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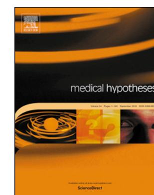
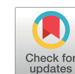


The possible role of a bacterial aspartate β-decarboxylase in the biosynthesis of alamandine



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ABSTRACT

The understanding of the renin-angiotensin system (RAS) has significantly expanded over the last two decades. The elucidation of angiotensin-converting enzyme 2 (ACE2) that converts angiotensin (Ang) II into Ang (1–7) led to the discovery of the cardio-protective axis of the RAS. In addition, novel components of the system, Angiotensin A (Ang A) and alamandine have been identified. Like Ang (1–7), alamandine is a vasodilator and can counteract the effects of Ang II by increasing nitric oxide release from the endothelium and decreasing nicotinamide adenine dinucleotide phosphate oxidase (NADPH)-related superoxide production. Theoretically, alamandine can be derived from Ang (1–7) by decarboxylation of the N-terminal aspartic acid residue to alanine, but the enzyme responsible for this is still unknown. To date, no human or mammalian enzyme with the assigned decarboxylase activity has been identified. However, several bacterial enzymes capable of converting aspartate to alanine have been reported. Therefore, we hypothesize that a bacterial enzyme, most likely present in the microbiome of the gastrointestinal tract, the heart, or systemic circulation could metabolize Ang II, and/or Ang 1–7, to Ang A and alamandine, respectively, in mammals.

Introduction

The renin-angiotensin system (RAS) plays a pivotal role in cardiovascular and renal pathophysiology [1,2]. Angiotensin (Ang) II, the active component of the RAS, is an octapeptide resulting from angiotensin-converting enzyme (ACE)-mediated cleavage of angiotensin I. Ang II binds to its receptors, AT1 and AT2 to mediate its effects. The ACE/Ang II/AT1 receptor axis mediates vasoconstriction, renal sodium reabsorption, thirst, release of vasopressin and aldosterone, inflammation, fibrosis and oxidative stress [3–5]. Strategies aimed at inhibiting ACE activity or blocking the AT1 Ang II receptor (AT1R) subtype (angiotensin receptor blockers, ARBs) for the treatment of hypertension and associated pathologies are widely used clinically, highlighting the importance of Ang II in this system. Indeed, several clinical trials are investigating the possibility that AT1R blockers (angiotensin receptor blockers, ARBs) may be beneficial in reducing the inflammatory response associated with COVID 19 [6]. Angiotensin-converting enzyme 2 (ACE2), a homolog of ACE with mono-carboxypeptidase activity, converts Ang II to Ang (1–7), contributing to the major cardioprotective arm of RAS, counteracting the pro-hypertensive effects of the classical ACE/Ang II/AT1R axis [7,8]. Recently, a heptapeptide alamandine and its receptor MrgD were identified as novel RAS components [9–11]. Alamandine and Ang (1–7) differ by only one amino acid residue, an alanine instead of aspartic acid at the N-terminal position. A similar observation of an alanine[1] substituted Ang II, Ang A, was reported previously [12]. *In-vivo* and *in-vitro* studies demonstrate that alamandine subserves similar functions to Ang (1–7), e.g., vasodilation, blood pressure reduction, anti-inflammation and antifibrosis [10,13]. Alamandine reduced blood pressure in spontaneously hypertensive rats equivalent to Ang (1–7), and reduced cardiac fibrosis in Sprague–-Dawley rats [14]. Despite these similar pharmacological profiles, Ang (1–7) and alamandine appear to signal through different receptors. Unlike the actions of Ang (1–7), the protective effects of alamandine are not inhibited by Mas receptor blockers such as A779, but are inhibited by D^7-Pro Ang (1–7) and β-alanine [10,15]

Alamandine as well as Ang A are found in human plasma, with increased levels reported in patients with end-stage renal disease (ESRD) or renal failure [10,12], however, their physiological significance in humans remains largely unexplored. It was shown that alamandine can be synthesized in rat hearts perfused with Ang (1–7), but the enzyme responsible for endogenous alamandine biosynthesis under these circumstances is still unknown [10]. Alamandine can also

