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Endothelial Nitric Oxide Synthase, Nitric Oxide and Metabolic Disturbances in the Vascular System

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1. Introduction

It is well documented that hyperlipidemia, obesity and diabetes increase the risk for the development of atherosclerosis and subsequent cardiovascular disease (Vinik, 2005, Ritchie & Connell 2007, Stapleton et al. 2010). However, until now the precise mechanism by which the above mentioned metabolic perturbations contribute to atherosclerosis has not been fully elucidated.

Numerous studies have focused on the detrimental effects of excessive body fat stores as a possible reason for both insulin resistance and disturbed lipoprotein metabolism with special attention paid to the adverse effects of visceral fat (Sharma et al., 2002, Matsuzawa, 2005). In overweight and/or obesity, free fatty acids (FFA) are released into the circulation and their availability for lipoprotein synthesis in the liver is markedly elevated (Jensen, 2006).

Moreover, high circulating FFA negatively affects whole body insulin sensitivity and disturbs carbohydrate and lipid metabolism (Kohen-Avramoglu et al., 2006). Furthermore, body fat excess brings about increased secretion of adipokines which depress insulin sensitivity (e.g. leptin, resistin), and decreased secretion of insulin-sensing adiponectin. Additionally, IL-6 and TNF- α , derived from adipose tissue, on the one hand induce inflammation, and on the other stimulate adipose tissue lipolysis and augment FFA availability for lipid and lipoprotein synthesis (Lago et al., 2009).

In addition, both insulin resistance and adipokines affect endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production and in consequence deteriorate blood vessel contractility (Muniyappa et al., 2008). Moreover, there are data indicating an adverse effect of LDL-cholesterol and positive action of HDL-cholesterol on eNOS expression and NO production (Stepp et al., 2002, R met et al., 2003).

All the above-mentioned metabolic disturbances have pronounced consequences for the cardiovascular system due to inflammation, atherosclerotic plaque formation and structural alterations in the endothelium and subsequently lead to its dysfunction.

Thus, in this sequence of metabolic perturbations the endothelium was recognized rather as a target of unfavorable events related to excessive body fat stores, insulin resistance and

dyslipidemia, but not as an independent player contributing to dysfunction of the cardiovascular system.

2. Vascular dysfunction – Primary or secondary target

However, there were also data suggesting that endothelial dysfunction was a major mechanism involved in the development of metabolic disturbances and subsequent atherogenesis (Yang & Ming, 2006).

Recently this hypothesis has been the focus much attention mostly as a consequence of data concerning a wide spectrum of metabolic eNOS/NO action. It has been recognized that eNOS itself is indispensable for physiological insulin action and glucose disposal in the working muscle (Roberts et al., 1997, Kingwell et al., 2002, Ross et al., 2007). Moreover, *in vitro* NO markedly increases glucose transporter (GLUT 4) expression in the muscle and regulates AMP-kinase (AMPK) signaling (Lira et al., 2007). Taking into account the special role of AMPK in the regulation of substrate utilization it is clear that eNOS activity and NO production markedly affect energetic processes in the muscle (Smith A.C., et al., 2005).

In contrast, eNOS deficiency in eNOS $-/-$ mice depresses oxidative processes and brings about defective mitochondrial fatty acid oxidation (Momken et al., 2002, Le Gouill et al., 2007). Recent data have shown that the ablation of eNOS in mice accelerates glucose and free fatty acid uptake by muscles and increases liver and muscle glycogenolysis (Lee-Young et al., 2010). In consequence, eNOS knockout animals exhibit hypoglycemia and limited exercise capacity during exercise.

It is well documented that *in vitro* NO contributes to the regulation of lipid metabolism in the liver by inhibiting acetyl-CoA carboxylase (ACC) activity and *de novo* free fatty acid synthesis (Garcia-Villafranca et al., 2003). There are also data suggesting that both *in vitro* and *in vivo* NO exerts a hypocholesterolemic effect, since stimulation of NO synthesis in rabbits decreases circulating LDL-cholesterol (Kurowska & Carrol, 1998).

At present eNOS/NO system contribution to the regulation of metabolism is far from being fully elucidated. However, it is accepted that the vascular endothelium is not exclusively a target responding to metabolic disturbances accompanying cardiovascular disease, but is an important and independent player in the complicated relationships between cardiovascular disease, obesity and diabetes.

This assumption is partially supported by research indicating that adverse changes in vasculature in response to high fat diet (inflammation, insulin resistance, reduced NO production) precede detrimental effects in muscle, liver, or adipose tissue (Kim et al., 2008).

3. Endothelial Nitric Oxide Synthase (eNOS) and Nitric Oxide (NO) system coupling and uncoupling

It should be pointed out that the endothelium is one of the largest systems in human body spread throughout the capillaries and arterioles in all tissues, forming a selectively permeable barrier between the outer vascular wall and the bloodstream. It also the tissue producing nitric oxide (NO) responsible for vasorelaxation, platelet aggregation, leukocyte-endothelium adhesion and vascular smooth muscle cell migration and proliferation (Michel & Vanhoutte, 2010).

