REVIEW

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Effect of selected drugs on plasma asymmetric dimethylarginine (ADMA) levels

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Asymmetric dimethylarginine (ADMA) is an endogenous methylated amino acid derived from arginine which can inhibit the activity of nitric oxide synthases. In various pathological states such as hypercholesterolemia, hyperglycemia, hyperhomocysteinemia, hypertension, coronary artery disease, heart failure, and stroke, plasma levels of ADMA may be increased and lead to inhibition of NO synthesis and endothelial dysfunction. Inhibition of ADMA synthesis or intensification of metabolism of this compound might indirectly lower ADMA. Antioxidants, estrogen, vitamin A, angiotensin converting enzyme inhibitors, angiotensin AT1 receptor antagonists, and also some hypolipemic, hypoglycemic and β-adrenoreceptor blocking drugs decrease ADMA levels. In some situations like neurological disorders, decreased plasma levels of ADMA are noticed and drugs increasing the concentration of this compound could exert protective effects. It is reasonable to explore which drugs can increase or decrease ADMA levels and what their mechanism of that action is.

1. Introduction

Asymmetric and symmetric dimethylarginines (N^G,N^G-dimethyl-L-arginine, ADMA, and N^G,$N^{G'}$-dimethyl-L-arginine, SDMA) as well as monomethylarginine (N^G-monomethyl-L-arginine, L-NMMA) are products of metabolism of arginine. Contrary to SDMA, ADMA and L-NMMA inhibit nitrogen oxide synthesis (Cardounel et al. 2007) and abolish the compound's vascular protective effect (Holm et al. 2002).

Increased plasma levels of ADMA are observed in many disorders like hypercholesterolemia, hyperglycemia, hyperhomocysteinemia, cardiac failure, hypertension and diabetes (Usui et al. 1998; Böger et al. 2000a; Zoccali et al. 2002; Lu et al. 2003), in patients with reduced left ventricular ejection fraction (Zoccali et al. 2002), in peripheral vascular disease (Böger et al. 1998; Usui et al. 1998), in critically ill patients (Nijveldt et al. 2003), patients with renal insufficiency (Moncada et al. 1991) and liver cirrhosis (Lluch et al. 2004). It is a prognostic factor of cardio-vascular events in patients with coronary disease (Schnabel et al. 2005) and of adverse cardio-vascular events in patients who underwent angioplasty (Lu et al. 2003); it is also a weak independent risk factor of stroke and a strong factor for transient ischemic attack (TIA) (Wanby et al. 2006). A correlation between the level of methyl derivatives and hepatic function and post-transplant survival was also shown (Martin-Sanz et al. 2003). Increased levels of ADMA were also found in smokers (Wang et al. 2006). Under some conditions, including septic shock, endotoxemia, Alzheimer's disease and other neurotoxic defects ADMA may regulate excessive NO synthesis (Kang et al. 1999; Abe et al. 2001; Cardounel and Zweier 2002; Vallance and Leiper 2002).

Protein arginine *N*-methyltransferases (PRMTs, protein methylases) are responsible for methylation of protein arginine residues and what leads to production of ADMA as a result of degradation of methylated protein (MacAllister et al. 1996; Leiper and Vallance 1999; Ito et al. 1999; Vallance and Leiper 2004). It was demonstrated that exposition to glucose (Lin et al. 2002), homocysteine (Stühlinger et al. 2001) and to the low-density lipoprotein (LDL) and the oxidized low-density lipoprotein (oxLDL) (Ito et al. 1999; Böger et al. 2000) intensified PRMTs activities. Also the activity of arginase, an enzyme decomposing arginine to ornithine and urea, has an additional effect on ADMA levels (Wu and Morris 1998).

System y(+) carriers of the cationic amino acid transporter (CAT) family is responsible for ADMA transport through biological membranes (Bogle et al. 1995). It is worth noting that the ADMA level inside a cell is 5–10-fold higher than that in serum (Leiper and Vallance 1999; Cardounel et al. 2007). The activity of the transporting system is also intensified by inflammatory cytokines, including tumour necrosis factor α (TNFα) and interleukin 1β (Il-1β) (Malandro and Kilberg 1996).

Dimethylarginine dimethylaminohydrolase (DDAH) is an enzyme responsible for ADMA metabolism (Leiper and Vallance 1999). The enzyme occurs in two isoforms: I and II characterised by over 60% homology (Tran et al. 2003). DDAH I distribution is similar to that of neuronal nitrogen oxide synthetase (nNOS), and DDAH II is loosely connected with the presence of endothelial and inducible nitrogen oxide synthases (eNOS and iNOS) (Leiper and Vallance 1999; Palm et al. 2007). DDAH II is also present in organs of the immunological system (Leiper et al. 1999; Tran et al. 2000) and localisation of the gene for DDAH II in the MHCIII region is probably associated with regulation of immunological tolerance (Bultink et al. 2005; Palm et al. 2007). Probably, the gene for DDAH I plays a role in embryogenesis (Leiper et al. 2007).

