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REVIEW ARTICLE

L-Arginine and its metabolites in kidney and cardiovascular disease

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Abstract L-Arginine is a semi essential amino acid synthesised from glutamine, glutamate and proline via the intestinal-renal axis in humans and most mammals. L-Arginine degradation occurs via multiple pathways initiated by arginase, nitric-oxide synthase, Arg: glycine amidinotransferase, and Arg decarboxylase. These pathways produce nitric oxide, polyamines, proline, glutamate, creatine and agmatine with each having enormous biological importance. Several disease are associated to an L-arginine impaired levels and/or to its metabolites: in particular various L-arginine metabolites may participate in pathogenesis of kidney and cardiovascular disease. L-Arginine and its metabolites may constitute both a marker of pathology progression both the rationale for manipulating L-arginine metabolism as a strategy to ameliorate these disease. A large number of studies have been performed in experimental models of kidney disease with sometimes conflicting results, which underlie the complexity of Arg metabolism and our incomplete knowledge of all the mechanisms involved. Moreover several lines of evidence demonstrate the role of L-arg metabolites in cardiovascular disease and that L-arg administration role in reversing endothelial dysfunction, which is the leading cause of cardiovascular diseases, such as hypertension and atherosclerosis. This review will discuss the implication of the mains L-arginine metabolites and L-arginine-derived guanidine compounds in kidney and cardiovascular disease considering the more recent literature in the field.

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Introduction

L-Arginine (Arg) is a basic amino acid in physiological fluids. Its content is relatively high in seafood, watermelon juice, nuts, seeds, algae, meats, rice protein concentrate and soy protein isolate (Hou et al. 2008; King et al. 2008; Wu et al. 2007a), but low in the milk of most mammals (including cows, humans, and pigs; Davis et al. 1994; Wu and Knabe 1994). Arg is classified as semi-essential amino acid that in cases of immaturity, disease or injury, its endogenous production may be insufficient to meet higher demand (Rackè and Warnken 2010). The sources of Arg in the body are dietary proteins, endogenous synthesis and protein turnover. The majority of plasma Arg is derived from protein metabolism and turnover, whereas de novo synthesis accounts for only 5–15 % of the endogenous supply. In adults, endogenous synthesis of Arg involves the intestinal-renal axis (Wu and Morris 1998). Namely, citrulline is synthesized from glutamine, glutamate and proline in the mitochondria of enterocytes, released from the small intestine and taken up primarily by kidneys for Arg production (Fig. 1). In neonates, most of the citrulline synthesised in enterocytes is converted locally into Arg (Wu 1997; Wu and Knabe 1995). Interestingly, the uptake of citrulline by liver is negligible and this organ is not active in extracting Arg from the circulation (Wu et al. 2007b). Therefore, nearly 100 and 90 % of the gut-derived citrulline and Arg, respectively, bypass the liver in pigs (Wu et al. 2007b). Similar patterns of citrulline and Arg metabolism have been reported for humans (Ligthart-Melis et al. 2008; van de Poll et al. 2007). Arg constitutes approximately 57 % of the

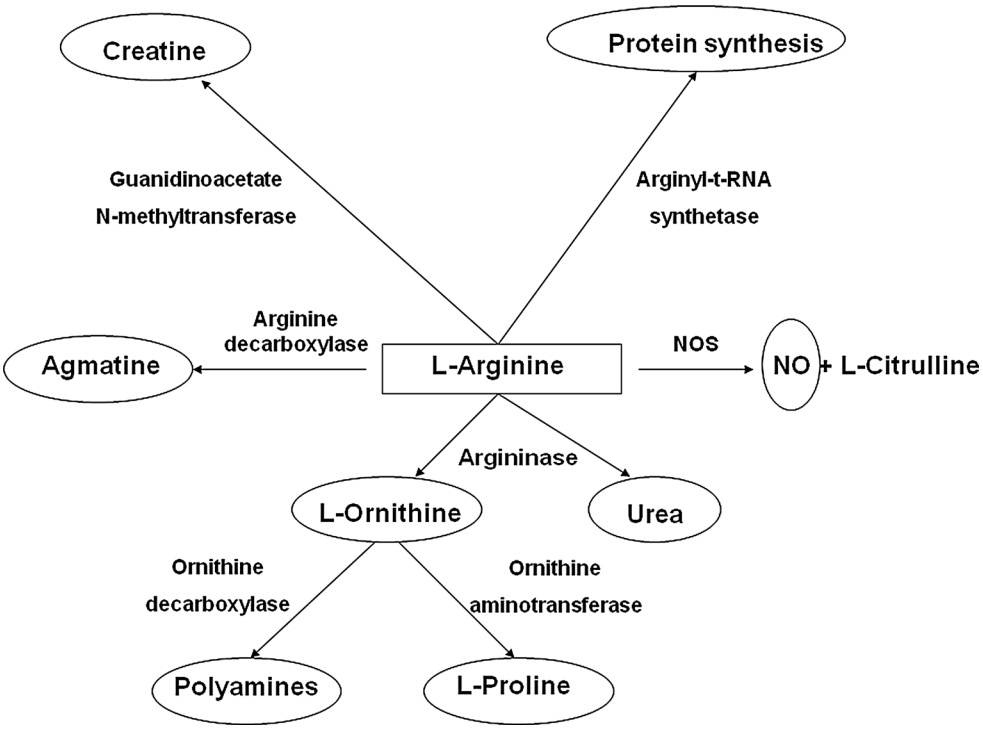

Fig. 1 Arginine metabolism in mammals

amino acid content of a normal healthy adult diet and it is found in the most proteins consumed to be either metabolized to glucose or produce energy (Raghavan and Dikshit 2004). Arg degradation occurs via multiple pathways that produce polyamines, nitric oxide (NO), proline, glutamate, creatine and agmatine all of them having enormous biological importance. Arg is also required for the detoxification of ammonia, which is an extremely toxic substance for the central nervous system.

There is compelling evidence that Arg regulates interorgan metabolism of energy substrates and the function of multiple organs. The results of both experimental and clinical studies indicate that Arg is a nutritionally essential amino acid for spermatogenesis, embryonic survival, fetal and neonatal growth, as well as maintenance of vascular tone and hemodynamics. Moreover, a growing body of evidence clearly indicates that dietary supplementation or intravenous administration of Arg is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, as well as facilitating wound healing, enhancing insulin sensitivity, and maintaining tissue integrity. Additionally Arg or may provide novel and effective therapies for obesity, diabetes, and the metabolic syndrome. The effect of Arg in treating many developmental and health problems is unique among amino acids and offers great promise for improved health and wellbeing of humans and animals. Several disease are associated to an Arg impaired levels and/or to its metabolites. Many Arg metabolites may participate in pathogenesis of kidney and cardiovascular disease and constitute the rationale for manipulating Arg metabolism as a strategy to ameliorate these pathologies. A large number of studies have been performed in experimental models of kidney disease with sometimes conflicting results, which underlie the complexity of Arg metabolism and our incomplete knowledge of all the mechanisms involved. This review will discuss the implication of Arg metabolites in renal and cardiovascular disease considering the more recent literature in the field.

