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EDITORIAL

Homoarginine, arginine, and relatives: analysis, metabolism, transport, physiology, and pathology

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Abstract The year 2008 witnessed the first report on the increase in the concentration of L-homoarginine (hArg) in the maternal plasma during human pregnancy. This observation, along with a well-known function of hArg, the methylene homologue of L-arginine (Arg), as a substrate for nitric oxide (NO) synthase, was the ignition for the start of intense research on the physiology and pathology of hArg. The circulating concentration of hArg was found to be lower in patients suffering from various diseases, and hArg emerged within only very few years as a novel cardiovascular risk factor. The compendium in hand comprises original and review articles covering several aspects of hArg, Arg and its symmetrically and asymmetrically guanidine (N^G)-dimethylated derivatives SDMA and ADMA, respectively. In contrast to ADMA and SDMA, low hArg concentrations in plasma or serum and in urine are associated with high risks for morbidity and mortality, notably in the renal and cardiovascular systems. Acutely and chronically administered Arg as a nutritional supplement or in the form of dietary proteins is safe in animals and humans and leads to concomitant formation of hArg and ADMA, albeit in a different hArg/ADMA ratio. Despite the close but opposite associations of hArg and ADMA with disease in adults, children and adolescents, the underlying biochemical processes are largely unknown, presumably not restricted to NO, and warrant deeper investigation. As the common substrate for hArg and ADMA, Arg may play a key role in the biosynthesis and homeostasis of hArg and ADMA, two putative antagonists. In animal models of stroke and obesity, hArg has beneficial effects. The potential utility of hArg as a therapeutic drug or nutritional supplement in humans and animals remains to be elaborated.

Keywords Adolescence · Adulthood · AGAT · Biomarker · Childhood · Disease · Health

Abbreviations

ADMA	Asymmetric dimethylarginine
AGAT	Arginineglycine amidinotransferase
GAMT	Guanidinoacetate methyltransferase
GC–MS	Gas chromatography–mass spectrometry
GC–MS/MS	Gas chromatography–tandem mass spectrometry
GHD	Growth hormone deficiency
hArg	L-Homoarginine
LC–MS	Liquid chromatography–mass spectrometry
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
MMA	Monomethyl arginine
NO	Nitric oxide
NOS	Nitric oxide synthase
OPA	*o*-Phthaldialdehyde
SDMA	Symmetric dimethylarginine

Introduction

In organic chemistry, the prefix "homo" (from Ancient Greek "ομος", the same) is used in the nomenclature to characterize a pair of substances which have chemical structures that differ by one methylene (CH_2) group. This nomenclature is widely applied to amino acids. The most prominent pair is

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L-cysteine and L-homocysteine. Other less widely known pairs of amino acids are L-citrulline and L-homocitrulline, and the tripeptides glutathione and homoglutathione due to its central L-homocysteine moiety. "Homo" amino acids should not be confused with "iso" amino acids, such as L-leucine and L-isoleucine, which are isomeric and have the same molecular mass. Another "homo" amino acid pair is L-arginine (Arg) and L-homoarginine (hArg) (Fig. 1). In chemistry, hArg has been known for at least a century. Yet, the scientific interest in this amino acid has been marginal until recently. hArg has been even believed for at least 50 years to be an exogenous compound with no significance at all for humans or animals. The primary interests in hArg were, therefore, its use as an internal standard for the HPLC analysis of other Arg metabolites, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), and in association with the guanidination reaction for determining reactive lysine, bioavailable lysine, and gut endogenous lysine (Rutherfurd 2015; Yin et al. 2015). Yet, things changed only very recently, when hArg was measured in human blood and its concentration was found to correlate with functional parameters, suggesting potential physiological functions in humans (Valtonen et al. 2008). Of course, by analogy, hArg has also been tested as a potential substrate for nitric oxide synthase (NOS) (Hecker et al. 1991; Moali et al. 1998), which catalyzes the conversion of Arg to nitric oxide (NO) and L-citrulline. NO is one of the smallest signaling molecules and possesses several biological functions in plants and animals, including humans. The potential utility of hArg as a substrate for NOS has early led to the assumption that, if hArg would have a biological role, that would be due to its function as an NO precursor. Likely, this assumption has initiated many experimental and clinical studies, which eventually revealed hArg, specifically at concentrations lower than average concentrations measured in healthy humans, as a novel cardiovascular risk factor (März et al. 2010; Pilz et al. 2011a, b; Pilz et al. 2014; Tomaschitz et al. 2015). This is in contrast to the use of higher concentrations of ADMA, the asymmetrically guanidine (N^G)-dimethylated Arg derivative, as a biomarker for risk of cardiovascular