DDAH activity, and therefore ADMA metabolism, is influenced by numerous factors participating in pathogenesis of various diseases. Coupling factor 6 (CF6) is responsible for reduced expression of the DDAH II gene (Tanaka et al 2006). Lipopolysaccharide and high glucose level inhibit protein expression for DDAH II (Sorrenti et al. 2006; Xin et al. 2007). TNFα (Böger et al. 1998; Ito et al. 1999) and oxLDL (Ueda et al. 2003) inhibit protein expression for DDAH I. It was also demonstrated that inhibition of the enzyme activity intensifies production of oxygen free radicals (Lin et al. 1997). On the other hand, oxidative stress causes disturbance to DDAH activity by modification of cysteine in the active centre of the enzyme (Ito et al. 1999; Murray-Rust et al. 2001; Stühlinger et al. 2001). It seems that in patients with hypertension and hypercholesterolemia increased ADMA is associated with reduced DDAH activity because of oxidative stress (Böger et al. 1998; Ito et al. 1999; Böger et al. 2000a; Murray-Rust et al. 2001; Stühlinger et al. 2001; Xiong et al. 2003). DDAH activity is also inhibited by homocysteine (Stühlinger et al. 2001, 2003) and hyperglycemia (Masuda et al. 1999; Lin et al. 2002; Xiong et al. 2003). Numerous studies demonstrated that under those conditions accumulated ADMA is a significant factor affecting endothelium function by inhibition of nitric oxide (NO) synthesis and impairment of vasorelaxation (MacAllister et al. 1996; Masuda et al. 1999).

Excessive DDAH expression causes reduction of ADMA levels (Jacobi et al. 2005). Increased expression of the gene for DDAH II and increased protein expression for DDAH II are associated, among others, with administration of all-trans retinoic acid (Achan et al. 2002), pioglitazone (Wakino et al. 2005) and estradiol (Monsalve et al. 2007). In turn, increased protein expression for DDAH I is observed as an effect of interleukin IL-1β (Ueda et al. 2003).

2. Drugs

Considering growing clinical significance of ADMA, precise exploration of all factors influencing the compound's level in an organism seems justified. Usually, a significant majority of diseases is associated with elevated ADMA levels, therefore it seems purposeful to search for drugs which can lead to reduction in ADMA level and consequential increased NO synthesis and improved function of many organs. Inhibition of PRMTs or intensification of DDAH activity might indirectly lower ADMA, however it is not well established how changes of these enzymes activities may influence cell function, e.g, inhibition of PRMT could inhibit histones methylation (Krause et al. 2007). On the other hand, there are also pathological conditions associated with intensified NO synthesis and reduced ADMA levels. In these cases drugs having an opposite effect are sought.

2.1. Acetylsalicylic acid

Administration of acetylsalicylic acid at doses of 100 and 30 mg/kg b.w. to rats, for five days before a single injection of native LDL (4 mg/kg b.w.) markedly reduced the inhibition of vasodilator response of endothelium to acetylcholine (ACh). This treatment inhibited MDA and TNFα levels increase, and at the lower dose – also of ADMA level increase, with simultaneous enhancement of DDAH activity. As hypercholesterolemia is associated with increased TNFα, which is responsible for ADMA elevation through inhibition of DDAH (Ito et al. 1999), it is suggested that acetylsalicylic acid could influence ADMA concentration indirectly and reduced ADMA level resulted from decreased TNFα after administration of this drug (Deng et al. 2004).

2.2. L-Arginine

L-Arginine is the main substrate for NO synthase. Administration of exogenous L-arginine improves wound healing, renews macrophage and lymphocyte function reduced after surgical procedures and reinforces resistance to infections. Arginine deficiency causes a drop in NO synthesis (Furchgott 1996). When arginine or a cofactor for eNOS – tetrahydrobiopterin (BH4) is deficient, eNOS assumes an uncoupled form. Under conditions of oxidative stress, eNOS inhibition is associated with a harmful effect of peroxynitrite. This compound is able to oxidize BH4 to inactive dihydropterin (BH2), or may directly attack eNOS oxidizing zinc bonds to sulfhydyl (SH) groups, which, in turn, causes a release of zinc from the enzyme and transformation of eNOS into the uncoupled form. Under that condition, electrons flowing from reductase domain to oxidase are directed towards molecular oxygen, instead of arginine which results in production of peroxide, instead of NO (Sydow and Münzel 2003).