Arg metabolism

Arg turns over rapidly in mammals with half lives in the circulation of 1.06 h for adult (Wu et al. 2007a). Arg transport by cells involves the system y^+ (a high-affinity, Na^+-independent transporter) and Na-dependent transporters in a cell-specific manner (Grillo et al. 2008). Given its diverse roles, Arg is metabolized by a complex and highly regulated set of enzymes in several pathways. In contrast to a single enzyme that produces Arg, four sets of enzymes mainly use this amino acid as a substrate in mammalian cells: arginase (ARG), nitric oxide synthase (NOS), arginine:glycine amidinotransferase (AGAT), and arginine decarboxylase (ADC). With the exception of ADC, all of

these enzymes act on the guanidine group of Arg. Arg is catabolised to various products: (1) in the cytosol NOS metabolizes Arg to nitric oxide (NO) and L-citrulline; (2) in the mitochondria Arg is metabolized to agmatine by ADC; (3) in the cytosol and into the mitochondria, arginase metabolizes Arg to urea and L-ornithine, which is the precursor for the synthesis of polyamines by ornithine decarboxylase; (4) in the mitochondria AGAT metabolizes Arg to creatine (Fig. 1). Creatinine synthesis inhitiated by AGAT in the kidney and pancreas to form guanidinoacetate, which is subsequently methylated in the liver by guanidinoacetate N-methyl transferase to form creatine, used by skeletal muscle and nerves (Raghavan and Dikshit 2004). Quantitatively, <1 and 2 % of metabolized Arg are utilized for polyamine synthesis and constitutive NO production, respectively, in mammalian cells (O'Quinn et al. 2002; Li et al. 2001).

Arginase pathway

The ARG pathway is quantitatively the most important for Arg catabolism in mammals. ARG includes a group of enzymes that are involved in tissue repair processes and that metabolize Arg to urea and L-ornithine (Rakèand Warnken 2010). Two ARG isoenzymes (designed as ARG-I and ARG-II) exist: they catalyse the same biochemical reaction but differs in cellular expression, regulation and subcellular localization (Jenkinson et al. 1996). The isoform ARG-I is abundantly expressed in hepatocytes (Morris 2007), as one of the enzyme of the urea cycle which detoxifies ammonia in mammals, and to a limited extent, in extrahepatic cells, including enterocytes of postweaning mammals, endothelial cells, mammary epithelial cells, macrophages, and red blood cells (only in primates; Li et al. 2002; O'Quinn et al. 2002; Wu et al. 1996). ARG-II protein is widely expressed as a mitochondrial protein, at relatively low levels, in a variety of peripheral mammalian tissue (including neuronal, renal, vascular, and muscle cells) and plays an important role in regulating the synthesis of NO, proline and polyamines (Li et al. 2001; Odenlund et al. 2008; Orlando et al. 2008). Due to its generation of L-ornithine ARG has a very important metabolic role being involved in several important downstream pathway. Infact, L-ornithine can be further metabolized via ornitine decarboxylase (ODC) to polyamines (putrescine, spermidine, spermine), small cationic molecules which participate to various important cellular functions. L-Ornithine can be also metabolized by ornithine aminotransferase (OAT) to L-proline, an essential component of collagen.

Increased ODC activity has been associated with tissue repair and cell growth (Reyes et al. 1994) and deregulation of the polyamine pathway enzymes may play an important role in various pathological conditions as stroke (Igarashi and Kashiwagi 2011a; Saiki et al. 2011; Tomitori et al. 2005; Yoshida et al. 2010) and renal failure (Igarashi et al. 2006). Despite the absolute need for polyamines, it has been known for more than 50 years that spermine and spermidine have acute toxic effects when injected into animals (Tabor and Rosenthal 1956) and many early studies have observed toxic effects of polyamines on the growth and viability of microorganisms, spermatozoa, cultured mammalian cells, and viruses (Tabor and Rosenthal 1956; Tabor and Tabor 1985). This toxicity could be due to direct action of the polyamines themselves. It is likely that excess intracellular polyamines derange cellular metabolism including protein synthesis by binding to acidic sites in nucleic acids, membranes, and proteins and/or by displacing othecations such as magnesium from these sites (Morris et al. 1991). Inhibition of blood clotting and transitory falls in blood pressure and respiratory symptoms were seen shortly after polyamines administration to experimental animals and neurotoxicity leading to renal insufficiency developed after a few days (Pegg 2013).

In chronic kidney disease (CKD) patients plasma a decrease in spermine and an increase in putrescine, polyamine oxidase and acrolein, derived from spermine degradation by polyamine oxidase, has been reported (Igarashi et al. 2006). Polyamines or their oxidation products were first postulated to be significant contributors to uremic toxins by Campbell and colleagues (Bagdade et al. 1979; Campbell 1987). More recent detailed studies have focused on oxidation products as mediators of toxicity in patients with chronic renal failure (Igarashi and Kashiwagi 2011b; Sakata et al. 2003a, b; Igarashi et al. 2006; Schophuizen et al. 2013). Both free and protein conjugated acrolein were increased in the plasma of patients with chronic renal failure and in a variety of kidney diseases including diabetic nephropathy, chronic glomerulonephritis, and nephrosclerosis (Sakata et al. 2003a, b). The accumulation of polyamines in blood due to the decrease in their excretion into urine in uremia and the release of polyamines and oxidative enzymes after renal damage may form a combination, exacerbating disease. Polyamines and acrolein inhibited renal organic cation transporters (Schophuizen et al. 2013). Spermidine/spermine-N1-acetyl transferas (SSAT), acetylates and reduces the charge on the polyamines, thus altering their ability to bind to acidic macromolecules, rendering them more susceptible to excretion from the cells. SSAT and spermine oxidase increase in kidneys subjected to injury after endotoxin or ischemia–reperfusion, and the resulting activation of polyamine catabolism is associated with oxidative DNA damage (Zahedi et al. 2007, 2010). Mice with the SSAT gene inactivated were more resistant to ischemia–reperfusion (Zahedi et al. 2009).

