al* 1992) and that levels of ADMA in these patients were high enough to attenuate the production of nitric oxide. In addition to being excreted by the kidneys ADMA is also metabolised; DDAH is expressed throughout the kidney and co-localises with NOS expression. Changes in ADMA levels are partially associated with impaired renal clearance, but in renal failure SDMA and creatinine levels rise concurrently whereas there is a smaller increase in ADMA indicating that some ADMA is metabolised by DDAH. In a cohort of patients with renal failure, haemodialysis to remove methylarginines was found to have an immediate short-term improvement on vasodilatation (Cross *et al* 2001).

In *in vivo* experiments NOS inhibition, by ADMA or L-NMMA, may be reversed by arginine, however the effects of arginine supplementation upon renal failure has been tested but conflicting reports have been published regarding the effects (Hand *et al* 1998 & Cross *et al* 2001).

Pulmonary hypertension:

Pulmonary hypertension is characterised by an increase in pulmonary blood pressure accompanied by a fall in NO levels. At birth and for the subsequent 24 hours there is increased DDAH activity in lungs correlating with increased NO generation (Arrigoni *et al* 2002). However in a porcine model of persistent pulmonary hypertension, which affects the newborn, the hypoxic conditions required to mimic this condition lead to a

fall in DDAHII expression and activity (Arrigoni *et al* 2002). Levels of ADMA have been measured in adults with pulmonary hypertension and were found to be significantly higher than in control subjects (Gorenflo & Zheng 2001). In another animal model of pulmonary hypertension, rats were found to have reduced DDAH activity and raised ADMA levels, the pulmonary blood pressure was increased with a fall in NO levels despite increased expression of eNOS (Millatt *et al* 2003).

ADMA as a marker for pre-eclampsia:

Pre-eclampsia is a disorder of maternal vasculature and affects 3-5 % of pregnancies. During the course of normal pregnancy plasma ADMA falls from 0.82 μ M to 0.52 μ M at 24 weeks gestation before gradually rising to the pre-pregnancy levels at term. (Fickling *et al* 1993; Holden *et al* 1998). This change in circulating ADMA parallels a fall in blood pressure and maternal vascular tone to 24 weeks of pregnancy, which then increases throughout the rest of the pregnancy. Women who were found to develop pre-eclampsia were reported to have ADMA levels greater than 1.45 μ M (Savvidou *et al* 2003), subjects who had higher levels of ADMA early in pregnancy were most likely to develop pre-eclampsia. Throughout pregnancy high levels of protein turnover occur in the uterus, which would be expected to increase the levels of methylarginines. In the placenta DDAHII is highly expressed (Leiper *et al* 1999) presumably to metabolise these increased concentrations of ADMA. It has been suggested that the raised levels of ADMA associated with pre-eclampsia might reflect dysregulation of DDAHII.

Hyperhomocysteinemia

Levels of S-adenosylhomocysteine (SAH), the end-product in the PRMT methylation of arginine residues, are associated with the risk of cardiovascular events. Circulating concentrations of ADMA are increased in animals fed on homocysteine rich diet (Boger *et al* 2000) and in humans following methionine loading (Boger *et al* 2001). ADMA levels seem to correlate with increased homocysteine levels and impaired arterial relaxation. In patients with hyperhomocysteinemia there may be increased oxidation of low density lipoproteins (LDL). In an *in vitro* model, levels of oxLDL appear to increase PRMT activity and downregulate the activity of DDAH, which is consistent with the increased ADMA observed in hyperhomocysteinemia. Homocysteine has also been proposed to oxidise the cysteine residue of DDAH at the active site to reduce DDAH activity (Stuhlinger *et al* 2003).

Atherosclerotic disease

The development of atheroma can be assessed by measuring the lumen diameter of a vessel, in a cohort of patients with end stage renal failure undergoing hemodialysis, ADMA levels were been reported to correlate with intima-media thickness (Zoccali *et al* 2002). In another study of healthy individuals measuring the intimal-medial thickness of the carotid artery, ADMA and age were found to be independent predictors of lumen occlusion (Miyazaki *et al* 1999). The risk of developing atheroma is significantly increased in patients with end-stage renal disease, hyperhomocysteinemia and type II diabetes conditions which also have elevated levels of plasma ADMA (Zoccali *et al* 2002; Stuhlinger *et al* 2001; Paiva *et al* 2003). Investigators have proposed that ADMA levels may predict the onset of atherosclerotic disease although the number and size of studies remain small.