It was demonstrated that with no exogenous L-arginine, ADMA at 5 μM concentration inhibits the NO-dependent relaxation of rat carotid artery in 52%, and at a concentration of 500 μM in 95%. In the presence of 100 μM L-arginine, ADMA activity is less pronounced and its effect is 7% and 84%, respectively (Cardounel et al. 2007). Therefore, an arginine paradox describes the dependence between NO production and administration of exogenous L-arginine, despite saturation of NOS active centre by endogenous arginine (Sydow and Münzel 2003). Km is defined as concentration of arginine causing half maximal saturation of the enzyme active centre, and for eNOS the value is 2.9 μM. Intracellular arginine levels are far greater than that value. However, administration of exogenous L-arginine increases NO synthesis and improves NO-dependent endothelial function, which may be associated with the fact that methyl derivatives inhibit eNOS in just 10%, and addition of L-arginine overcomes that inhibition (Förstermann et al. 1991; Sydow and Münzel 2003; Vallance and Leiper 2004). The arginine paradox is sometimes also explained by intensified activity of arginase – an enzyme metabolising arginine to ornithine and by antioxidative properties of L-arginine (Sydow and Münzel 2003).

Results of studies on L-arginine are not unequivocal. Many of them demonstrated a protective effect of L-arginine in animals with hypercholesterolemia (Tsao et al. 1994; Wang et al. 1996), while others failed to demonstrate an effect (Suda et al. 2004). In studies on hepatocytes administration of L-arginine inhibited DDAH activity in a dose-dependent manner, competing probably with ADMA on the binding site in the active centre of the enzyme (Wang et al. 2006a). Those results have not been confirmed in studies *in vivo*. In patients with hypercholesterolemia, administration of L-arginine normalised the endothelium-dependent relaxation and reduced elevated ADMA level (Böger et al. 1998). Administration of L-arginine to genetically modified mice (DDAH+/−) reversed numerous unfavourable effects of NO deficiency (Leiper et al. 2007).

It seems that various effects of L-arginine depend on initial ADMA level, and administration of L-arginine is justified in patients with low L-Arg:ADMA concentration ratio. Improved vasodilatatory function of endothelium was observed in patients with chronic cardiac failure in whom ADMA level was elevated. The same effect was not observed in patients with low ADMA level (Hornig et al. 1998).

2.3. Agonists of the farnesoid X receptor

Several ligand-activated nuclear receptors, including liver X receptors, peroxisome proliferator-activated receptors (PPAR), and thyroid hormone receptors, may be the targets for pharmaco-

therapeutic interventions in metabolic syndrome (Shulman and Mangelsdorf 2005). The farnesoid X receptor belongs to a group of receptors for metabolic intermediate products, and regulates the metabolism of lipids and carbohydrates (Makishima et al. 1999; Parks et al. 1999). It affects expression of genes responsible for regulation of bile acid synthesis and transport (Ananthanarayanan et al. 2001; Yu et al. 2005). Administration of the receptor's agonist (GW4064) to female Zucker diabetic fatty (ZDF) rats causes a dose-dependent, 6-fold increase in expression of the gene for DDAH I, and therefore reduction of ADMA level and increased NO concentration. Sequence analysis of hepatic genes in those rats demonstrated that the gene for DDAH I has a binding site for the farnesoid X receptor (Hu et al. 2006). Recently, in another work it was also reported that farnesoid X receptor may play an important role in modulation of ADMA levels through regulation not only of DDAH-1 but also CAT-1 because the treatment of mice with GW4064 led to increased expression of the gene for DDAH-1 and CAT-1 in both liver and kidney. In cultured human hepatocytes and kidney proximal tubular epithelial cells, GW4064 also increased CAT-1 expression with increased cellular uptake of ADMA. A functional response element of farnesoid X receptor was found in the promoter region of CAT-1 gene (Li et al. 2009).

2.4. Antioxidants

Use of antioxidants restore DDAH activity impaired because of oxidative stress (Stühlinger et al. 2001; Lin et al. 2002), or inhibit PRMT1 activity (Jiang et al. 2006) leading in consequence to decreased ADMA levels (Achan et al. 2003).

Vitamin E is well-known as a strong antioxidant. In both *in vivo,* and *in vitro* studies the vitamin reduces ADMA concentration, inhibits lipid peroxidation and improves endothelium-dependent vasorelaxation to acetylcholine, inhibited in hypercholesterolemia (Jiang et al. 2002a; Tang et al. 2006). Therefore, it is used in numerous experimental settings in order to compare its effect to activity of other compounds of potential antioxidative effect (Jiang et al. 2002a, Tang et al. 2006).

Similarly, pyrolidine dithiocarbamate inhibits oxidative stress, reduces elevated ADMA levels and inhibits PRMT1 expression, simultaneously increasing activity of DDAH and eNOS both in endothelial cell culture (Stühlinger et al. 2001), and in rats with hypercholesterolemia induced by intravenous oxLDL administration (Jiang et al. 2006).