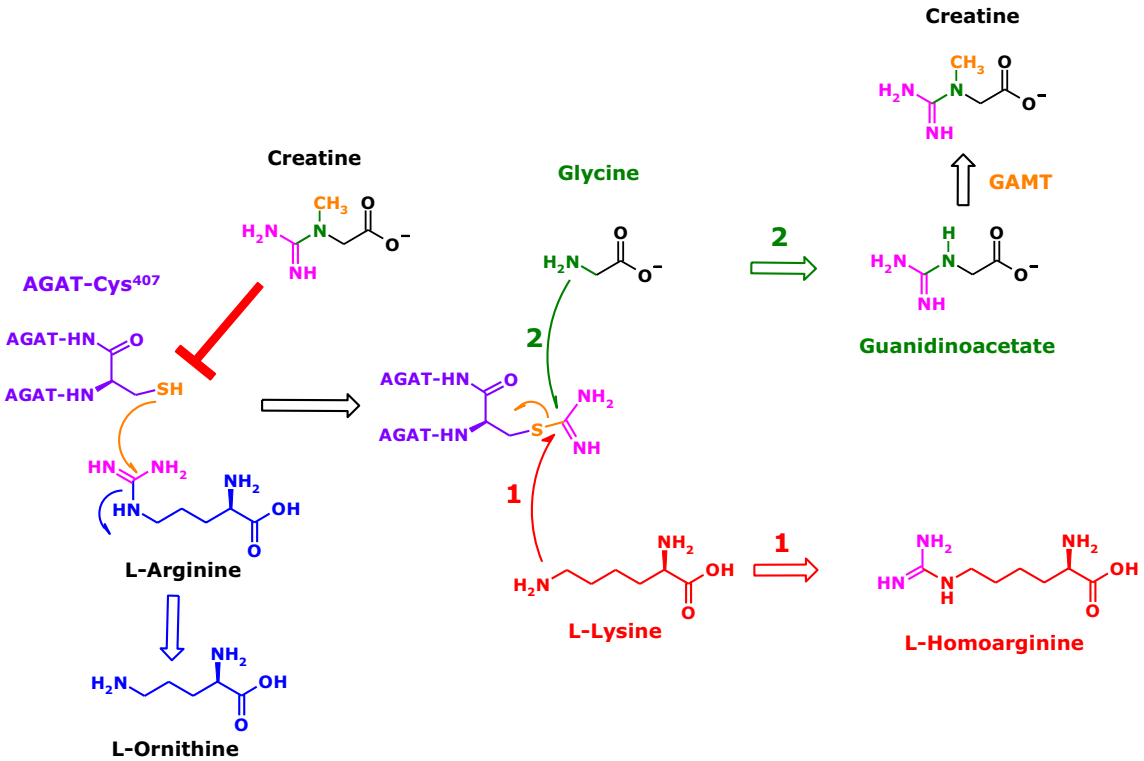

Fig. 1 Proposed mechanisms for the biosynthesis of L-homoarginine and guanidinoacetate from L-arginine. Arginine:glycine amidinotransferase (AGAT) catalyzes the formation of guanidinoacetate from L-arginine and glycine, with L-ornithine being a co-product (Humm et al. 1997). The mechanism has been proposed to include nucleophilic attach of the sulfhydryl (SH) group of Cys407 of the recombinant human AGAT (AGAT-Cys^{407}) to form a thiocarbamide derivative stabilized by Asp170 and Asp305 (Humm et al. 1997). Nucleophilic attack of the amino group of glycine on the C atom of the thiocarbamide moiety releases guanidinoacetate (reaction 2). AGAT-catalyzed L-homoarginine synthesis by such a mechanism would require nucleophilic attack of the terminal amino group of L-lysine on the C atom of the thiocarbamide moiety (reaction 1). Guanidinoacetate methyltransferase (GAMT) methylates guanidinoacetate to form creatine. Creatine inhibits AGAT-catalyzed synthesis of L-homoarginine in vivo in mice (Choe et al. 2013; Kayacelebi et al. 2015b), presumably by reacting with the SH group of AGAT-Cys^{407}

disorders. ADMA is generally believed to exclusively exert its biological actions by inhibiting NOS-catalyzed synthesis of NO from Arg. Considerably lower circulating concentrations of hArg in blood and lower affinity of hArg to several NOS isoforms, as compared to Arg, challenge the current general belief that NO produced from hArg is the sole mechanism that explains the recently discovered pathophysiological functions of hArg. There are also doubts that the inhibitory action of ADMA on NO synthesis is exclusively responsible for the cardiovascular risk of ADMA. The very weak inhibitory potency of ADMA towards endothelial NOS (IC_{50} 12 μM; Kielstein et al. 2007) is the strongest argument that challenges the still prevailing dogma of ADMA's principal action in the renal and cardiovascular systems.