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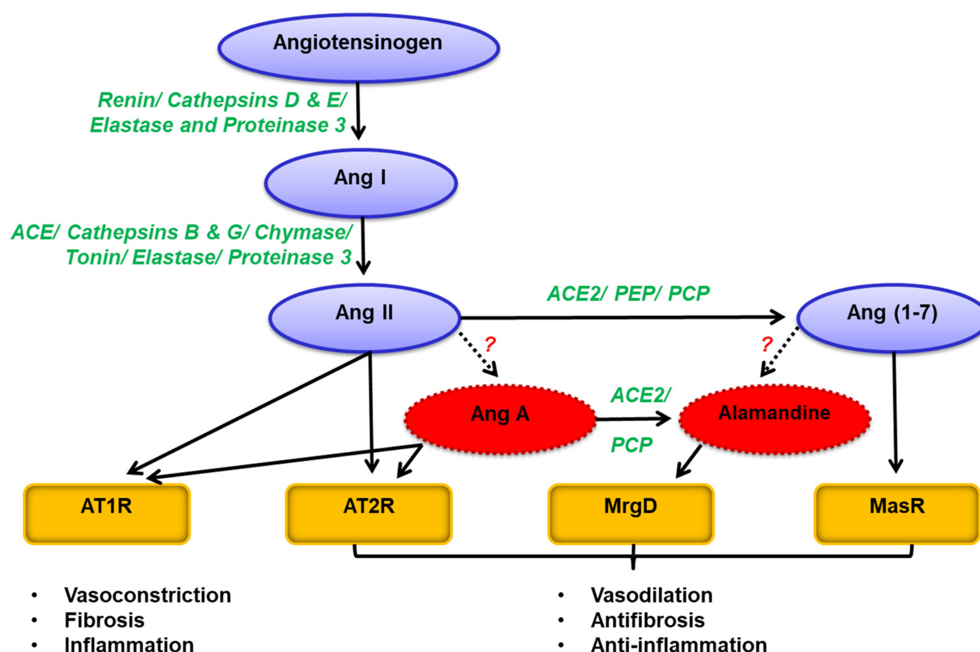

Fig 1. A simplified scheme of the renin-angiotensin system. The enzymes of the system are shown in green; novel RAS components are shown in red; receptors are shown in yellow boxes (adapted from [10,13,46]). ACE, angiotensin-converting enzyme; Ang, angiotensin; PEP, prolyl-endopeptidase, previously known as post-proline cleaving enzyme [47]; PCP, prolylcarboxypeptidase, previously known as angiotensinase C [48]; AT_1R, angiotensin II type-1 receptor; *Mas*R, *Mas* receptor and *Mrg*D, *Mas*-related G-protein-coupled receptor D. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be formed via ACE2-mediated catalytic hydrolysis of Ang A, a similar aspartate → alanine homolog of Ang II [16]. It is believed that both Ang A and alamandine are produced by the N-terminal aspartate decarboxylation of Ang II and Ang (1–7) respectively (Fig. 1). Aspartate β-decarboxylase (EC 4.1.1.12), first discovered in the 1950s, catalyzes the conversion of L-aspartic acid to L-alanine [17–19]. The majority of the aspartate β-decarboxylases reported till now have a bacterial origin, which points towards the possible involvement of a bacterial symbiont in alamandine formation.

Hypothesis

Given the absence of any reported human enzyme that can catalyse the conversion of N-terminal aspartate of Ang (1–7) to alanine, we hypothesize the involvement of a gut or systemic bacterial aspartate β-decarboxylase E.C. 4.1.1.12 (also known as aspartate beta decarboxylase and aspartate 4-decarboxylase, by virtue of its selectivity for the side-chain carboxylate moiety as opposed to the alpha carbon carboxylate which when decarboxylated forms beta-alanine) in the biosynthesis of Ang A and alamandine. While the bacterial aspartate decarboxylase has only been shown to be active on free aspartic acid, our hypothesis also posits that the location of the aspartic acid in Ang II and Ang (1–7) as the amino terminal amino acid, would allow for it to fit into the binding pocket of the bacterial aspartate β-decarboxylase, with the remainder of the peptide being outside of the binding pocket, thus not posing any steric hindrance to the enzyme. Of note, one research group [20,21] reported a rodent aspartate ß-decarboxylase, with the highest expression in the liver. This enzyme was distinctly different from bacterial aspartate β-decarboxylase, however, there are no subsequent reports of this enzyme.

Evidence for hypothesis

An EC number-based search on Uniprot Knowledgebase [22] returned 232 bacterial enzymes (Table 1). The closest homolog of aspartate β-decarboxylase in human is a putative tyrosine aminotransferase, which shares only 25% sequence identity with the bacterial enzyme. Interestingly, many of the aspartate β-decarboxylases come from bacterial phyla and classes dominantly present in the gastrointestinal or gut microbiota, such as Bacteroidetes, Proteobacteria, Actinobacteria and Firmicutes [23,24].

Table 1
UniprotKB search for aspartate β-decarboxylase.

