The importance of the arginine/ADMA ratio on the bioavailability of nitric oxide and organ function in critically ill patients

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Chapter 1

General introduction and outline of the thesis

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GENERAL INTRODUCTION

Introduction

One of the major endothelium derived vasoactive mediators in the human body is nitric oxide (NO). NO is a gaseous signalling molecule and is involved in a wide variety of regulatory mechanisms of the cardiovascular system including regulation of the vasomotor tone, cell adhesion to the endothelium, inhibition of platelet aggregation, and vascular smooth muscle cell proliferation (1). However, the role of NO is not only restricted to the cardiovascular system but covers a broader spectrum, from pulmonary inflammation (2) to protection against oxidative cellular damage (3) and tumour cell invasion (4).
NO is abundantly synthesized from the amino acid arginine by the action of NO-synthases (NOS), a family of enzymes with endothelial, neuronal, and inducible isoforms (5). Dysfunction of the arginine-NO pathway is a common mechanism by which several cardiovascular risk factors mediate their deleterious effects on the vascular wall i.e. diabetes mellitus, hypercholesterolemia, hypertension, smoking, and hyperhomocysteinemia (6).
Recent insights into NO metabolism have shown an important role of endogenously produced inhibitors of the enzyme NOS in particular asymmetric dimethylarginine (ADMA) (7). Several studies have shown elevated concentrations of ADMA in patients with conditions characterized by endothelial dysfunction, including peripheral arterial disease (8), diabetes mellitus (9), hypercholesterolemia (10), and hyperhomocysteinemia (11). In addition, our study group indicated elevated concentrations of ADMA in critically ill patients with clinical evidence of organ dysfunction (12). In these patients, ADMA proved to be the strongest predictor of intensive care unit mortality with a 17-fold increased risk for patients who were in the highest quartile of ADMA.

Synthesis of ADMA

It has been estimated that humans generate approximately 300 μmol ADMA a day (13).
Free ADMA, and its stereo-isomer symmetric dimethylarginine (SDMA), are formed by the methylation of arginine residues in proteins. In this process, methyl groups from S-adenosylmethionine are transferred to the terminal guanidino group of arginine residues by the enzyme protein arginine methyltransferase (PRMT) (14). There are at least two types of PRMT in mammalian cells (15). Type 1 PRMT catalyze the formation of ADMA and monomethylarginine (MMA), whereas type 2 PRMT catalyze the formation of SDMA and MMA (16;17). The methylation of arginine is, to a large extent, irreversible and methylated arginine residues stay within the protein until it is

degraded. After proteolysis, the (di)methylarginines are released and appear in the cytosol. The free fractions of ADMA and MMA, in contrast to their protein bound form, are capable of inhibiting all NOS isoforms (18;19). In contrast to ADMA, SDMA has no direct inhibitory effect on NOS, but may interfere with NO synthesis by competing with arginine for cellular transport across cationic amino acid transporters (CAT) of system y^+. These transporters, which are abundantly expressed in the liver, are capable of transporting ADMA, SDMA, and arginine across the cell membrane. Through this transport system, the liver is able to take up ADMA from the circulation for degradation while arginine is used for NO synthesis (20).

Recently, Bulau and co-workers (21) indicated that the lung seems to be a major source of ADMA. It expresses high levels of specific PRMTs compared to the liver, kidney, or heart. Furthermore, the extent of asymmetric and symmetric dimethylation of arginine residues in lung proteins is almost four and respectively two times higher than the extent of dimethylation of the arginine residues from liver, kidney, and heart proteins. Since the lung also expresses enzymes which are capable to metabolic convert free cellular methylarginines, suggesting an important role for the lung in the ADMA metabolism.

Metabolism of ADMA

ADMA and SDMA are both excreted into the urine (22;23). For SDMA, this is the most important way of disposal, whereas ADMA is only partially (<20%) eliminated by renal excretion. The most important way of eliminating ADMA is via the enzyme dimethylarginine dimethylaminohydrolase (DDAH) which converts ADMA into citrulline and dimethylamine (24). From the about 300 μmol ADMA which is daily generated in humans, approximately 250 μmol (>80%) is metabolized by DDAH (13).

Two isoforms of DDAH have been identified that are widely expressed in human tissues (24;25). DDAH-1 is the most important isoform for the regulation of circulating ADMA and is mainly found in tissues expressing neuronal NOS (nNOS) and in peripheral tissues such as liver, kidney, adrenal gland, and testis. DDAH-2 has an important role in the regulation of NO responses and NO activity and is mainly found in tissues expressing endothelial NOS (eNOS) and inducible NOS (iNOS), such as the heart and the aorta (25-29).

Since DDAH plays a critical role in regulating intracellular ADMA levels, alterations of DDAH activity and/or expression lead to a change in ADMA levels. The important role of DDAH concerning ADMA levels has convincingly been shown by Dayoub and co-workers (30). They indicated that increased DDAH expression in transgenic mice resulted in lower plasma ADMA concentrations and an increase of NOS activity and NO elaboration. There are several factors that could increase the concentration or activity of DDAH. Recently it has been shown that GW4064, a farnesoid X receptor (FXR) agonist, increases hepatic DDAH-1

gene (but not the DDAH-2 gene) expression with a concomitant decrease in plasma ADMA levels (31). In addition, all-trans-Retinoic acid (atRA) is able to increase DDAH-2 expression in endothelial cells, by which it is possibly able to slightly lower ADMA plasma levels and increase NO production (32). Other compounds that have been shown to lower ADMA, possibly by increasing DDAH activity, are insulin (33;34), rosiglitazone (peroxisome proliferator-activated receptors (PPAR) gamma agonist) (35), estrogens (36-39), the sulfhydryl antioxidant pyrrolidine dithiocarbamate (40), Daviditin A (a xanthone compound) (41), and vitamin E (42).