The mechanism of endothelial eNOS regulation is not fully elucidated due to its complexity. However, there are data indicating that enzyme activity is subjected to complicated regulation by many intracellular factors including heat shock protein (HSP90), different phosphatases, kinases, but also by enzyme location in the cell and potentially motor proteins (Dudzinski & Michel, 2007).

On the other hand, it is well documented that eNOS activity is also regulated by factors generated outside the endothelium - negatively by resistin, TNF- α , and leptin and positively by estrogen ((Dai et al., 2004, Kougiyas et al., 2005, Valerio et al., 2006, Korda et al., 2008, LeBlanc et al. 2009).

Nitric oxide is synthesized from L-arginine in a reaction catalyzed by the endothelial eNOS (Moncada et al., 1991) (Fig. 1). Thus, any factors decreasing eNOS activity and/or increasing NO degradation i.e. affecting the eNOS/NO system have been recognized as a potential source of disturbed endothelium function.

Under physiological conditions and optimal eNOS activity L-arginine in the presence of O₂ is converted to NO and citrulline with minor production of superoxide (Alp & Channon, 2004). In consequence, NO production is "coupled" with eNOS activity.

In contrast, inadequate L-arginine intake and deficiency of the eNOS cofactor - tetrahydropterin (BH₄) brings about depressed NO synthesis, and promotes superoxide and peroxynitrite generation - a phenomenon named eNOS uncoupling (Huang, 2009).

Taking into account that L-arginine is the exclusive substrate for NO synthesis it is clear that its metabolism catalyzed by arginase has the potential to decrease eNOS activity and NO production (Wu et al., 2009).

In mammals there are two types of arginase, encoded by two genes - arginase I and II. Arginase I is expressed mostly in the liver catalyzing L-arginine conversion into urea and ornithine and in this way participating in ammonia detoxication. Arginase II is a mitochondrial enzyme of extrahepatic tissues contributing to biosynthesis of amino acids (glutamate, proline and ornithine) and polyamines, but also playing a fundamental role in the depression of endothelial NO production decreasing L-arginine availability for eNOS action. In addition, arginase II overexpression seems to induce superoxide and peroxynitrite generation - *per se* harmful for the endothelium. There are data suggesting increased arginase activity in atherosclerosis and hypertension, thus diseases characterized by endothelial dysfunction (Ryoo et al., 2011)

BH₄ bioavailability within the endothelium plays a fundamental role in eNOS/NO coupling. It has been demonstrated that the inhibition of the rate-limiting enzyme responsible for *de novo* BH₄ synthesis - GTP cyclohydrolase 1 - brings about eNOS/NO uncoupling and elevated superoxide production in isolated bovine or mouse aortic endothelial cells. Moreover, superoxide production was reduced by the sepiapterin - BH₄ precursor (Tiefenbacher et al., 2000, Wang et al., 2008).

However, recent data have indicated that the regulation of BH₄ levels in the endothelium is even more complicated since it is oxidized to 7,8-dihydrobiopterin (BH₂) which in turn is recycled into BH₄ in the reaction catalyzed by dihydrofolate reductase (DHFR). Moreover, a genetic DHFR knockout or pharmacological inhibition of the enzyme suppresses BH₄ synthesis and causes eNOS uncoupling (Crabtree et al., 2009) (Fig.2).