During metabolism of spermine and spermidine released from ribosomes (Watanabe et al. 1991), two toxic compounds, i.e., acrolein and hydrogen peroxide are produced. Of the two compounds, it was determined that acrolein was more toxic than hydrogen peroxide (Sharmin et al. 2001). It has been reported that the levels of protein-conjugated acrolein (PC-Acro) in plasma were well correlated with the seriousness of chronic renal failure (Igarashi et al. 2006).

The role of ODC and polyamine metabolism in cardiac hypertrophy was described since long ago (Caldarera et al. 1971; Pegg and Hibasami 1980). It has been well established that all inducers of cardiac hypertrophy (e.g. ascending aortic stenosis, stress, physical exercise, adrenoceptors agonist) are correlated with an increase in polyamine concentrations (Govoni et al. 2010) which seem to be responsible for histone hyperacetylation and elevated RNA and protein synthesis. In fact, inhibition of polyamine synthesis decreased histone acetylation and RNA transcription, while spermine reversed this effect (Caldarera et al. 1975). Administration of α-difluoromethylornithine, a suicide inactivator of ODC, reduced polyamine content and attenuated isoproterenol- and clenbuterol-induced cardiac hypertrophy (Cubría et al. 1998; Tipnis et al. 2000; Schlüter et al. 2000). Another inhibitor of ODC, α-methylornithine, also inhibited both ODC induction and development of an hypertrophic phenotype in cardiac myocytes with high transforming growth factor-β-activity (Tipnis et al. 2000). It's well known that polyamine and NO pathways are interregulated. In the heart tissue, ornithine decarboxylase transforms ornithine into putresceine, and the latter is metabolized to spermidine and spermine. Arg appears to attenuate cardiac hypertrophy by decreasing polyamine via inhibiton of polyamine synthesis and promotion of polyamine degradation (Lin et al. 2008).

Nitric oxise synthase pathway

Arg is the main source for the generation of NO via NOS. About the 1 % of daily L-arg intake is metabolized by NOS (Moncada 1997). There are three distinct isoform of NOS which differ both in structure and in function: type I or neuronal NOS (nNOS), type II or inducible NOS (iNOS), type III or endothelial NOS (eNOS). eNOS and nNOS are constitutively expressed in a variety of different cells and their activities are regulated by Ca^{2+}-dependent calmodulin binding as well as by serin phosphorylation/dephosphorylation (Alderton et al. 2001). In contrast, iNOS is regulated only transcriptionally in a large variety of cells by bacterial toxins such as LPS and several pro-inflammatory cytokines such as interleukin 1-β, INF-γ or tumor necrosis factor α.

ARG and NOS compete for Arg. Therefore, relative changes in their enzymatic activities serve as major determinants of NO and polyamine production in many cell types (Durante et al. 2007; Li et al. 2001).

Free radicals and reactive oxygen species (ROS) were found to be important factors in the pathogenesis of chronic renal disease (Conference 1987). NO has been appreciated as an important ROS. NO has proven beyond doubt, to be a significant biological entity, because it had never been shown that a gas molecule could function as a signalling molecule in the body (Stratta et al. 1991). Arg is the main source for the generation of NO via NO synthase (NOS; Moncada 1997). Approximately 1 % of the daily Arg intake is metabolized through this pathway (Castillo et al. 1995). The three NOS isoforms have been found to be expressed in the kidney (Moncada 1997). In the kidney eNOS is important in the maintenance of glomerular filtration rate, regional vascular tone, and renal blood flow (Raij and Baylis 1995). nNOS is expressed primarily in the macula densa and participates in the control of glomerular hemodynamics via tubulo-glomerular feedback and renin release (Raij and Baylis 1995). iNOS is expressed in the kidney, under pathological conditions, in the glomerular mesangium, infiltrating macrophages and tubules (Raij and Baylis 1995). Expression of iNOS has also been reported in specific tubular segments but its physiological significance remains unclear (Kone 1997). At physiological concentrations, NO regulates glomerular and medullary hemodynamics, renin release, tubuloglomerular feedback response and extracellular fluid volume (Baylis 2008). However, excessive production of NO can lead to increased formation of peroxynitrite anion ($ONOO^-$), nitration of protein tyrosine, and production of hydroxyl radical, and may contribute to the pathogenesis of several common renal diseases, such as immune-mediated glomerulonephritis and postischemic renal failure (Baylis 2008). In these cases, excess dietary Arg may be detrimental. For example, Peters et al. (1999) reported that oral Arg administration (1 % Arg in drinking water) for 1-week increased mesangial cell injury and subsequent tissue fibrosis in a rat model of glomerulonephritis. On the other hand, decreased NO synthesis by constitutive NOS may contribute to the pathogenesis of volume-dependent hypertension and of glomerular injury resulting from elevated intraglomerular pressure (Baylis 2008). Thus, most studies have shown a beneficial effect of supplemental Arg in preventing or slowing the progression of a number of experimental renal diseases characterized by systemic hypertension and increased intraglomerular pressure (e.g. Bellinghieri et al. 2006; Ito et al. 2005).

The inadequate NO production within the kidneys plays a key role in causing/or mediating the complex haemodynamic disorders which are associated with the progression of CKD. In CKD, there is extensive reduction of the renal mass, which is associated with the development of hypertension and it exhibits a decrease in both the glumerular

filtration rate (GFR) and the renal blood flow (Aiello et al. 1997). This duality of NO's beneficial and detrimental effects has created extraordinary interest in this molecule and the need for a detailed understanding of the NO biosynthesis. An impaired NO synthetic pathway could play a key role in modulating the complex renal haemodynamic disorders which are associated with the progression of renal diseases (Matsumoto et al. 1999). There is evidence which has indicated that a renal NO deficiency occurs in the patients with CKD. Thus, the daily excretion of urinary nitrate/nitrate was significantly lower in the patients with moderate and severe renal failure, as compared to that in those with mild renal failure and in the controls; the lowest values were found in the severe renal failure group (William 1998).

In animal studies, experimentally induced chronic NOS inhibition causes systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury and proteinuria (Baylis 2008; Zatz and Baylis 1998). There is also considerable clinical and experimental evidence that NO deficiency develops as a result of CKD and that NO deficiency is linked to progression of renal dysfunction (Baylis 2008; Zatz and Baylis 1998; Martens and Edwards 2011; Zhou et al. 2007). NO acts locally, therefore the location of the NO deficiency dictates the pathology. Widespread vascular endothelial NO deficiency (=endothelial dysfunction) occurs throughout the course of CKD and contributes to the increased risk of adverse cardiovascular events (Martens and Edwards 2011). In addition, animal studies implicate intrarenal NO deficiency in the pathogenesis of CKD progression (Baylis 2008). In support of a key role for NO deficiency in the pathogenesis of renal disease, NO repletion by administration of nitrite (NO_2) or nitrate (NO_3) reduced blood pressure and greatly retarded progression of CKD in two rat models of hypertension and kidney damage (Tsuchiya et al. 2010; Carlström et al. 2011). Various approaches are been proposed to increase NO plasma concentrations, as Arg administration (Kharitonov et al. 1995), and it has been proposed that the high dietary content of NO_3 in vegetables and fruit may contribute to the cardiovascular protection afforded by these foods (Gilchrist et al. 2011).