In consideration of the emerging pathophysiological importance of hArg, as revealed by the numerous scientific reports of the last few years, the almost completely unknown underlying mechanisms for the actions of hArg, the incompletely understood or explained effects of ADMA in biological systems, together with the fact that Arg is the common precursor of hArg and ADMA, we thought that the time was ripe for the publication of a special issue in the journal *Amino Acids* just devoted to hArg, Arg and their relatives including ADMA and SDMA. We are very pleased to present to the readers the special issue in hand which we introduce to the readership in brief in the following sections.

Analytical methods for the qualitative and quantitative analysis of native and modified amino acids, peptides and proteins in biological samples are indispensable tools for understanding their multiple roles in living organisms, as well as for the development of strategies for reliable diagnosis and successful therapy of particular diseases. From an analytical point of view, amino acids and their metabolites may represent big challenges for particular techniques of separation and detection. Difficulties result from the relatively large number of amino acids and their diversity with respect to chemical structure and physicochemical properties (including stability), as well as from the occurrence at greatly differing concentrations in many cases. Thus, specific analysis of hArg requires its separation not only from Arg that coexists in large molar excess over hArg, but also from other coexisting Arg derivatives such as the N^G-methylated ADMA, SDMA and monomethyl arginine (MMA), as well as from other endogenous isobaric amino acids, notably trimethyllysine. By means of convenient HPLC with fluorescence detection after pre-column derivatization with *o*-phthaldialdehyde (OPA) and thiols such as *N*-acetylcysteine, in principle, all primary amino acids including hArg can be reliably determined in biological samples (Hou et al. 2015). Hyphenated techniques, notably the couple of mass spectrometry (MS) with liquid chromatography (LC) (i.e., LC–MS and LC–MS/MS) or gas chromatography (i.e., GC–MS, GC–MS/MS), allow not only for highly accurate measurement of these and other amino acids, but they are a unique analytical tool to study biosynthesis and metabolism of amino acids in complex biological samples such as plasma and urine (Cordts et al. 2015; Kayacelebi et al. 2015a, b). Commercially available immunological methods such as ELISA are in general very popular. ELISA is also widely used for the measurement of ADMA and hArg in clinical studies. These assays need validation by other more reliable methods such as LC–MS/MS and GC–MS/MS. Yet, one may expect diverging quantitative results (Cordts et al. 2015).

In adults, elevated concentrations of ADMA and SDMA, as well as reduced concentrations of hArg, are generally accepted cardiovascular risk factors. Recent clinical investigations on these Arg metabolites in adults extend their key importance to other diseases in adults, including multiple sclerosis, chronic liver and kidney disease, obesity, rheumatoid arthritis, coronary artery disease, and peripheral arterial occlusive disease (Dimitroulas et al. 2015; Frenay et al. 2015a, b; Haghikia et al. 2015; Kayacelebi et al. 2015c; Kruszelnicka et al. 2015; May et al. 2015; Pilz et al. 2015a; Schneider et al. 2015; Sitar et al. 2015). In childhood and adolescence, the significance of ADMA or hArg as cardiovascular risk factors is little investigated and incompletely understood. The circulating concentration of ADMA in healthy children is more than two times higher than in healthy adults (Lücke et al. 2007), suggesting that ADMA and presumably the whole Arg/NO pathway greatly differ between children/adolescents and adults, i.e., that children are not small adults. In the present work, emphasis was given to the Arg/NO pathway, including hArg in healthy children and adolescents, as well as in those suffering from type 1 diabetes mellitus, Duchenne muscular dystrophy, and growth hormone deficiency (GHD) (Carmann et al. 2015; Hörster et al. 2015; Langen et al. 2015; see also Thum et al. 2007).

In a mice model of stroke, oral administration of hArg has been demonstrated to restrict the seizure area. Interestingly, hArg supplementation was found to reduce blood glucose concentration in diet-induced obese mice (Stockebrand et al. 2015). These are promising observations, indicating a potential for pharmacological use of hArg in particular diseases, such as obesity and diabetes. In a rat model of acutely hyperhomocysteinemia-induced endothelial dysfunction, the role that ADMA and SDMA was investigated (Magné et al. 2015). Methionine load induced a sustained increase in total homocysteine and a decrease in vascular reactivity. The absence of an elevation of circulating ADMA and SDMA in this model suggested that endothelial dysfunction induced by acute hyperhomocysteinemia may be explained by a down-regulation of the proteasome (Magné et al. 2015).