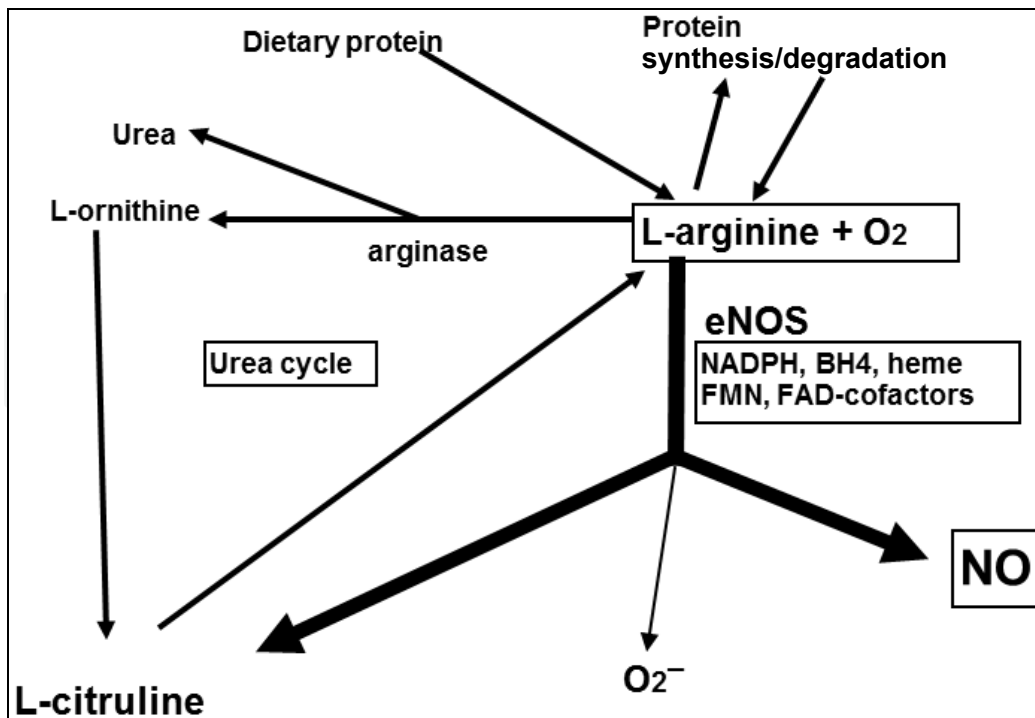


Fig. 1. L-arginine as a source of nitric oxide (NO) under physiological condition and minor superoxide production.

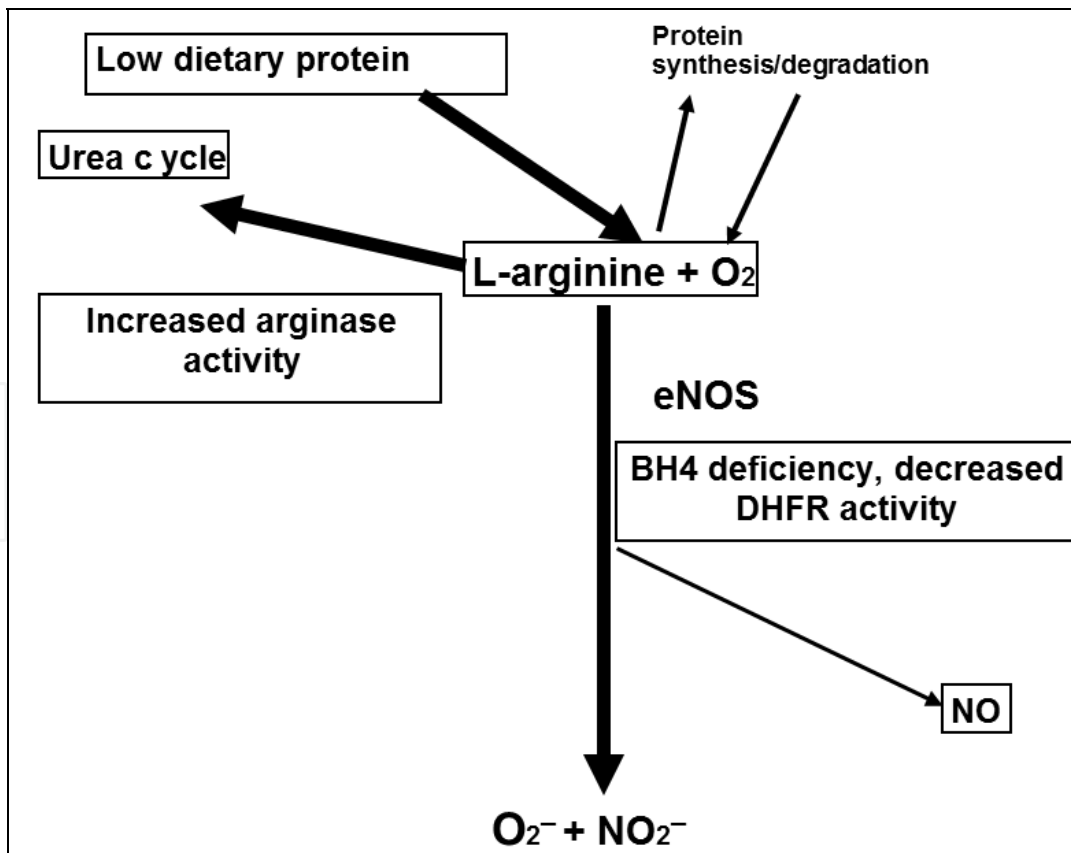


Fig. 2. eNOS/ NO uncoupling in response to metabolic disturbances resulting in increased superoxide and peroxynitrite production

It should be pointed out that regulation of cardiovascular system is not limited to eNOS action. Numerous research focus on neuronal (nNOS) and inducible (iNOS) nitric oxide synthase role in the cardiovascular system. It has been postulated that nNOS expressed outside of the vascular system might protect mice from diet-induced atherosclerosis through indirect action on hormonal and/or nervous system and blood pressure regulation. (Lowenstein, 2006). On the other hand, iNOS is expressed in a wide range of cells in response to cytokines and is overexpressed in macrophage and cardiovascular system of diabetic rats (Soskić et al., 2011). However, much more studies are needed to fully elucidate the relationship between three isoforms of NO in vascular system dysfunction.