Swertia davidi Franch (Gentianaceae) is a herbal product commonly used in China. The main compound isolated from *Swertia davidi* is demethylbellidifolin, a compound belonging to xanthones. The compound has a broad therapeutic effect. It inhibits lipid peroxidation, and blocks LDL oxidation. *In vivo* and *in vitro* studies demonstrated that its protective effect on endothelium may be a result of reduced ADMA level being a consequence of inhibited lipid peroxidation (Jiang et al. 2002, 2004). Similar results were obtained in a study on isolated rings of rat thoracic aorta in relation to davidine A – another compound also belonging to the group of xanthones (Jiang et al. 2003).

Green tea is one of the most popular beverages in the world. It has a protective effect on the cardio-vascular system, reduces cholesterol and triglyceride level. Compounds contained in green tea are mostly polyphenols, commonly known as catechins. Epigallocatechin is the main compound with antioxidative properties responsible for therapeutic effects of green tea (Ramadass et al. 2003; Tang et al. 2006). Administered to rats for five days before a single dose of LDL, it prevented endothelium dysfunction, nitrate level reduction and ADMA and MDA level increase. Similar results were obtained following *in vitro* use of epigallocatechin. The study demonstrated also its protective effect on DDAH activity, which was inhibited after administration of oxLDL (Tang et al. 2006). Similarly to acetylsalicylic acid (Deng et al. 2004) and fenofibrate (Yang et al. 2005), epigallocatechin also prevents increased activity of such pro-inflammatory cytokines as TNFα (Tang et al. 2006) that could be responsible for ADMA rise by DDAH inhibition (Ito et al. 1999). It was demonstrated as well that vasodilator response of endothelium triggered by epigallocatechin administration is associated with rapid eNOS activation (Lorenz et al. 2004).

N-Acetylcysteine is a thiol molecule with antioxidant actions. It decreases reactive oxidant species and increases the bioavailability of the DDAH enzyme. In patients with end-stage renal disease intravenous administration of N-acetylcysteine during a 4-hour hemodialysis session led to greater decrease in ADMA level compared with hemodialysis alone (Thaha et al. 2008).

2.5. Hypoglycemic drugs

Diabetes is associated with accelerated atherosclerosis, and increased prevalence of cardio-vascular conditions, constituting the main cause of death. Between contributing factors are impairment of endothelium-dependent vasorelaxation resulting from decreased NO level and intensified synthesis of constricting agents (Xiong et al. 2003). NO deficiency develops because of, among others, accumulation of endogenous NOS inhibitors, such as ADMA, concentration of which rises dramatically in uncontrolled diabetes (Xiong et al. 2002). Long-term therapy with insulin in rats with streptozotocin-induced diabetes (Xiong et al. 2003) reduces ADMA level and improves endothelial function. However, it is uncertain if ADMA level is reduced only as a result of glucose level reduction or as a direct effect of insulin.

Metformin has a similar effect in patients with type II diabetes. After 3 months of the drug administration to patients previously treated unsuccessfully with diet or maximum doses of sulphonylurea derivatives, ADMA level was significantly reduced, with concurring reduction of glycemia. Interestingly, the reduction was similar, regardless if metformin was used alone, or with sulphonylurea derivatives (Asagami et al. 2002).

In those experiments (Asagami et al. 2002; Xiong et al. 2003) insulin and metformin reduced MDA level increased in hyperglycemia, along with ADMA reduction. That observation confirms a thesis that increased ADMA level is closely associated with intensified oxidative stress in diabetes, manifested by enhanced lipid peroxidation. Increased production of free oxygen radicals causes DDAH inactivation, possibly by activation of xanthine oxidase and inactivation of superoxide dismutase (SOD). Incubation of human endothelial cell lines in a medium containing high glucose levels and polyethylene glycol-conjugated SOD (PEG-SOD) causes restoration of DDAH activity and elevation of reduced cGMP level, a marker of impaired NOS pathway (Lin et al. 2002).

Treatment with metformin led to a decrease in ADMA levels in women with the polycystic ovary syndrome (PCOS). ADMA is significantly higher in this group of patients and it is also positively correlated with body mass index (BMI), waist to hip ratio, parameters of insulin sensitivity, hyperandrogenemia (free testosterone, free androgen index), and intima media thickness (IMT) (Heutling et al. 2008). Another study demonstrated that in non-obese, non-hypertensive and young women with PCOS ADMA levels were significantly higher than in healthy controls. In this group of women metformin treatment also decreased ADMA levels (Ozgurtas et al. 2008).