Although increased NO synthesis due to increased DDAH expression or activity is usually desired in cardiovascular disease, it may have disadvantageous effects when occurring in tumours. It is known that tumours expressing high amounts of DDAH grow faster than tumours with normal DDAH expression (43;44). A possible explanation for this phenomenon may be that DDAH overexpression indirectly, by degradation of ADMA, enhances NO synthesis and directly enhances vascular endothelial cell growth factor (VEGF) expression (45). VEGF stimulates the formation of tube like structures, leading to increased tumour vascularisation and increased tumour growth.

Next to DDAH increasing factors, there are also factors that decrease DDAH activity or expression such as tumour necrosis factor-alpha (TNF-α) (46), oxidized low-density lipoprotein (ox-LDL) (46), hypercholesterolemia (10), hyperglycaemia (47), and hyperhomocysteinemia (11).

Furthermore, it has been shown that S-nitrosylation of the reactive cysteine residue (Cys-249) inactivates DDAH (48), which provides probably an important homeostatic mechanism whereby high levels of NO upregulate ADMA levels, thereby limiting further NO generation.

Outline of the thesis

Nitric oxide (NO) synthesis plays an important role in regulating vascular tone and thereby organ perfusion and function. In addition, NO is important for the regulation of mucosal blood flow and the barrier function of the gut. One of the most common gastrointestinal emergencies in the premature infant that requires surgical intervention is necrotizing enterocolitis (NEC) (49). Plasma concentrations of arginine, the substrate for NO synthase (NOS), are reduced in infants with NEC (50;51). Since ischemia-induced mucosal injury is a potentially important contributor to the pathogenesis of NEC, we postulated that not only the concentrations of arginine are low in premature infants with NEC, but also that concentrations of asymmetric dimethylarginine (ADMA) are high. In the case–control study described in **chapter 2**, we investigated this hypothesis, measuring plasma concentrations of arginine, ADMA, and their ratio in

premature infants with and without NEC, and in survivors and non-survivors of NEC.

In addition to the endothelial synthesis of NO, recent studies have demonstrated that the lung plays an important role in NO metabolism (52-54). NO produced in the lung is an important mediator of normal lung development, vascular smooth muscle relaxation, and ventilation perfusion matching (55). In addition to the lung being a major source of NO, it would also appear to be a major source of ADMA (21). We hypothesized that the synthesis of NO is inhibited by the elevated levels of ADMA in preterm infants, possibly resulting in reduced pulmonary function. In the study presented in **chapter 3**, we compared ADMA and arginine levels in preterm infants requiring mechanical ventilation and in preterm infants not requiring mechanical ventilation. We also investigated the relation between ADMA and the duration of mechanical ventilation in these infants.

As shown in many studies, elevated ADMA levels and decreased arginine levels are found in various conditions (56). For example, arginine concentrations are reduced after major surgery, such as thoracoabdominal aortic surgery (57) and surgery for esophageal and lung cancer (58), but also after trauma (59) and during sepsis (60). ADMA levels are elevated not only in preterm infants, but also in patients with endothelial dysfunction, peripheral arterial disease, or diabetes mellitus, and in critically ill patients (56). ADMA has been identified as an independent predictor of intensive care unit mortality (12). We speculated that the combination of low arginine levels and high ADMA levels seen in critically ill patients after major surgery influences NO-induced vasodilatation and organ blood flow. The study reported in **chapter 4** investigated the effect of low arginine plasma concentrations in combination with high ADMA plasma concentrations on hemodynamics and organ blood flow in an animal model.

In subsequent studies, the relation between ADMA concentrations and tight glycemic control was investigated, because strict maintenance of normoglycemia by intensive insulin therapy improves morbidity and mortality in critically ill surgical patients (61). Modulation of NO metabolism has emerged as a potentially important mechanism underlying the clinical benefit of tight glycemic control. In addition, intensive insulin therapy to prevent hyperglycemia also lowers plasma concentrations of ADMA in critically ill patients and affects regional NO metabolism (62). In the studies presented in **chapters 5 and 6**, we assessed the relative impact of glycemic control and glycemia-independent actions of insulin on levels of arginine and ADMA in major organs such as the myocardium, liver, and kidneys. We also measured the activity of dimethylarginine dimethylaminohydrolase (DDAH), the enzymes that metabolize ADMA, and the activity and expression of the NOS enzymes in an animal model of prolonged critical illness.

Given that high ADMA levels are associated with organ dysfunction, it is important to lower ADMA levels in critically ill patients. The peroxisome proliferator-activated receptor (PPAR)-gamma agonist rosiglitazone has been shown to reduce plasma ADMA levels (35;63). We hypothesized that rosiglitazone would reduce plasma ADMA levels and concomitantly have a beneficial effect on organ function and morbidity in critically ill patients. In the randomized controlled study described in **chapter 7**, we measured ADMA levels in 21 critically ill patients on the intensive care unit. Twelve patients received rosiglitazone (4 mg) once a day for a maximum of 6 weeks or until discharge or death. Nine patients served as controls. The total sequential organ failure assessment (SOFA) score, kidney function, and liver function were measured.
In **chapter 8** the results of this thesis are summarized and discussed, and directions for future research are outlined.

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