Defects in the Arg:NO pathway have been proposed to play an important role in the pathogenesis of acute kidney injury (AKI; Goligorsky et al. 1999; Schramm et al. 1996). Several studies have suggested that NO bioactivity is reduced in models of post ischemic AKI as assessed by a blunted response to endothelium-dependent vasodilators such as acetylcholine and bradykinin (Conger et al. 1995, 1988; Sternbergh et al. 1993) and increased constrictor responses to renal nerve stimulation (Conger et al. 1988) and Ang II. Interestingly, these reductions in NO bioactivity are accompanied by increases in iNOS expression and activity (Schneider et al. 2003) and in the case of eNOS there was either no change in its expression (Conger et al. 1995) or a transitory increase followed by a reduced expression (Schneider et al. 2003). In models of ischemic AKI these changes in iNOS expression are accompanied by increased production of superoxide anion and $ONOO^-$ leading to nitrosative stress. NO rapidly reacts with O_2^- resulting in the generation of the highly reactive $ONOO^-$ and reduced NO bioactivity. $ONOO^-$ itself can produce lipid peroxidation and DNA damage and in addition can produce NOS uncoupling by affecting the NOS dimeric structure. Increased O_2^- production has been found in several models of ischemic AKI. Inhibition of iNOS has been shown to be beneficial in models of ischemia reperfusion, which suggests that increased iNOS expression and activity may have roles in the pathogenesis of ischemic AKI (Chatterjee et al. 2002). In contrast, NOS inhibition during endotoxemia results in glomerular thrombosis suggesting that increased iNOS activity may also have a protective role under specific conditions (Jaimes et al. 2001; Shultz and Raij 1992).

It has also been suggested that in renal failure, an NO deficiency could result from a reduced arginine availability, since the kidney is a major site of an endogenous arginine synthesis (Mitch and Chesney 1983; Chan et al. 1974). However, a recent study which was done by Boudy and coworkers showed that the renal arginine synthesis and the arginine plasma levels were not diminished in the remnant kidneys, despite a significant reduction in the GFR (Boudy et al. 1993). Based on this, it is unlikely that the substrate supply of arginine would be rate limiting for the NOS, even with the severe reduction of the functional renal mass, unless there are extraordinary arginine demands (i.e., sepsis or vigorous cytokine-induced NOS activation, as in dialysis). Thus experimental evidence supports both a beneficial as well as a deleterious role for Arg in the pathogenesis of specific models of renal disease. L-Arg seems to promote renal injury in some models of glomerulonephritis including ATS glomerulonephrits and lupus nephritis. In contrast, Arg seems to be beneficial in experimental models of acute renal failure as well as in models of chronic renal disease such as renal ablation and ureteral obstruction. Arg also ameliorates renal injury in animal models of preeclampsia as well as in some models of hypertensive renal injury. Unfortunately only a few clinical trials have been carried out with disappointing results. Additional experimental and clinical studies are needed to better understand the role of Arg the pathogenesis and treatment of renal disease (Cherla and Jaimes 2004). Research into the regulation of the NO synthases activity and the development of NOS inhibitors for blocking the specific isoforms of NO, as well as the stable compounds that release it, would be a major challenge for the therapeutic development (Víteček et al. 2012).

The comparison of the two proposed vital parameters, i.e., serum NO and serum creatinine, may find its use as an indicator of the prognostic follow up in the chronic renal failure patients who are on dialysis. A humble beginning has been made, which if followed, would prove useful for the CKD patients who are on dialysis. Further avenues for generating novel ideas and designing studies to address the queries which are related to its real significance, have to be carried out.

The central role for NO in endothelium-dependent relaxation was first described in 1987 (Ignarro et al. 1987; Jover et al. 1993). In subsequent years, several authors have shown a number of biological effects of NO beyond vasodilation, including the regulation of smooth muscle cell (VSMC) proliferation and migration, inflammation and platelet function (Kopincova et al. 2012).

In VSMC, NO induces an increase in cGMP levels which activate the isoform c-GMP-dependent protein kinase I (cGKIα). VSMC relaxation is the resultant of different pathways regulated by cGKIα. cGKIα, in fact, inhibits Rho kinase which regulates myosin light chains phosphorylation; inhibits the stretch induced activation of K^+ channels (TREK-1) or the Ca^{2+}-activated K^+ channels or inhibits phospholipase C-mediates increases in protein kinase to prevent the increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). cGKIα activates cAMP phosphodiesterase and reduces the levels of cAMP. It also inhibits mitogen-activated protein kinase (MAPK) phosphatase-1 and prevents phosphorylation of extracellular signal regulated kinase (Erk). Finally, cGKIα modulates nuclear factor κB (NF-κB) to activate the synthesis of cytokines such as TNFα, which in turn inhibits the expression of eNOS (Fukunaga et al. 2001; Surks et al. 1999; Fig. 2).

NO maintains vascular homeostasis also by tightly regulating the $[Ca^{2+}]_i$. In fact, on endothelial and smooth muscle cell, NO regulates the levels of Ca^{2+} at several step: (i) activates the plasma membrane Ca^{2+}-ATPase and the Na^+/Ca^{2+} exchanger; (ii) activates SERCA and ryanodine receptors as well as IP_3-coupled Ca^{2+}-refilling; (iii) activates Ca^{2+}-activated K^+ channels and the TREK-1. NO can also signal via S-nitrosation, oxidation or ADP rybosilation of proteins. NO-induced ADP-rybosilation, in fact, prevents adhesion of neutrophils to the endothelium and its aggregation (Forslund et al. 2000) and decreases ADP rybosilation of G proteins, due to reduction in NO availability, accounts for the increased vasoconstriction during hypertension (Kanagy et al. 1995). The reduction of NO levels may be linked to a decrease in eNOS levels, or to a reduction in the levels of substrates and cofactors for eNOS (such as L-arg and tetrahydrobiopterin). Diminished levels of NO may contribute to pathological states such as systemic hypertension, pulmonary arterial hypertension, atherosclerosis