Thiazolidinediones are another group of drugs used in diabetes mellitus treatment. Pioglitazone decreased ADMA by indu-

cing DDAH activity in rats (Wakino et al. 2005). Rosiglitazone administered for 8 weeks to patients with insulin-resistance and hypertension improved insulin-sensitivity, with simultaneous reduction of ADMA serum levels (Stühlinger et al. 2002). The opposite effect was observed in an animal model of high cardiovascular risk (aged hyperhomocysteinemic methylene tetrahydrofolate reductase gene (MTHFR) heterozygous knockout mice (mthfr+/−) fed a high cholesterol diet). In those animals rosiglitazone prevented carotid remodeling, but impaired endothelial function in part through enhanced oxidative stress and increased ADMA production (Savoia et al. 2010).

2.6. Hypolipemic drugs

It was demonstrated that besides inhibition of cholesterol synthesis, statins affect also endothelium function eg. increase NOS activity and intensify NO synthesis. It was also demonstrated that simvastatin reverses the inhibitory effect of oxLDL on NO production in a dose-dependent manner (Laufs et al. 1998; Jones et al. 2002). However, effect of statins on ADMA concentration is not that obvious and it seems to depend on, among others, a particular drug. Several studies did not demonstrate an effect of statins, such as simvastatin, atorvastatin and pravastatin (Paiva et al. 2003; Eid et al. 2003) on ADMA concentration. It was demonstrated that atorvastatin treatment in patients with non-ischaemic chronic heart failure (EF < 40%, NYHA II, III) improves endothelial function but has no effect on ADMA or the L-arginine to ADMA ratio (Young et al. 2008). Similarly to acetylsalicylic acid, simvastatin reduces TNFα levels and improves endothelium function in hypercholesterolemia, but has no effect on ADMA levels (Eid et al. 2003; Paiva et al. 2003; Jiang et al. 2004a). In patients with chronic kidney disease simvastatin did not change increased levels of ADMA (Panichi et al. 2008). Interestingly, in a study on a group of patients with increased ADMA level, simvastatin improves the vasodilatatory response of the endothelium, but only when it was administered concomitantly with L-arginine (Böger et al. 2004).

There are also studies demonstrating a statin effect on ADMA level. Atorvastatin administered for extended periods of time reduced ADMA in rats with arterial hypertension, simultaneously increasing the survival rate and reducing stroke prevalence rate (Hayashi et al. 2004). Rosuvastatin is another example of an ADMA level reducing agent. A multicentre, randomised, double-blind trial on 46 patients with elevated LDL level demonstrated that the drug administered at a daily dose of 10 mg for 6 weeks causes reduction in LDL levels and significantly reduces ADMA serum concentrations, and improves endothelial function. With ADMA reduction also the level of 8-isoprostanes, markers of oxidative stress, is reduced (Lu et al. 2004). Also fluvastatin at the dose of 80 mg/day, administered for 6 weeks in patients with metabolic syndrome and hypercholesterolemia lowered serum ADMA levels (Oguz et al. 2008).

Fenofibrate administered to rats with hyperlipidemia alleviated endothelial dysfunction reducing ADMA and TNFα levels and inhibiting lipid peroxidation (Yang et al. 2004). Similar effects could be observed in a trial of human umbilical vein endothelial cell (HUVEC) lines. In that trial fenofibrate prevented also activation of nuclear factor κB (NF-κB). Specific antagonists of the peroxysome proliferator activated receptor α (PPARα) abolished the preventive effect of fenofibrate. Therefore a suggestion that reduction of NF-κB by fenofibrate is associated with activation of PPARα receptors (Yang et al. 2005). It was demonstrated that NF-κB plays a significant role in atherosclerosis by regulation pro-inflammatory gene expression. Activated NF-κB is present in atherosclerotic vessels, but absent in regular ones; therefore inhibition of the factor is directly associated with inhibition of atherogenesis (Collins and Cybulsky 2001).

Ezetimibe, a newer hypolipemic drug may also have pleiotropic actions. This specific inhibitor of cholesterol absorption administered for 6 months at the dose of 10 mg/day significantly decreased ADMA levels and improved renal injury in non-diabetic patients with chronic kidney disease and dyslipidemia in a cholesterol-independent manner (Nakamura et al. 2009).

Probucol is a hypolipemic agent possessing additional antioxidative properties. It inhibits oxidative modifications of LDL molecules and improves endothelium function in animals with hypercholesterolemia (Simon et al. 1993). Previous use of the drug in rats given LDL intravenously reduced elevated ADMA levels and inhibited lipid peroxidation (Jiang et al. 2002a). In another study, decline in ADMA level was accompanied also by reduction of PRMT1 expression intensified in hypercholesterolemia, increase in inhibited DDAH activity and expression of eNOS (Jiang et al. 2006). Reduced DDAH expression was achieved also in endothelial cell cultures (Pluta et al. 2005). However, not all studies demonstrated a protective effect of probucol on the endothelium (Tagawa et al. 2004; Pluta et al. 2005).