4. Asymmetrical dimethylarginine (ADMA) and the vascular system

Recently numerous studies have focused on the role of endogenous inhibitor of eNOS activity and NO production – asymmetrical dimethylarginine (ADMA). ADMA is synthesized in many tissues, including the endothelium, by the methylation of L-arginine released from proteins which undergo regular turnover. The methylation process is catalyzed by arginine methyltransferase type I (PRMT I) and ADMA production is related to both protein turnover and enzyme activity (Pope et al., 2009) (Fig.3). However, about 90% of ADMA is metabolized to citrulline and dimethylamine by dimethylarginine dimethylaminohydrolase (DDAH), with the remainder partially excreted with urine (Tran et al., 2003). Numerous studies have indicated a substantial role for DDAH in ADMA turnover. DDAH is expressed as two isoforms (DDAH I and DDAH II) encoded by different genes (Leiper et al., 1999). Animal studies have revealed that in mice overexpressing DDAH I plasma ADMA levels are reduced with concomitant increase in tissue NOS activity. (Dayoub et al., 2003). Moreover, in humans genetic variants of DDAH I and DDAH II genes are significantly associated with plasma ADMA levels (Abhary et al., 2010). Moreover, ADMA concentration in tissues and plasma is also affected by cationic amino acid transporter (CAT) in exchange for arginine and other cationic amino acids (Teerlink et al., 2009). Reference values of circulating ADMA in healthy subjects vary widely, even when similar analytic methods are used (Meinitzer et al., 2007). However, the risk of acute coronary events and mortality increases with elevated plasma ADMA concentrations (Valkonen et al., 2001, Zoccali et al., 2001). Moreover, it is well documented that circulating ADMA is inversely related to endothelial function in hypertensive and healthy subjects (Perticone et al., 2003, Böger et al., 2007). Furthermore, it has been established that the intima-media thickness of the carotid artery and aortic stenosis are related to circulating ADMA (Furuki et al., 2007, Ngo et al., 2007). Additionally, circulating ADMA has been recognized as an independent factor determining flow mediated dilatation in cardiac syndrome X (Haberka et al., 2010).

The mechanism of detrimental ADMA action in the vascular system is not fully established. It is still under debate whether ADMA represents a novel risk factor for the development of endothelial dysfunction or its production reflects endothelium response to other metabolic disturbances such as oxidative stress (Sydow & Münzel, 2003). This latter hypothesis could not be excluded since *in vitro* oxidative stress decreases ADMA-demethylating enzyme (DDAH) activity and causes elevated ADMA levels (Leiper et al., 2002).