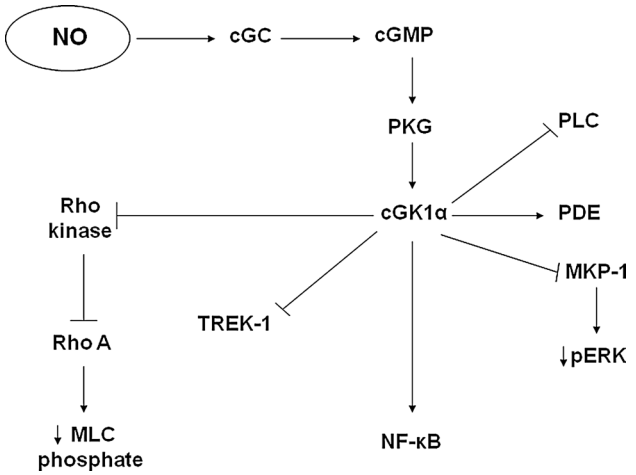

Fig. 2 Scheme viewing the cGMP-dependent effects of NO. *NO* Nitric oxide, *sGC* soluble guanylyl cyclase, *cGKIα* c-GMP-dependent protein kinase I, *PKG* protein kinase G, *MLC* myosin light chains, *TREK-1* stretch induced activated K^+ channels, *NF-κB* nuclear factor κB, *PLC* phospholipase C, *PDE* cAMP phosphodiesterase, *MKP-1* mitogen-activated protein kinase (MAPK) phosphatase-1, *pErk* phosphorylate extracellular signal regulated kinase *rightarrow* activate, *perpendicular* inactivate

and vasospasm. Most commonly, NO bioavailability is secondary to interaction with ROS such as superoxide. Superoxide reacts rapidly with NO, resulting in the formation of $ONOO^-$ and loss of NO bioavailability (Lakshmi et al. 2009). Oxidative stress contributes markedly to endothelial dysfunction, the leading cause of several cardiovascular diseases, such as hypertension, atherosclerosis and heart failure (Popolo et al. 2013). Oxidative stress, in fact, promotes entry of Ca^{2+} into the VSMC and myocytes and thus may stimulate neointimal hyperplasia. Such ROS may be produced in the vasculature by NADPH oxidase, xanthine oxidase, or NOS enzymes when they become uncoupled secondary to decreased substrate availability (Ataya et al. 2011).

Several lines of evidence demonstrate that Arg administration is effective in reversing endothelial dysfunction under these conditions (Wu et al. 2009). It has been demonstrated that dietary Arg supplementation reversed the defective endothelium-dependent relaxation (Pieper et al. 1997); endothelium-dependent relaxation in Zucker diabetic fatty rats (Wu et al. 2007c); improves endothelium-dependent relaxation in hypercholesterolemic humans (Clarkson et al. 1996). The mechanisms by which Arg administration may prevent cardiovascular dysfunction include: i) restoring endothelial NO synthesis and decreasing superoxide production; ii) reducing vascular oxidative damage; and iii) inhibiting platelet adherence and aggregation, leukocyte adherence to the endothelium, and the proliferation of VSMC (Wu and Meininger 2000, 2009).

Arginine decarboxylase pathway

This pathway of Arg metabolism involves the generation of agmatine via the enzyme ADC (Li et al. 1994). ADC, which produces CO2 and agmatine [4-(aminobutyl) guanidine] from Arg, had long been known to be present in plants and bacteria, but was thought to be absent from mammalian cells (Tabor and Tabor 1984). However, ADC activity and agmatine synthesis have now been identifed in brain, liver, kidney, adrenal gland, macrophages and small intestine (Li et al. 1994; Morrissey et al. 1995; Lortie et al. 1996; Sastre et al. 1998). This enzyme is localized within the mitochondrial fraction of cell homogenates (Morrissey et al. 1995; Li et al. 1995). ADC activity is absent from pig enterocytes (Wu et al. 1996), suggesting either that there are species or developmental differences in intestinal expression of this enzyme or that the identity of the intestinal cell types that express arginine decarboxylase remains to be determined. Although the physiological roles of agmatine are still under investigation (Lortie et al. 1996; Schwartz et al. 1997; Morrissey and Klahr 1997), three lines of investigation have suggested possible functions of this Arg metabolite. Agmatine binds to α_2-adrenergic and imidazoline receptors (Li et al. 1994), suggesting a role in cell signalling. Agmatine can also inhibit ODC activity by inducing synthesis of antizyme, thus suppressing cell proliferation by reducing cellular polyamine concentrations (Satriano et al. 1998). Finally, agmatine is a weak competitive inhibitor of the NOS isoenzymes (Li et al. 1994), suggesting that it may be an endogenous regulator of NO synthesis if local agmatine concentrations are sufficiently high. It should be emphasized that concentrations of agmatine sufficient to inhibit synthesis of NO or polyamines may be difficult to achieve in vivo because agmatine is also a feedback inhibitor of ADC (Li et al. 1994). So far as we are aware, it has not been determined whether endogenously produced agmatine has a signifcant impact on NO or polyamine synthesis from Arg.

Agmatine can activate α-1 adrenoreceptors and imidazolguanidine receptors (Li et al. 1994) and when infused into the renal interstitium increases glomerular filtration and tubular reabsorption (Schwartz et al. 1997). Moreover agmatine administration reduced collagen accumulation in kidneys of diabetic mice (Marx et al. 1995) as observed with low doses of Arg administration (Lubec et al. 1997b; Radner et al. 1994). ADC activity is high in the normal kidney (Morrissey et al. 1995) and therefore it is possible that agmatine may be mediating some of the biological effects of Arg supplementation in renal disease.

Agmatine has significant potential in cardiovascular biology even if the literature available to date is not sufficient to associate a therapeutic importance with it. It's well known that agmatine modulates functions of heart, brain and vasculature by acting on calcium homeostasis (Raghavan and Dikshit 2004). Agmatine, in fact, inhibits increase in $[Ca^{2+}]_i$ in myocytes by blocking L-type voltage dependent Ca^{2+} channels and reduces the influx of calcium and efflux of potassium thus reducing the rate of depolarization and the amplitude of action potential in the heart mediated by α2 and imidazoline receptors. It also exerted protective effects against ischemia–reperfusion injury in isolated rat heart and recovery was attributed to its vasodilatory effects (Greenberg et al. 1999, 2001). Agmatine exerts specific effects on the regulation of cell proliferation and hypertrophy by interfering with polyamine biosynthesis by ODC. ODC is a highly regulated enzyme system, both from the standpoint of transcriptional regulation and from the standpoint of termination of its activity. In addition, polyamine synthesis can be regulated, in part, by expression of transporters for the polyamine precursor, putrescine. Normally, ODC is a very short lived enzyme primarily owing to the fact that an antizyme is generated by translational regulation which leads to the termination of ODC activity by preventing its dimerization making the enzyme susceptible to protease degradation. It appears that the protein, antizyme, also can act to terminate activity of the putrescine transporter. It has been demonstrated that agmatine serves the dual regulatory functions of suppressing polyamine biosynthesis by inhibition of ODC and by suppression of the putrescine transporter via an antizyme mechanism (Satriano et al. 1998). Arg induces a translational frameshift of antizyme mRNA to produce a full length antizyme protein. Agmatine, via this mechanism, depletes intracellular polyamine levels to suppress cell proliferation.