2.7. β-Blockers

The effect of that group of drugs on ADMA concentration is controversially described. In a study on patients with idiopathic hypertension, bisoprolol did not reduce the elevated ADMA concentration. It had also no effect on MDA level and the von Willebrand factor (vWF) (Ito et al. 2001). Similarly, no influence on ADMA was observed with atenolol and metoprolol (Pasini et al. 2008; Sen et al. 2009). However, some drugs belonging to this group and possessing additional properties such as NO release and relaxation of vessels demonstrate different results. In HUVECs nebivolol decreases ADMA/SDMA ratio and increase in DDAH II mRNA and protein expression and activity in a dose-dependent manner (Garbin et al. 2007). In essential hypertensive patients nebivolol also decreased ADMA levels and increased flow-mediated dilation (FMD). A significant correlation between changes in ADMA levels and changes in FMD was found (Pasini et al. 2008). In patients with cardiac syndrome X who had received nebivolol for 12 weeks plasma NOx and L-arginine concentrations, the L-arginine/ADMA ratio were increased and the level of ADMA was decreased compared to those of the patients taking metoprolol. Furthermore, in exercise stress test nebivolol improved parameters to a greater degree than metoprolol (Sen et al. 2009). In patients with heart failure ADMA level was decreased after carvedilol treatment only in responders (when LVEF had increased at least 5%) and an inverse correlation was observed between ADMA level and changes in LVEF. Additionally, regardless of the LV response, this drug can reduce the expression of inflammation (increase in IL-10 and decrease in IL-18) (Alfieri et al. 2008).

2.8. Angiotensin converting enzyme inhibitors (ACEI) and AT1 receptor blockers (ARB)

An increasing number of studies indicate that both ACEI and ARB improve endothelial function in patients with arterial hypertension, which is to some extent associated with increased NOS activity as a result of bradykinin degradation impairment and more intensive NO release due to the angiotensin II effect on AT2 receptors (Mancini 2000; Carey et al. 2000). Angiotensin II intensifies the production of superoxide anions by activation of NADPH oxidase (Zhang et al. 1999), and causes ADMA growth (Ito et al. 2002; Delles et al. 2003). Following ACEI or

ARB administration, a drop in ADMA levels was observed in patients with hypertension (Ito et al. 2002; Delles et al. 2003; Napoli et al. 2004). The mechanism of that effect is not fully understood. It seems that it is at least partially independent from the hypotensive effect of those drugs and their impact on angiotensin II concentration. Eprosartan and enalapril, administered separately or combined, reduced ADMA concentration in young males, regardless their effect on arterial pressure and activity of angiotensin II (Delles et al. 2003). Similar results were obtained in studies on enalapril and perindopril in patients with hypertension or diabetes (Ito et al. 2001, 2002; Delles et al. 2003).

In several studies vWF was determined as endothelial damage indicator (Ito et al. 2001, 2002). Perindopril and losartan significantly reduced both the level of this factor and the concentration of ADMA. However, no correlation was demonstrated between those parameters (Ito et al. 2001).

It is suggested that effects of both those drug groups may be associated with their antioxidative potential. ACEI were demonstrated to reduce levels of free radicals in patients with coronary artery disease (Berry et al. 2001), and an AT1 antagonist (losartan) – to reduce MDA concentration (Ito et al. 2001). Recently, it was reported that incubation of human monocytoid cells with losartan and ADMA attenuated monocytic adhesiveness elicited by ADMA what may be related to downregulation of the expression of chemokine receptors by inhibiting the reactive oxygen species (ROS) and NF-κB activity and expression (Chen et al. 2009).

Some authors suggest that the antioxidative effect of those drugs is associated with the presence of SH groups in their structure. Captopril possessing the SH group can reduce ADMA concentration, improve endothelial function and decrease oxidative stress in rats with hyperhomocysteinemia (Fu et al. 2005). In another experiment captopril administrated 15 minutes before incubation of rat aorta with homocysteine exerted similar effects to those obtained following simultaneous administration of SOD and L-arginine (Fu et al. 2003). Zofenopril, a novel ACE inhibitor with a SH group also decreased oxidative stress in patients with hypertension and reduced ADMA level even stronger than enalapril (Napoli et al. 2004). It seems that whereas the ability to scavenge free radicals depends on the presence of SH groups, improvement of endothelial function (ramiprilat, lisinopril) (Gillis et al. 1992; Xiong et al. 1994), reactivity of cerebral vessels impaired by hyperhomocysteinemia (quinalapril) (Chao and Lee 2000), and reduction of ADMA level (perindopril) (Ito et al. 2001), is also characteristic for drugs possessing no SH groups in their molecular structure (Chopra et al. 1992). Therefore, protective effect of that group of drugs is not necessarily associated with the presence of SH groups.