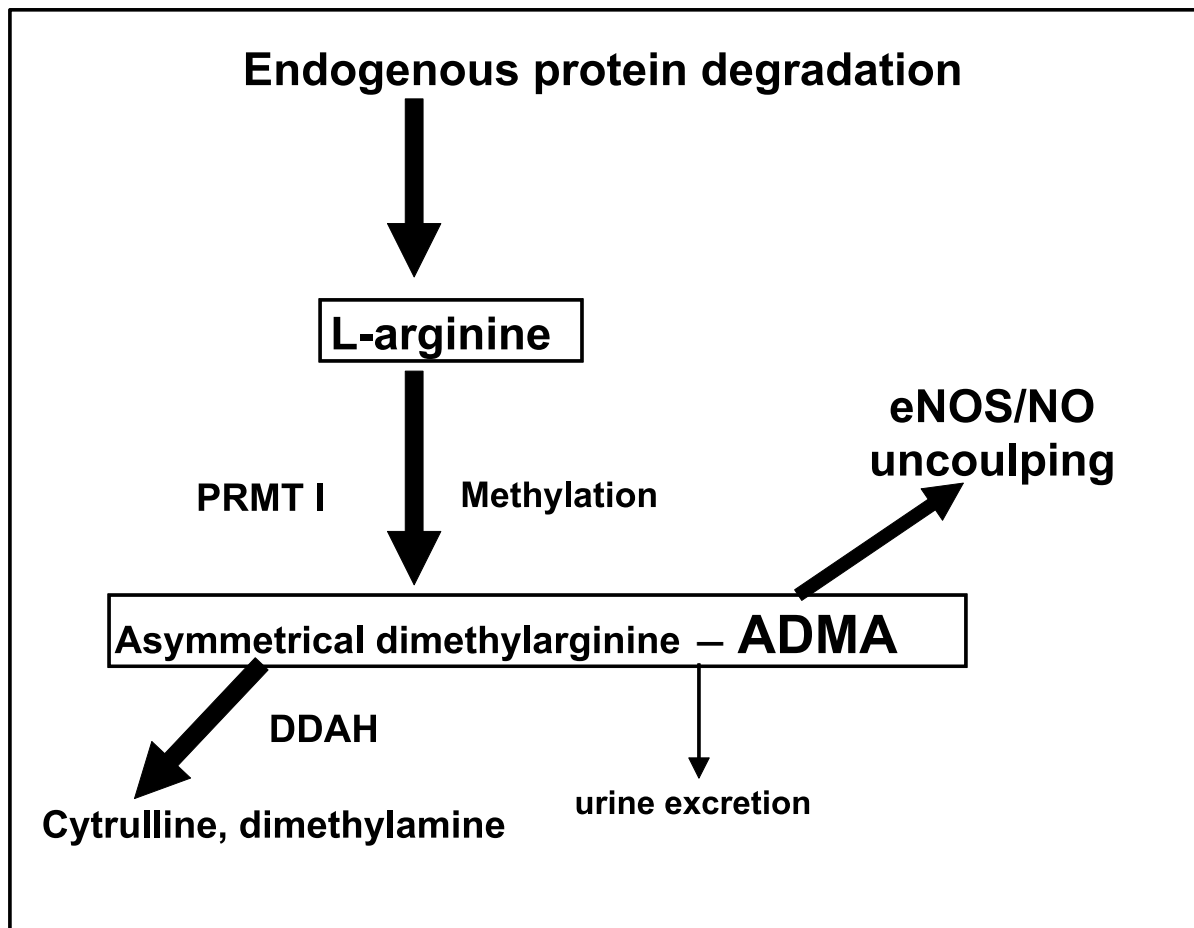


Fig. 3. Asymmetrical dimethyl arginine (ADMA) synthesis and action on eNOS/NO system

On the other hand, the analysis of 131 cases with coronary heart disease (CHD) and 131 controls matched for age, sex and body mass index has revealed that plasma ADMA concentrations in patients were higher than in controls and ADMA is an independent risk factor for CHD (Schultze et al., 2006). Similarly, in 138 patients with acute myocardial infarction ADMA was recognized as a marker of cardiovascular risk independent of traditional risk factors (Korandji et al., 2007).

Despite these doubts the detrimental effects of ADMA on the endothelium are well documented. First of all ADMA is a potent inhibitor of eNOS inducing eNOS/NO uncoupling (Jin & Loscalzo, 2010). Moreover, it has been found that ADMA is an endogenous inhibitor of mobilization, differentiation and function of endothelial progenitor cells which participate in continuous endothelial renewal and neovascularization of ischemic tissues (Thum et al., 2005). Additionally, *in vitro* pathological concentrations of ADMA are sufficient to elicit marked changes in coronary artery endothelial cell gene expression of bone morphogenic protein receptor, and PRMT – the enzyme responsible for methylation of arginine to ADMA. Moreover, in mice treated with high ADMA doses (2 μ M) more than 50 genes in endothelium were significantly altered (Smith C.L., et al., 2005). Some data also suggest proinflammatory ADMA action in human endothelial cells (Chen et al., 2007).

Thus, it should be pointed out that ADMA-mediated pathological processes are not exclusively due to eNOS uncoupling, however, eNOS inhibition is most likely being the dominant ADMA vascular effect (Cooke, 2004).

5. Lifestyle and vascular system

There is no doubt that lifestyle has a pronounced effect on health, decreasing body fat stores, improving insulin sensitivity, lipid and lipoprotein metabolism and positively affecting the cardiovascular system (Lamon-Fave et al., 1996, Lee et al., 2005, Takahashi et al., 2011). Numerous data have revealed that both eNOS and NO production are the target of lifestyle interventions such as dietary habits and physical activity.

5.1 Dietary habits, eNOS and NO

Dietary habits are associated with both acute and chronic effects on the vascular system. In healthy, normolipidemic young and middle-aged men a single high fat meal has been found to adversely affect endothelial function depressing the flow-mediated vasodilation of the brachial artery (Vogel et al., 1997, Marchesi et al., 2000). Moreover, a decrease in endothelial function has been observed in response to both glucose and fat load, with a more pronounced effect when high fat and glucose were combined (Ceriello et al., 2002). Thus, postprandial state has to be taken into consideration as a possible reason for diet-induced depression in vascular reactivity.

The mechanism of the effects of postprandial state on vascular function is not fully elucidated, however it seems that oxidative stress due to elevated plasma remnant lipoproteins, triglycerides, and glucose concentrations contributes to the adverse effects of a single meal on vascularity (Doi et al., 2000, Bae et al., 2001, Ceriello et al., 2004). Moreover, recent data have suggested that in addition to oxidative stress, oral fat load enhances metalloproteinase-2 and metalloproteinase-9 activity which in turn bring about unfavorable vascular remodeling (Derosa et al., 2010).

However, it should be pointed out that adverse effects of fat load on the vascular system are mostly due to saturated fat (Vogel et al., 2000, Cortez et al., 2006, Berry et al., 2008). In contrast, an exchange of saturated for unsaturated fat load has been found to improve postprandial vascular function probably due to the positive effect of the latter on endothelial eNOS/NO system (Armah et al., 2008, Masson & Mesink, 2011).