Another interesting feature is the ability of agmatine to induce eNOS activation and to reduce iNOS synthesis. Agmatine, in fact, is metabolized to agmatine aldheide by diamine oxidase. It has been demonstrated that addition of this enzyme to cells in culture enhances the effects of agmatine as an inhibitor of iNOS, while inhibitors of aldheide dehydrogenase further decrease NO generation (Blantz et al. 2000).

Arg-derived guanidino compounds

Guanidino compounds, intermediates of Arg metabolism, are altered in many pathological conditions especially those involving the urea cycle. Most serum guanidino compound concentrations are increased in hemodialysis patients (De Deyn et al. 1986, 1987) and in nondialyzed patients with chronic renal failure (Marescau et al. 1997). Guanidines are a large group of structural metabolites of arginine. Among them are well-known uremic retention solutes such as creatinine and methylguanidine. Several of the guanidino

compounds modify key biologic functions. Creatinine has been held responsible for chloride channel blocking (De Deyn and MacDonald 1990; D'Hooge et al. 1992), reduces the contractility of cultured myocardial cells (Weisensee et al. 1993), although only at concentrations exceeding five times those encountered in CKD, and is a precursor of methylguanidine (Yokozawa et al. 1993). Guanidinosuccinic acid and guanidinopropionic acid inhibit neutrophil superoxide production (Hiravama et al. 1997). Guanidinosuccinic acid, g-guanidinobutyric acid, methylguanidine, homoarginine, and creatine induce seizures after systemic and/or cerebroventricular administration in animals (De Deyn and MacDonald 1990; D'Hooge et al. 1992). A mixture of guanidino compounds suppresses the natural killer cell response to interleukin-2 (Asaka et al. 1988).While urea and creatinine have a rather limited biologic toxicity, several guanidine compounds, on the contrary, are related to neurotoxicity (D'Hooge et al. 1999), cardiovascular (Macallister et al. 1994), and hematologic complications (Horowitz et al. 1967; Giovannetti et al. 1968) and alterations of leukocyte function (Glorieux et al. 2004). Guanidino succinic acid has been associated to uremic bleeding diathesis (Horowitz et al. 1967), and contributes to the toxic phenomena affecting the function of the central nervous system (De Deyn et al. 2003) and, together with G, been held responsible for hemolysis (Giovannetti et al. 1968, 1969). Methylguanidine and guanidine have been suggested to relate to uremic polyneuropathy (Giovannetti et al. 1969), and are considered to be epileptogenic (Matsumoto and Mori 1976). These guanidine compounds also affect immune response, reducing the macrophage function during inflammation (Marzocco et al. 2004a, b, c; Marzocco et al. 2013a, b; Autore et al. 1999) and astrocyte functions in CKD (Marzocco et al. 2010). Moreover also Arg is able to influence immune mediators as interleukin-1α (Hayde et al. 1994) and to stimulate the immune system at the lymphocyte level (Lubec et al. 1996). The guanidino group seems also to be important to block reactive carbonils because both Arg, creatinine and aminoguanidine reduce N-carboxymethyllysine concentration and renal collagen accumulation (Lubec et al. 1994).

Arg, which is also a guanidino compound, markedly enhances the production of NO. Some of the other guanidines as arginine-analogues are strong competitive inhibitors of NOS (Vanholder and De Smet 1999).

There are several potential mechanisms by which NO deficiency could occur in CKD as the presence of endogenous NOS inhibitors which compete with the NOS substrate arginine. Asymmetric dimethylarginine (ADMA) is an endogenous NOS inhibitor recognized as a major cardiovascular risk factor (Böger et al. 2009). Elevations in plasma ADMA are seen in many pathologies including renal disease and individuals in the upper range have the worst outcome (Böger et al. 2009). As a note of caution, while a high plasma ADMA probably represents an elevation in intracellular ADMA, the relationship between circulating and tissue levels of ADMA is not straightforward and will likely vary for different tissues (Böger et al. 2009; Teerlink et al. 2009).

ADMA is an amino acid (MW: 202 Daltons) normally synthesized intracellularly and circulating in the plasma. It is relatively stable and can diffuse between cells (easy entry-exit) and is excreted in urine and can be found in tissues and cells and inhibits NOS (Kielstein et al. 2009; Anderstam et al. 1997). ADMA is produced by methylation of arginine residues in intracellular proteins via protein arginine methyltransferases (PRMT). In mammalian cells, PRMT have been classified into type I (PRMT1–4, 6, 8 and 10–11) and type II (PRMT5, 7 and 9), depending on their specific catalytic activity. Both types of PRMT catalyze the formation of mono-methylarginine (MMA) from Arg. Type I catalyzes asymmetrical dimethylation and monomethylation of arginine residues and yields ADMA and NG-monomethyl-L-arg (L-NMMA), whereas type II catalyzes symmetrical dimethylation and monomethylation of arginine residues and produces symmetric dimethylarginine (SDMA) and L-NMMA but not ADMA (Rawal et al. 1995). An health human being generates approxi-mately 300 μmol of ADMA per day. Because ADMA was found to be increased in endstage renal disease patients, renal excretion of ADMA was considered to be the main route of elimination (Vallance et al. 1992). However, an early study in rabbits showed renal excretion not to be the major route for ADMA elimination, suggesting the presence of a catabolic pathway (Schepers et al. 2014). More than 90 % of ADMA is metabolized by other two catabolic pathways. The first pathway is specific for ADMA metabolized into citrulline and dimethylamine by the action of dimethylarginine dimethy-laminohydrolase (DDAH; Leiper et al. 1999), and accounts for >80 % of their in vivo metabolism. Two isoforms of DDAH (DDAH-I and DDAH-II) have been identified. DDAH-I is predominantly found in tissues expressing neuronal NOS, liver, kidney and lung, whereas DDAH-II is located in vasculature tissues expressing endothelial NOS, immune tissues expressing inducible NOS, heart, placenta and kidney (Beltowski and Kedra 2006; Onozato et al. 2008; Ogawa et al. 1989; Tran et al. 2000; Wang et al. 2007). The other pathway is that minor ADMA is catalyzed by alanine-glycoxylate aminotransferase (AGXT2; Rodionov et al. 2010; Martens-Lobenhoffer et al. 2011). Recently, a third route to decrease ADMA levels was discovered. ADMA can be transaminated by the enzyme alanine glyoxylate aminotransferase 2 to DMGV [α-keto-δ-(N(G),N(G)-dimethylguanidino) valeric acid], a mitochondrial aminotransferase expressed primarily in the kidney (Rodionov et al. 2010). Now that we are able to

determine DMGV in plasma, urine, and tissues (Martens-Lobenhoffer et al. 2011), the in vivo importance of this pathway for regulation of systemic ADMA levels can be shown (Kittel et al. 2013). In contrast to DDAHs, AGXT 2 can metabolize not only ADMA but also SDMA, which is recently receiving great interest as marker of renal function and cardiovascular risk (Betz et al. 2013). With the kidney in the center of ADMA elimination via excretion as well as metabolization by DDAH and AGXT 2, one would assume that ADMA correlates superbly with renal function. Studies do not uniformly support this assumption.