The effect of some AT1 blockers may be connected with activation of PPARγ signaling. During the process of aging of endothelial cells, PPARγ protein expression decreased significantly, whereas the expression of AT1 receptor increased. Incubation of endothelial cells with telmisartan – a drug which in addition to blocking AT1 receptor can activate PPARγ signaling reversed these effects. Senescence was delayed and reactive oxygen species and 8-iso-prostaglandin F2α formation were decreased. Additionally, this drug increased activity and protein expression of DDAH, and decreased ADMA concentration. The effect of telmisartan on ADMA and DDAH was prevented by a blockade of PPARγ signaling. Incubation with angiotensin II failed to reverse the action of telmisartan on senescence. Eprosartan – another drug that has no influence on PPARγ signaling had no effect on the ADMA system (Scalera et al. 2008). Telmisartan administered to patients with hypertension decreased ADMA levels with a decrease in pulse-wave velocity value, the blood pressure, total- and LDL-cholesterol levels and an improvement of HbA_{1c} values (Ono et al. 2009). The effect of telmisartan on ADMA levels may be also connected with a decrease in expression of PRMT1 what was demonstrated in the work on streptozotocin-induced diabetic rats (Onozato et al. 2008).

2.9. Estrogens

Estradiol's structure is similar to that of tocopherol (Mooradian 1993). This compound has antioxidative properties and has a protective effect on the endothelium, increases NO synthesis, reduced leukocyte adhesion, inhibits proliferation of vascular smooth muscle cells and aggregation of platelets (Nascimento et al. 1999; Enderle et al. 2000; Shaw et al. 2000; Thibodeau et al. 2002; Dai et al. 2004). It can also reduce LDL concentration and improve LDL resistance to oxidation (Pines et al. 1997; Mijatovic et al. 1998). In gonad-depleted monkeys estradiol deficiency caused intensification of endothelial dysfunction (Wagner et al. 1996). In cultured human endothelial cells β-estradiol inhibited ADMA production induced by oxLDL (Monsalve et al. 2007). Application of this drug prior to a single administration of LDL significantly reduced inhibition of endothelial response to ACh, inhibits ADMA and MDA level rise (Dai et al. 2004). A short-term, non-genomic effect of estradiol is associated with estrogen receptors on cell surface, stimulation of which caused an increase in NOS activity and in prostacycline production (Rubio-Gayosso et al. 2000). Long-term administration of estradiol leads to activation of eNOS through increased mRNA expression in genomic mechanism (Grady et al. 2002).

It was demonstrated that women who do not use oral contraceptives have significantly higher ADMA and SDMA levels in the luteal phase compared to the follicular phase of the menstrual cycle. In oral contraceptives users, there were no significant differences in ADMA levels across the menstrual cycle. In users of estrogen containing pills ADMA levels were significantly lower than in non-users, but treatment with progestin-only contraceptive pills failed to decrease ADMA levels (Valtonen et al. 2009).

Hormonal replacement therapy with estrogen also causes a significant drop in ADMA level what was demonstrated in a two year randomized double-blind trial on 40 females after hysterectomy. That kind of effect was not observed for raloxifene – a selective estrogen receptor modulator (Mijatovic et al. 1998).

2.10. B Group vitamins

Results of studies on effect of group B vitamins are equivocal. A protective effect of folic acid on endothelium in hyperhomocysteinemia, expressed by improved endothelium-dependent vasodilatation to ACh and increased nitrate concentration was demonstrated (Holven et al. 2001). Additionally, in another study folic acid reduced increased ADMA and homocysteine levels (Holven et al. 2003). In a study on 25 patients with coronary artery disease, supplementation of folic acid for 4 months improved endothelium-dependent vasodilatation (Title et al. 2000). A similar effect was caused by high doses of folic acid administered after infusion of methionine (Usui et al. 1999). However, not all studies were able to demonstrate such effect of folic acid. In monkeys with hyperhomocysteinemia after 6 months administration of group B vitamins (B6, B12 and folic acid) no ADMA level or endothelial function decrease were observed, while homocysteine level was reduced (Lentz et al. 1997; Böger et al. 2000a). Similar results were observed in patients with obliterative arteriosclerosis of lower limbs and hyperhomocysteinemia (Sydow et al. 2003). Dietary supple-

mentation with group B vitamins intensified reactions leading to reduction of homocysteine concentration because vitamin B6 is a cofactor of transformation of homocysteine into cystathionine and of vitamin B12 and folic acid into methionine. However, they have no effect on ADMA levels, because they do not inhibit protein methylation. On the contrary, intracellular S-adenosylmethionine concentration – a substrate for protein methylation – may even be increased as a result of increased transformation of homocysteine into methionine (Ubbink et al. 1994; Miller et al. 1994). Therefore it seems that a protective effect of those vitamins is not associated with their influence on ADMA concentration. The effect of folic acid on endothelial function may be rather associated with the fact that this compound is a precursor for terahydrobiopterin, which is a cofactor for eNOS (Scott et al. 1998).