Nitric oxide is important in preventing monocyte adhesion, platelet aggregation and vascular smooth muscle cell proliferation. The reduced bioavailability of NO is thought to contribute to endothelial dysfunction and the early stages of atheroma development. It is not known whether the activities of DDAH or PRMT are effected during the progression of atherosclerosis although oxLDL, a marker for the progression of atheroma, has been demonstrated to increase PRMT activity and reduce DDAH activity (Ito *et al* 1999; Boger *et al* 2000).

ADMA in Type II diabetes

The plasma concentration of ADMA appears to have a positive correlation with insulin resistance (Stuhlinger *et al* 2002) and is increased in individuals with Type II diabetes. Metformin (Asagami *et al* 2002) and rosiglitazone (Stuhlinger *et al* 2002) have both been demonstrated to reduce the levels of ADMA associated with Type II diabetes and it remains to be seen whether these drugs have an effect through modulating either DDAH or PRMT activities. It has been reported that glucose may downregulate DDAH activity in an *in vivo* model correlating with a rise in ADMA levels and impaired NO production (Lin *et al* 2002). However the mechanism by which glucose is effects the activity of DDAH remains undetermined.

ADMA in Alzheimer's

There is conflicting evidence surrounding the involvement of DDAH and ADMA levels in Alzheimer's disease. DDAH may be upregulated in the cytoplasm of neurons with cytoskeletal pathology (Nakagomi *et al* 1999) and ADMA was reported to be

lower in Alzheimer's patients compared to control subjects (Abe *et al* 2001). However, further measurements of ADMA levels in CSF have indicated that there are no changes between normal and moderately effected patients (Mulder *et al* 2002).

Summary

ADMA levels are altered in a wide series of pathophysiological states and the importance of measuring the circulating levels of ADMA has been demonstrated in predicting cardiovascular events. Techniques for measuring ADMA have improved over the past 30 years but it would be of great advantage to the field if multiple samples could be screened in parallel. We have mentioned the polymorphisms which have been identified in DDAH and PRMT isoforms, in the future genotyping might provide additional information to assist in diagnosing cardiovascular events.

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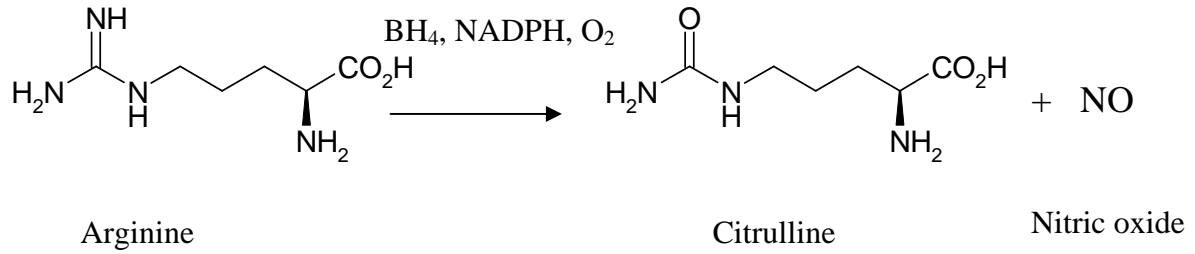
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Figure 1A] – Nitric oxide synthase reaction 1B] – structures of endogenous methylarginines

A]



B]

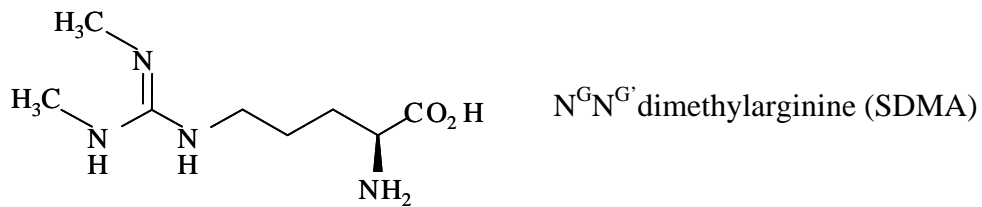
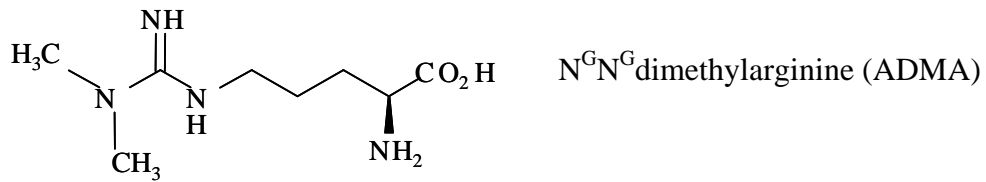
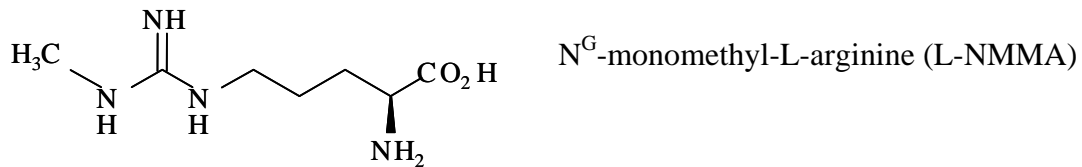


