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Review article

AGXT2: An unnegligible aminotransferase in cardiovascular and urinary systems

Xiao-Lei Hu[a,b], Mu-Peng Li[a,b], Pei-Yuan Song[a,b], Jie Tang[a,b,*], Xiao-Ping Chen[a,b,*]

[a] Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha 410008, China
[b] Institute of Clinical Pharmacology, Central South University, Hunan Key Laboratory of Pharmacogenetics, Changsha 410078, China

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ABSTRACT

Cardiovascular diseases (CVDs) and renal impairment interact in a complex and interdependent manner, which makes clarification of possible pathogenesis between CVDs and renal diseases very challenging and important. There is increasing evidence showing that both asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) play a crucial role in the development of CVDs as well as in the prediction of cardiovascular events. Also, the plasma levels of ADMA and SDMA were reported to be significantly associated with renal function. Alanine-glyoxylate aminotransferase 2 (AGXT2) is reported to be involved in ADMA and SDMA metabolism, thus deficiency in the expression or activity of AGXT2 may play a part in the progression of cardiovascular or renal diseases through affecting ADMA/SDMA levels. Here, we focused our attention on AGXT2 and discussed its potential impact on CVDs and renal diseases. Meanwhile, the review also summarized the functions and recent advances of *AGXT2*, as well as the clinical association studies of *AGXT2* in cardiovascular and urinary systems, which might arouse the interest of researchers in these fields.

Cardiovascular diseases (CVDs) still account for 31.3% of all-cause deaths worldwide in spite of the highly developed holistic modern healthcare of current society [1]. The total number of inpatient cardiovascular operations and procedures increased by 28% from 2000 to 2010, which caused enormous social and economic burden. CVDs often coexist with a number of prognosis-relevant comorbidities, such as renal impairment, which mainly manifested as baseline reduction in glomerular filtration or a worsening of renal function (WRF) over time. CVDs and renal impairment interact in a complex and interdependent manner. It is extraordinary challenging and important to summarize and clarify possible pathogenesis in CVDs and renal diseases. Here, we focused on the enzyme namely alanine-glyoxylate aminotransferase 2 (AGXT2) and discussed its potential impact on CVDs and renal diseases.

1. Dimethylarginines in CVDs and renal diseases

Atherosclerosis (AS) is a multifactorial pathology and the basic pathological changes for CVDs. The majority of CVDs are results of complications caused by AS [2]. Endothelial dysfunction is an early step in the development of AS and is mainly characterized by a reduction in the bioavailability of nitric oxide (NO) [3]. NO is an endogenous signaling molecule that regulates vessel dilatation, cardiac contraction, platelet aggregation and so on [4–7]. Increasing evidence has shown that NO plays an important protective role in the cardiovascular system [8,9]. Besides, considerable clinical and experimental evidence also suggests that reduction in NO bioavailability might facilitate the development of chronic kidney disease (CKD) and kidney impairment [10–12]. Nitric oxide synthase (NOS), an essential enzyme responsible for the synthesis of NO, could catalyze the oxidation of L-arginine and mediates the release of NO in vascular endothelial cells [13,14].

Asymmetric dimethylarginine (ADMA), an endogenous analog of L-arginine, can competitively bond with NOS and obstruct the synthesis of NO. Evidence has shown that ADMA plays an important role in the development of hypertension [15,16], promoting vascular damage, and increasing cardiovascular risk in hypertensive patients [17]. Imbalance of arginine and ADMA was independently involved in the progression of AS [18]. Besides, plasma levels of ADMA are elevated in chronic cardiac failure (CHF) patients [19] and positively correlated with disease severity in CHF [20]. In brief, ADMA has been regarded as an important cardiovascular risk factor in CVDs [21–24]. In addition,