To test the involvement of ADMA in CKD progression, in uninephrectomized mice, the effects of chronic ADMA administration on renal structure were compared with NG-nitro-L-arg methyl ester (L-NAME) treatment, a widely used exogenous inhibitor of NOS that induces CKD. The obtained results demonstrated that ADMA elevated concentrations were associated with the development of renal fibrosis through a mechanism involving collagen and TGF-β1 synthesis (Mihout et al. 2011). On the contrary it was been reported that, in diabetic state, Arg reduces kidney lipid peroxidation, glycoxidation and collagen accumulation (Lubec et al. 1995, 1997a).

For a long time the ability of ADMA to reduce NO formation and to induce vascular dysfunction was attributed solely to the competitive inhibition of eNOS binding to the endogenous high-affinity substrate Arg. However, short-term studies using Arg to reverse the competitive inhibition exerted by ADMA on NOS generated conflicting results. This raises the possibility that ADMA may impair NO production by mechanisms independent of substrate inhibition. A potential mechanism, described by Kajimoto et al. (2012) targets inhibition of eNOS Ser 1,177 phosphorylation, potentially preventing recruitment of eNOS to the plasma membrane and activation. Both competetive inhibition with Arg and decreased eNOS phosphorylation can lead to lower NO production. In turn, NO deficiency may cause endothelial dysfunction, increased inflammation, and reduced angiogenesis, all potential causes of end-stage renal disease (ESRD) and cardiovascular comorbidities such as hypertension, atherosclerosis, and diabetes. Interestingly, Kajimoto et al. (2012) showed that CKD occurs following nephrectomy even in mice with low ADMA levels, unlikely to competitively inhibit eNOS binding to Arg (Kajimoto et al. 2012). This suggests that the renal effects of ADMA in the context of reduced renal mass could be mediated via eNOS mechanisms different from substrate inhibition or via mechanisms independent of eNOS altogether. ADMA may be associated with intrarenal lesions and can be used as a useful surrogate marker for the effects of treatment in the early stages of CKD (Fujii et al. 2014).

AKI is a common clinical disease with variable outcome, ranging from complete restitution to high mortality and ischemia/reperfusion (IR) injury is a major cause of AKI (Schrier et al. 2004). It has been reported that Arg supplementation in different models of AKI results in an amelioration of renal function (Schneider et al. 2003; Schramm 2002). Betz et al. (2013) in a model of ischemic AKI in rats, showed a significant reduction in Arg tissue levels, after 24 h of IR injury, and an increased Arg serum levels. Because the observed ADMA increase could be compensated by elevated Arg levels the authors suppose that ADMA may not have a pathogenic effect on NO during AKI. On the contrary the fourfold increase in SDMA, that effectively competes with Arg for cellular transport mediated by CAT system, could determine a lack in intracellular Arg supply thus contributing to NO-mediated endothelial dysfunction in AKI injury (Goligorsky et al. 2002) During AKI serum ADMA levels significantly increased (Betz et al. 2013), as in CKD (Matsuguma et al. 2006).

As expression and/or activity of PRMT and DDAH are regulated by ROS (Kaida et al. 2012) and oxidative stress has a role in IR injury, (Lin et al. 2002; Ishibashi et al. 2012) it is conceivable that ADMA generation in the kidney is increased under oxidative stress conditions of IR injury and that beneficial effects of NO on renal microvasculature are compromised, which could lead to the development and progression of AKI. To address the issues (Nakayama et al. 2014). Asymmetric dimethylarginine accumulates in the kidney during ischemia/reperfusion injury recently examined the kinetics of ADMA, PRMT-1 and DDAH-1 levels in the kidney of IR-injured mice. Their results indicated that IR-elicited oxidative stress might contribute to the development and progression of AKI by promoting ADMA elevation in the kidney, probably via oxidative stress–induced proteosomal degradation of DDAH-1. Thus DDAH-1 enhancement of its activity may be useful for the treatment of renal IR injury (Nakayama et al. 2014).

Given that ADMA has also been associated with endothelial dysfunction in animal models and patients with chronic kidney disease (Okubo et al. 2005), it is conceivable that the development of proteinuria may have a role in the accumulation of ADMA via the overexpression of PRMT that facilitates the synthesis of ADMA (Kaida et al. 2012). In line with this, positive correlations have been observed between ADMA and proteinuria (Caglar et al. 2006) and, in an animal model, some researchers have observed a decrease in the activity of the DDAH enzyme (Matsumoto et al. 2007), which is abundantly expressed in the renal tubular cells. There is a huge variety from good to absent or poor relationship between ADMA and renal function (Eloot et al. 2011; Kielstein et al. 2006). This discrepancy between studies can be explained by the fact that depending on the reason for renal impairment, the decrease in renal excretory function is or is not paralleled by a reduction of DDAH and AGXT 2 activity in the

kidney. Moreover is important to consider the recognition of SDMA as a pathophysiologically important substance in renal disease.

In recent years, it has been demonstrated that Arg supplementation restores NO production, improves renal function and reduces inflammation in kidney transplant patients (Vos et al. 2001). A key objective in renal patients is to decrease ADMA levels (Baylis 2006). For this reason, arginine supplementation has been used, reversing ADMA-induced inhibition of NO synthesis. According to several studies, arginine also improves endothelial dysfunction in patients on haemodialysis by regulating ADMA levels (El-Mesallamy et al. 2008); that is, the inhibitory action of ADMA on NOS is reverted by Arg loading. Arg supplementation may increase the production of guanidinoacetate and creatine, through the conversion of *S*-adenosylmethionine to *S*-adenosylhomocysteine and Hcys, which may themselves have adverse effects on endothelial function (Bodamer et al. 2005). In kidney transplant recipients, however, in whom there is already endothelial dysfunction for various reasons, supplementation with arginine contributes to improving renal function, normalizing the Arg/ADMA ratio, increasing NO production, and eliminating nitrites and nitrates, which improves endothelial function (Schramm et al. 2002). It has even been demonstrated that the intake of citrulline may have similar effects since it is converted into Arg, with no adverse effects and with a good tolerance (Schwedhelm et al. 2008).