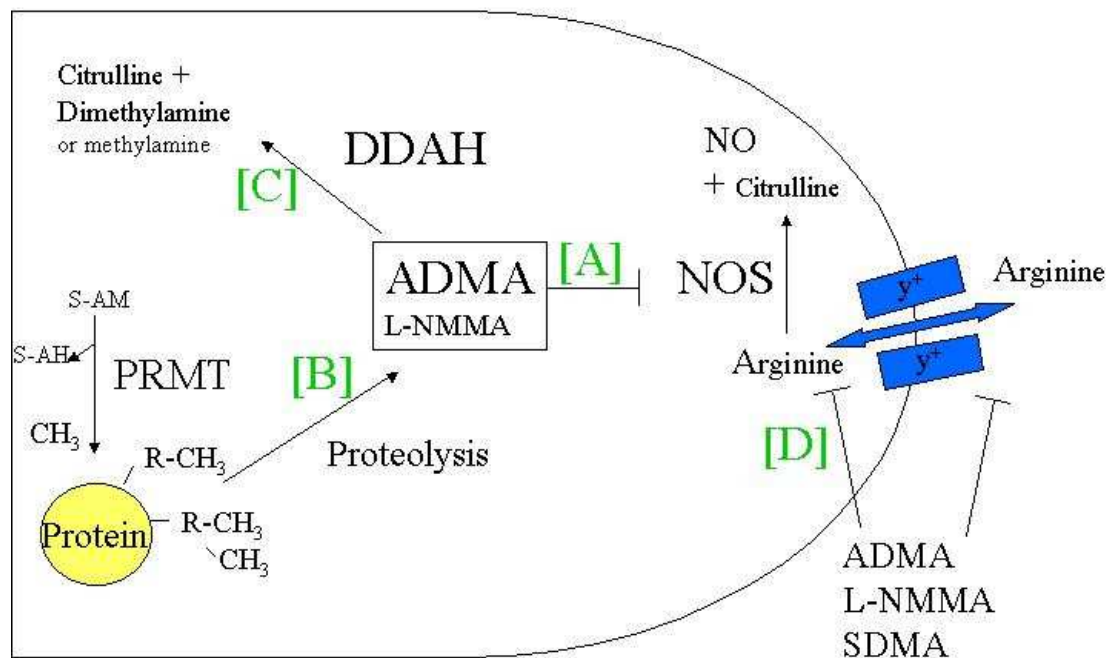
Figure 2 -

A] ADMA & L-NMMA inhibit nitric oxide synthases.

B] Arginine residues on proteins are methylated by PRMT with S-adenosylmethionine acting as a methyl donor, the arginine residues can be either mono- or di-methylated. Free L-NMMA, ADMA and SDMA are released as the protein undergoes proteolysis

C] DDAH metabolises ADMA & L-NMMA to citrulline and dimethylamine or methylamine respectively.

D] ADMA, L-NMMA and SDMA may compete with the cationic amino acid γ^+ transporter to reduce arginine transport.



List of abbreviations:

ADMA (N^GN^G dimethylarginine), SDMA (N^GN^G-dimethylarginine), L-NMMA (L- N^G-monomethylarginine), SAH (S-adenosylhomocysteine), SAM (S-adenosylmethionine), PRMT (protein arginine methyltransferase); DDAH (dimethylarginine dimethylaminohydrolase); NO (nitric oxide); NOS (nitric oxide synthase).