Abbreviations: ADMA, asymmetric dimethylarginine (N^G, N^G-dimethyl-L-arginine); SDMA, symmetric dimethylarginine (N^G, N^G-dimethyl-L-arginine); L-NMMA, monomethylarginine (N^G-monomethyl-L-arginine); DDAH, dimethylarginine dimethylaminohydrolase; AGXT2, alanine-glyoxylate aminotransferase 2; DMGV, α-keto-δ-(N^G, N^G-dimethylguanidino) valeric acid; DM′GV, α-keto-δ-(N^G, N'^G-dimethylguanidino) valeric acid; PRMT, protein-arginine methyltransferase; CAT, cationic amino acid transporter; SLC25A2, Solute carrier family 25A2; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine

* Corresponding authors at: Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China.
E-mail addresses: jietang@csu.edu.cn (J. Tang), chenxp74@hotmail.com (X.-P. Chen).

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numerous experimental studies have demonstrated that increased plasma ADMA was a powerful predictor of CKD independent of estimated glomerular filtration rate (eGFR) and other risk factors [25–27]. A recent study suggested that decreased renal tubular ADMA metabolism protected from WRF and ADMA may play both pathogenic and protective roles in different disease sites, and time courses [28,29].

Compared with ADMA, symmetric dimethylarginine (SDMA) does not inhibit the enzymatic activity of NOS, but can compete for L-arginine transport on the membrane [30]. SDMA is transported efficiently by cationic amino acid transporter 2B (CAT-2B) which is accompanied by transmembrane exchange of intracellular L-arginine, resulting in a suppression of NO synthesis indirectly. Serum SDMA level was observed to be positively correlated with serum creatinine and eGFR [25], two crucial indicators of renal function. Circulating SDMA was elevated in patients with renal disease and tended to increase progressively with worsening renal impairment [27]. Besides, serum SDMA level could also predict all-cause mortality in patients with ischemic stroke [31] and symptomatic peripheral arterial disease [32]. Increasing evidence indicates that SDMA might be an important parameter for renal function and the extent of coronary artery disease [33].

2. Biosynthesis and metabolism of dimethylarginines

2.1. The biosynthesis of dimethylarginines

Dimethylarginines are the methylate products of proteins containing L-arginine and the methylation is catalyzed by a family of enzymes termed protein-arginine methyltransferases (PRMTs), of which two types (Type I and II) exist [34]. Both types of PRMTs mediate methylation of arginine residual in proteins by using S-adenosylmethionine (SAM) as the methyl group donor. PRMTs catalyze the monomethylation of arginine but, when a second methyl group is attached to monomethylarginine, the product is PRMT dependent [35]. Type I PRMTs catalyze the formation of asymmetric dimethylarginine (ADMA), whereas type II PRMTs mediate the formation of symmetric dimethylarginine (SDMA) (Fig. 1).

2.2. The metabolism of dimethylarginines

ADMA and SDMA show distinct metabolic pathways in the body, though they share the similar biosynthesis pathways. Most of ADMA in the body is degraded by enzymatic reactions while SDMA is mainly eliminated *via* renal excretion as a form of prototype [36]. There are two known metabolic pathways involved in the elimination of ADMA in humans, one pathway is the hydrolysis of ADMA to citrulline and dimethylamine in the cytoplasm by dimethylarginine dimethylaminohydrolases (DDAHs) [37], while the other pathway is the transamination of ADMA to α-keto-δ-(N^G,N^G-dimethylguanidino) valeric acid (DMGV) by alanine-glyoxylate amino-transferase 2 (AGXT2) in the mitochondria [38]. A fraction of SDMA may as well be degraded by AGXT2 and formed the metabolite α-keto-δ-(N^G,N'^G-dimethylguanidino) valeric acid (DM'GV) [39]. The influx of intracellular ADMA into mitochondrial is transported by the solute carrier family 25A2 (SLC25A2), while the mechanism for the influx of intracellular SDMA into mitochondria still remains unclear [40] (Fig. 1).