On the other hand, in patients with high plasma Arg and citrulline levels, the efficacy of supplementation of this amino acid has been questioned due to its potential adverse effects. It should also be taken into account that Arg is an acidifying agent that may alter the acid–base equilibrium in patients with reduced GFRs; accordingly, in such cases, it should be administered in the form of arginine salts other than chlorates. This may explain why data on the effects of the arginine supplementation are inconsistent, some studies having found no significant beneficial effects on vascular function and others finding no differences in endothelial NO synthesis with respect to placebo placebo (Yilmaz et al. 2007).

Animal models of DDHA-1 overexpression and knockdown have provided evidence for the role of this enzyme in regulating vascular tone. Both deleting the DDHA-1 gene in mice and inhibiting its activity through DDAH-specific inhibitors caused endothelial dysfunction, increased systemic vascular resistance and elevated systemic and pulmonary blood pressure have been observed (Anderssohn et al. 2010). In humans, elevated plasma concentrations of ADMA have been reported in a variety of cardiovascular diseases as well as in patient population with almost any traditional and emerging cardiovascular risk factor (Sibal et al. 2010). An interesting association between ADMA and ROS, other important markers of cardiovascular diseases, has been highlighted recently (Wilcox 2012). In fact, it has been proposed that the activity of DDAH is impaired by oxidative stress, permitting ADMA to accumulate and to block NO synthesis. Böger et al. demonstrated that ROS could enhance the generation of S-adenosylmethionine that increased the methylation of arginine epitopes by PRMT (Böger and Ron 2005). A wide range of pathological stimuli induces endothelial oxidative stress such as oxidized LDL cholesterol, inflammatory cytokines, hyperhomocystinemia, hyperglycemia, and infectious agents. Each of these insults attenuates DDAH activity and is associated with increased plasma ADMA levels (Ito et al. 1999; Stühlinger et al. 2001).

It's important to note that both ADMA and ROS have considerable potential to mediate hypertension and its adverse effects on cardiovascular and CKD. They share a similar pathophysiological end point where both can reduce bioactive NO albeit via different mechanisms. Thus, ADMA reduces NO primarily by inhibition of NOS, whereas ROS inhibit NO by its bioinactivation to $ONOO^-$ and by oxidation and inactivation of the NOS cofactor tetrahydrobiopterin, which uncouples the enzyme and directs it to generate ROS rather than NO. So, ADMA and ROS represent a single, self-reinforcing system whereby ROS engage ADMA and vice versa (Wilcox 2012; Fig. 3).

Supplementation with ARG has been shown to restore vascular function and to improve the clinical sympoms of various diseases associated with vascular dysfunction. However, it's important to note that ARG supplementation improved endothelium dependent vasodilation only in patients who had elevated ADMA concentration, whereas L-arg did not affect endothelium dependent vasodilation in healthy human who had low ADMA concentrations.

There have been several explanations for this phenomenon, although none of them can explain the so-called "arginine paradox" fully: (1) ARG -induced insulin, which has vasodilatory actions. (2) Neither extracellular nor intracellular concentration determines the NOS activity but rather the L-arg amount transported across the plasma membrane may do so. (3) Endogenous NOS inhibitors reduce the enzyme sensitivity to L-arg. These inhibitors include, NG, NG-dimethyl-L-arg, L-citrulline, argininosuccinic acid and agmatine. (4) Intracellular L-citrulline, an NOS product, is a potent inhibitor of NOS so that the cells may need extra L-arg to compete with L-citrulline inhibition.

Conclusions

There are compelling evidences that Arg regulates interorgan metabolism of energy substrates and the function of multiple organs. Arg is substrate for the synthesis of NO, polyamines and agmatine that have pivotal role in

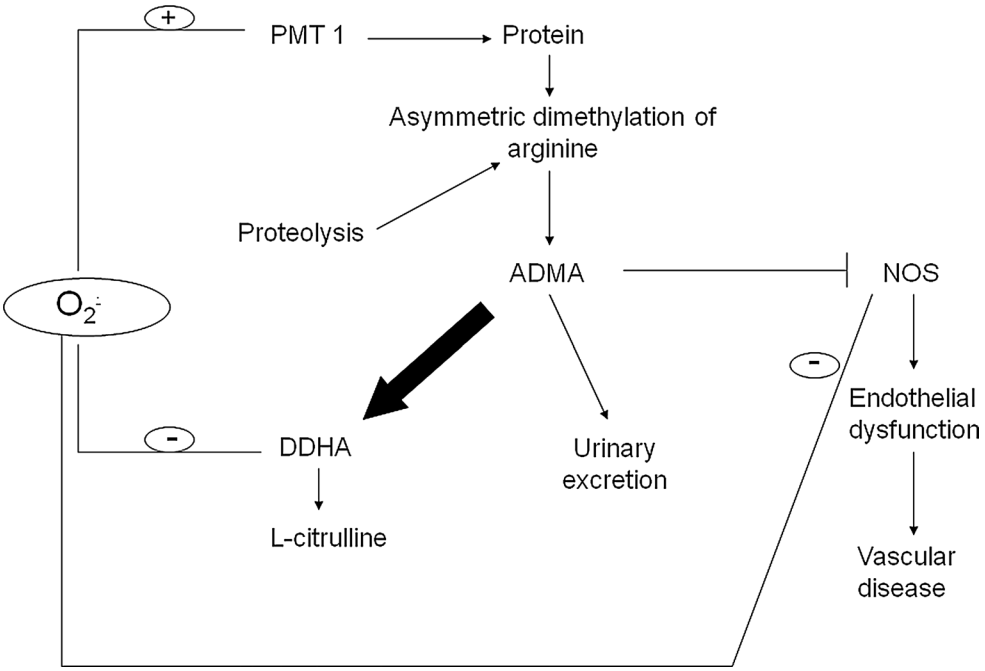

Fig. 3 Overview of pathways of synthesis and metabolism of ADMA

regulating kidney and cardiovascular function, and dysfunction. Thus it is useful to determine the levels of arg and its derivatives as a part of the analysis of kidney disease and the cardiovascular risk. Here we reported the extensive array of data describing the role of Arg metabolites in kidney and cardiovascular diseases, their possible interaction and informations to improve the understanding the arg role as profilactic/therapeutic agent.

Conflict of interest The authors declare that they have no conflict of interest.

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