Numerous experimental studies have focused on chronic effects of dietary habits on endothelium function and vasoreactivity, however, their results are inconsistent. In patients with coronary artery disease a long-term (6 weeks) treatment with purified eicosapentaenoic acid (EPA) markedly improved NO-mediated forearm vasodilatation (Tagawa et al., 1999). Similarly, improved forearm microcirculation has been noted in hyperlipidemic, overweight subjects following a 6 week treatment with purified docosahexaenoic acid (DHA), but not with EPA (Mori et al., 2000). On the contrary, positive action of longer (7 weeks) EPA and DHA supplementation on systemic arterial compliance has been demonstrated in dyslipidemic elderly men (Nestel et al., 2002). Additionally, it has been noted that 32 weeks EPA and DHA-rich fish oil supplementation improve endothelial function and vascular tone in healthy middle-aged men and women (Khan et al., 2003).

Thus, it seems that duration of supplementation possibly contributes to discordant results concerning the response of the vascular system to polyunsaturated fatty acid (PUFA) treatment.

There are also data suggesting that EPA and DHA-rich fish oil exert a more pronounced effect on vascular function than other oils. In rats fed a fish-oil rich diet the aortic content of eNOS protein and enzyme activity are markedly (by 70% and 102 %, respectively) higher than in rats fed corn oil (Lopez et al., 2004). Moreover, improved vascular reactivity and enhanced eNOS expression have been indicated in aortic rings of spontaneously hypertensive rats fed diet rich in pomace olive oil, but not refined olive or corn oil (Rodriguez-Rodriguez et al., 2007). Thus, the positive effect of unsaturated fat provision seems to be related to its composition.

Recent data have indicated a positive effect of conjugated linoleic acid (CLA) on vascularity in obese *fa/fa* rats due to CLA-induced elevation in adiponectin production and subsequent eNOS phosphorylation increasing enzyme activity and NO production (DeClerq et al., 2011). Therefore, it seems feasible that well-known beneficial effects of oil consumption on health are at least partially due to its action on the eNOS/NO system.

Much attention has been paid to effects of dietary protein on vascular function. It has been demonstrated that in hypertensive men there is an inverse relationship between blood pressure and protein consumption with more pronounced action of soy and fish than animal protein intake. Further studies have shown that this effect is due to various amino acids such as cysteine, glutamate, and arginine which decrease oxidative stress, improve renal function and insulin resistance (Vasdev & Stuckles, 2010). However, numerous studies have focused on L-arginine contribution to vascular system regulation since, as was mentioned earlier, L-arginine serves as a substrate for NO synthesis.

In young hypercholesterolemic adults after 4 week L-arginine supplementation (7 grams x 3/day) marked improvement in endothelium-dependent vasodilation has been noted (Clarkson et al., 1994). Similarly, it has been observed that in patients with heart failure 6 weeks L-arginine treatment (5.5 to 12.6 g/ day) positively affects vascular system (Rector, et al. 1996).

Growing evidence indicates that L-arginine supplementation brings about improved insulin sensitivity and decreases circulating free fatty acids and triglycerides in chemically induced diabetic and genetically obese rats (Kohli et al., 2004, Fu et al., 2005). Moreover, similar effects have been observed in obese and type II diabetic patients receiving oral/or intravenous L-arginine (Lucotti et al., 2006). Furthermore, it has been documented that postprandial lipemia-induced endothelial dysfunction is neutralized by addition of proteins to the fatty meals due to increased L-arginine to ADMA ratio (Westphal et al., 2006). Moreover, in healthy volunteers addition of 2.5 g L-arginine to fatty meal prevents the lipemia-induced endothelial dysfunction (Borucki et al., 2009).

The above data suggest a possible beneficial effect of L-arginine treatment in cardiovascular dysfunction. However, it should be pointed out that some studies do not show any beneficial effect of L-arginine treatment (Chin-Dusting et al., 1996, Oomen et al., 2000). It could not be excluded that this discrepancy is due to individual variability in the response to L-arginine treatment (Evans et al., 2004). Recently it has been postulated that beneficial L-arginine action in vascular system is related to circulating ADMA with no effect in subjects with low metabolite levels (Böger, 2007).

On the other hand, it should be stressed that the acute provision of exogenous L-arginine possibly depresses NO production due to induction of arginases which metabolize L-arginine to urea and in consequence divert it from eNOS and in this way adversely affects cardiovascular system (Dioguardi, 2011).

Data concerning dietary carbohydrate effects on the eNOS/NO system are fragmentary. In obese Zucker rats a low carbohydrate diet (10 %) improves vascular function with no effect on NO production in comparison with that containing 59 % carbohydrates (Focaroli et al., 2007).

However, it is well documented that in the rat excessive fructose supply adversely affects endothelium-dependent vasodilation both *in vitro* and *in vivo* and this effect is probably due to inhibition of NO synthesis (Verma et al., 1997, Rickey et al., 1998, Kamata et al., 1999). Similarly, high glucose concentration *in vitro* decreases eNOS protein expression and enzyme activity as a result of destroyed enzyme interaction with HSP-90 (Noyman et al., 2002, Mohan et al., 2009).

On the other hand, many diet components have the potential to reduce detrimental effects of poor dietary habits.