Actually, there are two distinct alanine-glyoxylate aminotransferase (AGXT) isoenzymes in human: AGXT1 and AGXT2. Both AGXTs are pyridoxal phosphate (PLP)-dependent and catalyze the transfer of an amino group from alanine to glyoxylate [41–43] (Fig. 2). However, the two human AGXT isoenzymes show different organ distribution in the body. Data from the human protein atlas database (http://www.proteinatlas.org/) indicate that AGXT1 is primarily expressed in the liver while AGXT2 is mainly expressed in the kidney. Besides, the two isoenzymes show differences in both intracellular localization and biochemical activity (Fig. 2). AGXT1 is primarily distributed in peroxisomes and plays a major role in the clearance of glyoxylate. In the past decades, AGXT1 has been extensively studied owing to its important role in the detoxification of glyoxylate and the pathogenesis of primary hyperoxaluria type I (PH1) [44–46]. Meanwhile, few studies were focused on AGXT2 until Roman and colleagues 'rediscovered' the potential pathophysiological roles of AGXT2 and demonstrated that AGXT2 could protect from inhibition of NO production [38]. AGXT2 is mainly located in the mitochondria. In addition to its alanine-glyoxylate aminotransferase activity, AGXT2 shows several other enzymatic activities that are not shared by AGXT1. Animal study with C57BL/6 mice showed that overexpression of human AGXT2 in the liver using an

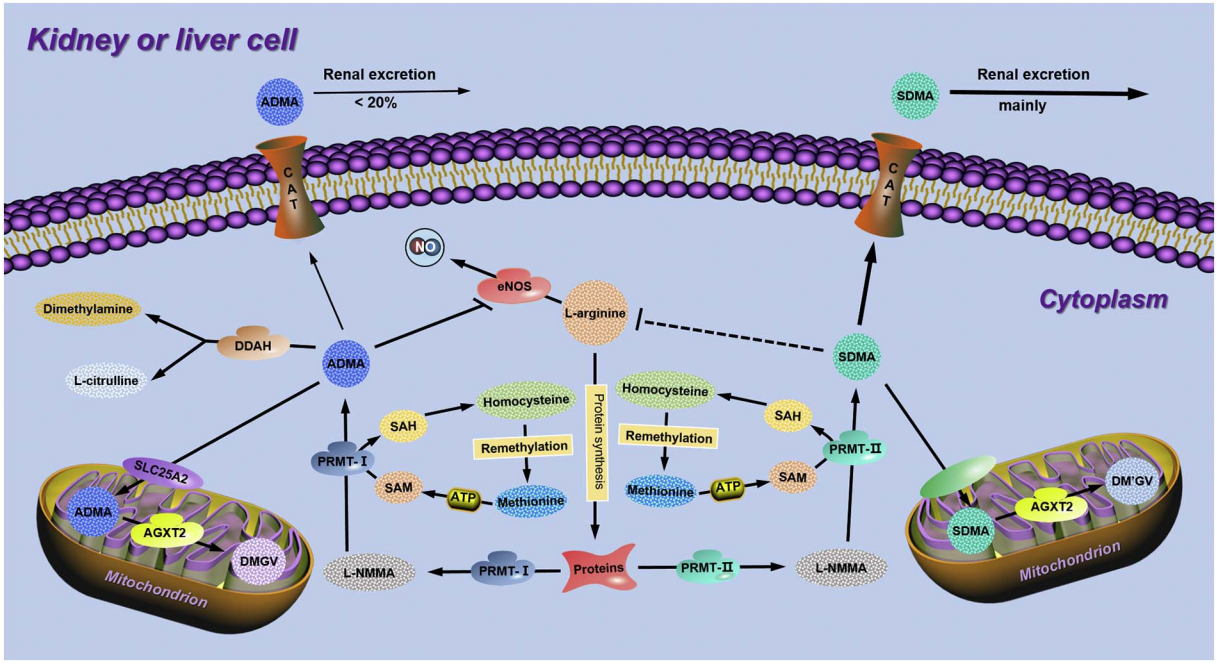

Fig. 1. Pathways of dimethylarginines synthesis and degradation in human.