Previous animal and human (Bode-Böger 2006) studies indicated that short-term oral administration of Arg, the common precursor of hArg, ADMA and SDMA, at daily doses up to 10 g is safe. Long-term oral administration of Arg supports the pharmacological safety of Arg in animals and humans (Kayacelebi et al. 2015b; Yang et al. 2015). Also, acute intravenous administration of large amounts of Arg, as performed in the so called Arginine Test which is used clinically in the diagnosis of GHD, underlines the pharmacological safety of Arg even in children (Hu et al. 2015; Kayacelebi et al. 2015b). Interestingly, acute and long-term oral administration of Arg has different effects with respect to hArg and ADMA than acute intravenous administration of high doses of Arg. Benefits from pharmacological or supplemental use of Arg are expected to be more than enhancement of NO synthesis by increasing the substrate availability of Arg (Wu et al. 2009). Potential benefits of oral administration of Arg could be saving nitrite bioavailability due to improved reabsorption of nitrite in the proximal tubule of the nephron (Schneider et al. 2015), as nitrite is the major NO reservoir (Gladwin et al. 2006), and due to enhanced hArg biosynthesis in comparison to ADMA (Kayacelebi et al. 2015b). This may be of particular importance because hArg and ADMA seem to act antagonistically at least in the circulatory system (Tsikas and Kayacelebi 2014).

Although the first report on the biological importance of hArg appeared only very recently (Valtonen et al. 2008), hArg attracts the increasing attention of scientists from various disciplines, and the number of scientific reports dealing with hArg increases exponentially. The current state of the pathophysiology of hArg and the N^{G}-methylated Arg analogs ADMA and SDMA in the circulation and in some organs (including the brain) in conditions such as pregnancy is thoroughly reviewed and discussed in the present special issue (Bernstein et al. 2015; Khalil et al. 2015; Papageorgiou et al. 2015; Pilz et al. 2015b). The transport of ornithine (a product of Arg hydrolysis by the cytosolic arginase I and the mitochondrial arginase II) and related basic amino acids was also reviewed and discussed in relation to Arg and hArg homeostasis in cells and the whole body (Monné et al. 2015; Schlune et al. 2015). Arg has been reported to serve as a substrate for an endothelial-like NOS in platelets and erythrocytes. Yet, proteomic studies indicated that human platelets lack any NOS proteins, and measurement of NOS activity in stimulated and non-stimulated platelets by a sensitive and specific stable-isotope dilution GC–MS method failed to detect any NOS activity (for a review see Gambaryan and Tsikas 2015).

Our knowledge of the physiological and pathological importance of hArg grew enormously in the last few years. Nevertheless, there is a deep knowledge gap with respect to the basic aspects of hArg. These issues include the biosynthesis and metabolism of hArg. There is strong evidence from in vitro and in vivo animal experiments (Choe et al. 2013) and valuable information from very few human individuals (Davids et al. 2012) that arginine:glycine amidinotransferase (AGAT; EC 2.1.4.1) is the enzyme that is mainly responsible for the synthesis of hArg. Yet, the precise mechanism of this biosynthetic route and the factors which may modulate this reaction are essentially unknown. Actually, human AGAT catalyzes the synthesis of guanidinoacetate from L-arginine and glycine, thereby generating L-ornithine (Fig. 1). The commercial inaccessibility of isolated and purified AGAT or recombinant AGAT preparations is a major limitation in the current research of the biochemistry of hArg. Animal experiments indicate that the AGAT route is not the only pathway by which hArg is biosynthesized from Arg and L-lysine. These potentially alternative mechanisms remain to be elucidated. hArg has been reported to serve as a substrate for several NOS isoforms (Hecker et al. 1991; Moali et al. 1998). The function of hArg as a substrate for NOS demands deeper investigations using pure enzyme preparations, including recombinant enzymes and specific measurement of NO and its metabolites nitrite and nitrate. Guanidine-^{15}N labeled hArg would be the most suitable substrate for future investigations to answer open questions regarding the function of hArg as a precursor of NO. Besides serving as a substrate for NOS, hArg seems to act differently with regard to oxidative stress in vitro in erythrocytes and organs of the rat, albeit at supraphysiological concentrations (Sasso et al. 2015). Analogous to Arg, yet at a much lower concentration, one may suppose that hArg may participate in many of those pathways in which Arg is involved. This is worth of investigation in forthcoming studies.

Closing the Editorial, we would like to thank Prof. Gert Lubec for giving us the opportunity to organize this special issue for *Amino Acids* and for his great support and guidance of editing. We also would like to thank the authors and their coworkers for contributing to this special issue. We are grateful to the reviewers who spent their valuable time to improve the quality of the papers included in this work.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

Ethical statement In this work no animal or human studies were performed.

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