2.11. Vitamin A

Vitamin A derivatives, in particular all-trans-retinoic acid, inhibit proliferation and intensify cell differentiation. That effect is important for the cardio-vascular system. Regulating angiogenesis the compounds are able to, among others, delay the development of atherosclerosis (Shaish et al. 1995). Their effect on endothelium was demonstrated, besides the effect on vascular smooth muscles (Neuville et al. 1999). In a murine endothelial cell culture model all-trans-retinoic acid could increase NO concentration despite any effect on eNOS mRNA expression. This compound intensified DDAH II activity and expression, and therefore intensified ADMA decomposition. The use of a DDAH II inhibitor - 4124W in cells stimulated with the drug caused a drop in NO concentration. Effect of all-trans-retinoic acid on DDAH II is rather associated with regulation of the enzyme gene transcription, than with any effect on mRNA stability (Achan et al. 2002).

2.12. Others

Recently, it was demonstrated that in patient treated with either valproic acid or carbamazepine ADMA levels significantly increased what may be partially a reason for the increased cardiovascular risk in patients with epilepsy (Oz et al. 2009).

Cardiac allograft vasculopathy is a major cause of death after heart transplantation. It was demonstrated that ADMA levels were associated with subsequent development of intimal hyperplasia. However, ADMA levels did not correlate with negative coronary remodeling. Treatment with sirolimus, compared with mycophenolate mofetil, could significantly decrease ADMA levels and was associated with less intimal hyperplasia (Potena et al. 2008).

Addition of NO donors: *S*-nitrono-*N*-acetylpenicillamine (SNAP) and 3-morpholino-syndnonimin (SIN-1) to cellular culture *in vitro* significantly intensified NO production without any effect on ADMA levels (Ueda et al. 2003).

Aminoguanidine is a selective iNOS inhibitor (Alderton et al. 2001) possessing a suggested antioxidative effect (Giardino et al. 1998). The drug also prevents the development of angiopathy (Forbes et al. 2004). It inhibits formation of advanced glycosylation end products (AGEs), formed during non-enzymatic reactions between glucose and proteins and through an interaction with specific receptors (RAGE). Those products intensify oxidative stress and cause vascular damage in patients with diabetes (Tan et al. 2002). Aminoguanidine caused reduction of ADMA and MDA levels, and an increase in activity of NOS, DDAH and SOD. This compound protects also rat aorta endothelium against a damage caused by administration of glycated bovine albumins (GBSA) both in injections for four weeks, and by incubation of fragments of rat aorta with GBSA (Yin et al. 2007).

3. Summary

Numerous studies examine the effect of various drugs on ADMA serum level, condition of endothelium, oxido-redox status and other effects of decreased NO level. Our knowledge on that field is incomplete and results of published studies differ and sometimes are even contradictory. It should be also remembered that most of the investigations were performed either on animals or on small groups of patients.

Most experiments indicate that substances possessing antioxidative properties can decrease ADMA levels and improve endothelial function. Estrogen and vitamin A also lower the concentration of this compound as demonstrated by many studies. The effect of ACEI and ARB on ADMA is rather well documented but the mechanism of that action is not fully understood. It may be associated with their antioxidative properties, or with the presence of SH groups in their structure. In the case of ARB activation of PPARγ signaling could not be excluded. Similarly, the effect of fenofibrate on ADMA is probably connected with activation of PPARα. Ezetimibe, probucol, metformin, insulin and thiazolidinediones also decrease ADMA levels, but the evidence for this is rather scant. The action of hypoglycemic drugs may result from reduced glucose level. The effect of acetylsalicylic acid, statins, vitamin B, and β-blockers on ADMA levels is not so obvious. This effect was documented for a particular drug from these groups e.g., fluvastatin, rosuvastatin, cavedilol, or nebivolol.

Based on the data available it should be claimed that the ability to modify ADMA concentration may constitute an additional aim of therapies under various pathological conditions. Therefore, it is reasonable to conduct new experiments with old drugs and to search for new drugs decreasing ADMA levels. Lower ADMA levels may lead to increased NO synthesis and improvement of the function of different organs. On the other hand, excess of NO in such states as septic shock or neuronal injury may be a reason for pathological changes in tissues. In such a situation, drugs increasing ADMA levels could exert protective effects.

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