Consumption of antioxidant - rich products such as fruits and vegetables in humans prevents the detrimental action of a saturated fat load due to their positive effect on the eNOS/NO system (Plotnick et al., 2003, Traber & Stevens, 2011). Similarly, low cholesterol, walnut-enriched and the Mediterranean diets are effective in improving the eNOS/NO system and vascular function (Winkler- Möbius et al., 2010).

Data concerning diet effects on ADMA - an endogenous eNOS inhibitor and risk factor are scarce. Päävä et al., (2004) have indicated that in a middle-aged population with mild hypercholesterolemia circulating ADMA is inversely related to carbohydrate consumption. Additionally, Puchau et al. (2009) have demonstrated that in healthy young men circulating ADMA is inversely related to zinc and selenium status.

In elderly subjects polyunsaturated fatty acid (PUFA) supplementation markedly elevates circulating L- arginine and in this way decreases L-arginine/ADMA ratio what might be discussed as an improvement of endothelial function (Eid et al., 2006). However, there are also data which question the fat contribution to increased ADMA level in the blood. Recently Engeli et al. (2011) have revealed that the variation in fat consumption (20% and above 40% of energy) exerts divergent effect on circulating ADMA. In obese subjects higher fat consumption slightly (by 4%) decreases ADMA level. In contrast, in lean subjects both low and high fat consumption causes 6% elevation in ADMA concentration. The authors have postulated that contradictory data concerning dietary fat intake on ADMA levels are mostly due to methodological issues concerning ADMA determination.

Thus, the effects of dietary habits on ADMA plasma levels are far from being elucidated. Moreover, in analysis of the effect of the diet on the eNOS/NO system not only diet composition but also total caloric intake has to be taken into consideration. Animal studies have demonstrated that caloric restriction for 3 or 13 months significantly improves the expression of eNOS protein in various tissues (Nisoli et al., 2005).

5.2 Physical activity and eNOS/NO system

For many years physical activity which decreases body fat stores, improves lipid and lipoprotein metabolism and insulin sensitivity and positively affects cardiovascular system has been recommended in the therapy of obesity, hypertension, type 2 diabetes and cardiovascular disease (Shephard & Balady, 1999).

Assuming the importance of the eNOS/ NO system in the regulation of many metabolic processes in recent years numerous studies have focused on the relationship between endothelial function and physical activity. This issue seems to be of special importance since animal studies have indicated that physical inactivity induces endothelial dysfunction due to decreased eNOS activity (Suvarova et al., 2004).

It is well documented that in rats both acute exercise and regular physical activity (2-4 weeks) markedly enhance eNOS activity and endothelial NO synthesis in skeletal muscle arterioles (Sun et al., 1994, Roberts et al., 1999). Similarly, in dogs following exercise elevated NO synthesis has been noted in coronary circulation being responsible for ¼ of the vasodilation response (Bernstein et al., 1996, Ishibashi et al., 1998). Moreover, in active animals eNOS phosphorylation and activity is significantly elevated after 12 weeks of training (Touati et al., 2011).

In apparently healthy young men and women acute aerobic exercise markedly counteracts detrimental effects of a high-fat meal on flow-mediated dilatation (FMD), but also improves FMD in participants consuming a low-fat meal possibly due to reduction of circulating lipids, insulin resistance and oxidative stress (Padilla et al., 2006, Silvestre et al., 2008, Tyldum et al., 2009). Thus, it has been postulated that physical activity can attenuate adverse postprandial changes in vascular function (Johnson et al., 2011).

It should be pointed out that a positive effect of physical activity on the eNOS/NO system has also been noted in patients with stroke, chronic heart failure, and myocardial infarction (Gertz et al., 2006, Mendes-Ribeiro et al., 2009, De Waard et al., 2010).

The mechanism of exercise-induced positive changes in the eNOS/NO system is not fully elucidated. However, it is well documented that physical activity brings about hyperemia and subsequently endothelial shear stress (ESS) defined as a fractional force exerted by blood flow (Boushei et al., 2000, Taylor et al., 2002, Boo & Jo, 2003).

It is well documented that shear stress markedly affects a myriad of intracellular events in endothelial cells including remodeling, inflammation and NO production with low ESS inducing plaque formation (Harrison, 2005, Koskinas et al., 2010).

Early studies have demonstrated that in bovine aortic endothelial cells the elevation of shear stress causes elevation in eNOS phosphorylation and expression which in turn increases enzyme activity (Corson et al., 1996, Malek et al. 1999). Furthermore, in human vessels increase in shear stress inhibits lipid peroxidation induced by high glucose and arachidonic acid in the medium (Mun et al., 2008). Thus, direct effects of physical activity on eNOS/NO system and inhibition of oxidative processes contribute to exercise - induced improvement in endothelium function. However, it is worth noting that positive action of physical activity is limited to moderate intensity, since it has been demonstrated that high intensity exercise (90 % VO₂ max) enhances platelet reactivity to shear stress and induces coagulation which in turn increases the risk of thrombosis (Ikaguri et al., 2003).

Taking into account all data cited in this review it is clear that eNOS/NO system undergoes complicated regulation by both genetic and lifestyle factors (Fig. 4).

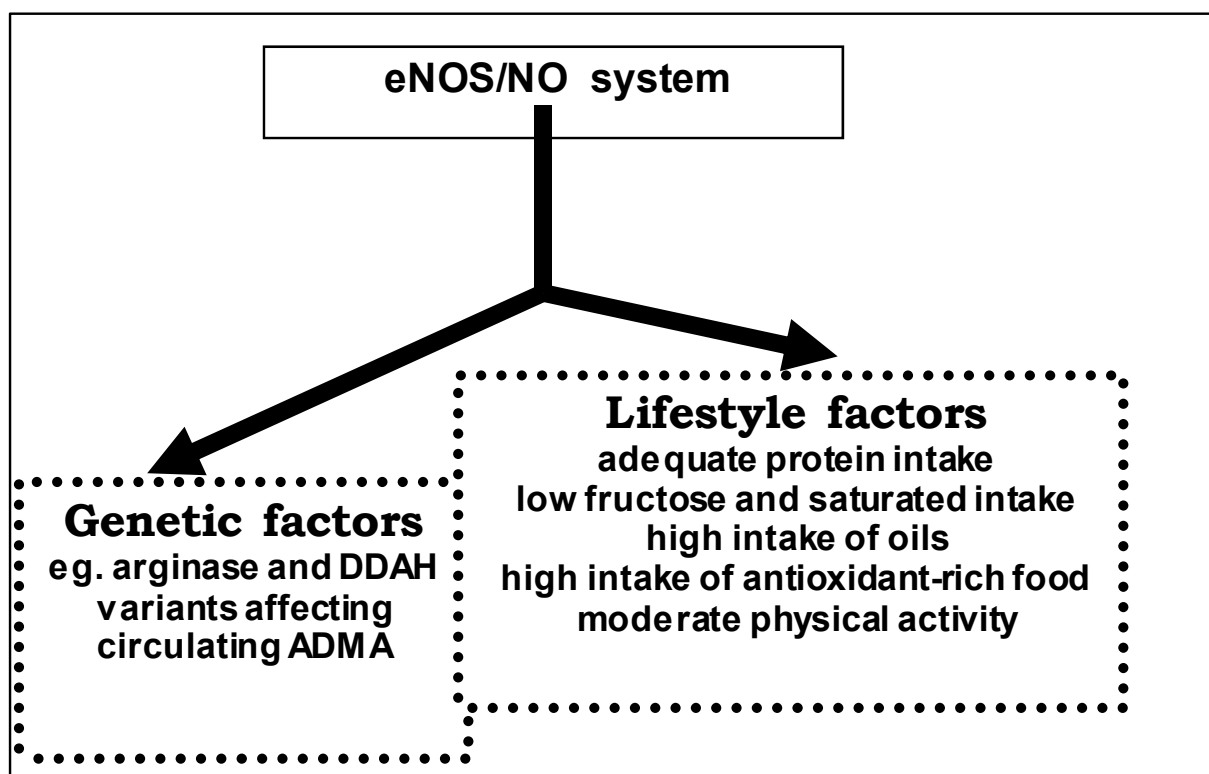


Fig. 4. Interplay between genetic and lifestyle factors affecting eNOS/NO system

6. Conclusion

Our present knowledge about eNOS and NO effects on overall metabolic processes at least partially supports the hypothesis concerning a special and possibly central role of endothelium as an active tissue, and not only the target of metabolic disturbances. Moreover, circulating ADMA seems to be a risk factor of endothelial disturbances and disturbed cardiovascular system. In consequence, further research is required on strategies improving the eNOS/NO system and decreasing ADMA synthesis, including both pharmacological and lifestyle interventions.

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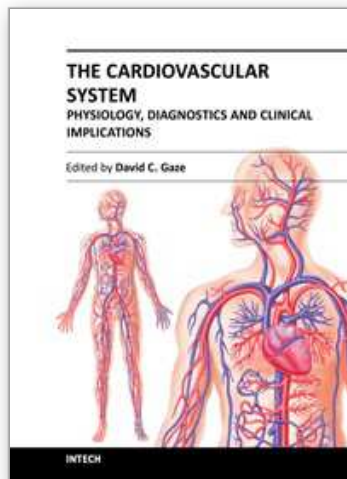
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The cardiovascular system includes the heart located centrally in the thorax and the vessels of the body which carry blood. The cardiovascular (or circulatory) system supplies oxygen from inspired air, via the lungs to the tissues around the body. It is also responsible for the removal of the waste product, carbon dioxide via air expired from the lungs. The cardiovascular system also transports nutrients such as electrolytes, amino acids, enzymes, hormones which are integral to cellular respiration, metabolism and immunity. This book is not meant to be an all encompassing text on cardiovascular physiology and pathology rather a selection of chapters from experts in the field who describe recent advances in basic and clinical sciences. As such, the text is divided into three main sections: Cardiovascular Physiology, Cardiovascular Diagnostics and lastly, Clinical Impact of Cardiovascular Physiology and Pathophysiology.

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