Bacterial phylum and class	Number of family members reported in UniprotKB[1]
Bacteroidetes	
Bacteroidia	129
Flavobacteriia	2
Proteobacteria	
Alphaproteobacteria	28
Burkholderiales	13
Deltaproteobacteria	15
Gammaproteobacteria	12
Actinobacteria	
Actinomycetes	7
Actinobacteria	3
Firmicutes	
Bacilli	10
Clostridia	4

[1] https://www.uniprot.org/

Rationale for the hypothesis

Gut bacteria and RAS

There is emerging evidence suggesting that gut microbiota are critical in maintaining physiological homeostasis [25,26]. Intestinal bacteria are not only involved in the metabolism of dietary amino acids, but also in their synthesis [27]. Recent studies have also implicated the gut microbiota in cardiovascular and metabolic disorders [28–30]. Ang II has been reported to be present in the gut [31] along with ACE2, expressed on the luminal side of epithelial cells of the intestinal tract [32]. mRNA for angiotensinogen (the precursor for Ang peptides), ACE, ACE2, AT1R, and Mas has been observed in human intestinal epithelium biopsies [33], and both ACE inhibitors and ARBs have been shown to have therapeutic efficacy in treating inflammatory bowel disease and Crohn's Disease [33,34]. Immunoreactive ACE, ACE2, Ang 1–7 and Mas as well as ACE2 enzymatic activity are also present in intestinal epithelium [33] further supporting the existence of an intraintestinal RAS. Thus the presence of Ang II and Ang 1–7 in the intestinal tract, along with bacteria possessing aspartate β-decarboxylase activity strongly supports the likelihood of intraintestinal Ang A and alamandine formation. Since ESRD is associated with increased intestinal wall

permeability, it is likely that the increased levels of Ang A and alamandine in ESRD reflect intestinal Ang A and alamandine that leaked through the compromised intestinal wall barrier.

Gut bacterial translocation (GBT) in health and disease

In addition to the interplay between gut bacteria and the intraintestinal RAS, a plethora of studies indicate the possibility of GBT, a process whereby intestinal bacteria pass through the intestinal epithelium to enter the systemic circulation and organs of the body in pathological conditions [35]. Examples of GBT are seen in inflammatory bowel disease [36], ESRD [37–39] and cardiovascular diseases (CVDs) [40,41] further supporting the hypothesis that bacterial aspartate ß-decarboxylase forms alamandine and Ang A. Loss of intestinal epithelium integrity in ESRD leads to GBT, causing chronic inflammation [37,42]. Elevated levels of circulating lipopolysaccharide, considered as a surrogate marker of GBT contributes to a chronic inflammatory state [37]. Higher systemic circulation of gut microbiome derived bacteria was observed in CVD patients, compared to healthy individuals [40]. GBT has also been implicated in the pathogenesis of heart failure. Increased bacterial translocation and consequently increased endotoxin levels were reported to contribute to the underlying inflammation found in heart failure patients [41]. An age-dependent increase in the levels of bacterial DNA arising from the gastrointestinal microbiome was present in coronary plaques of patients with coronary heart disease [43]. Altered microbial diversity in lung alveoli was found to be a hallmark of diseases like pulmonary tuberculosis and interstitial pneumonia [44]. These reports, combined with the elevated levels of alamandine in renal disorders [10,12], suggest that gut bacteria can enter the systemic circulation, particularly under pathological conditions and may be instrumental in formation of “protective” metabolites like alamandine to counter the inflammatory response caused by bacteria that translocate from the gut. In addition to gut bacterial translocation in health and disease, it appears that there are additional sources for bacteria that make up the human blood microbiome in healthy individuals as recently reviewed [45]

Limitations

While a decarboxylation of aspartic acid in Ang 1–7 or Ang II to form alamandine or Ang A is the most likely mechanism for formation of these peptides, it remains to be explored whether a bacterial enzyme would be capable of decarboxylating the aspartic acid in Ang peptides. Specifically, the bacterial enzyme would need to be secreted from the bacterial cytoplasm or released intact from dying bacteria into the extracellular milieu. Alternatively, the bacteria would need to take up Ang II or Ang 1–7, decarboxylate the aspartic acid, then secrete the Ang A or alamandine into the extracellular milieu. Additionally, the K_M values of the bacterial aspartate ß-decarboxylase for aspartic acid, ~1 mM, are far in excess of the concentrations of Ang II and Ang 1–7 (< 1 nM) in the body. However, it is plausible that the enzyme has a greater affinity for the peptide substrates, as compared to the single amino acid. Therefore, experimental evidence is necessary to ascertain if the rate of formation of Ang A and alamandine by bacterial aspartate ß-decarboxylase is sufficient to generate the amounts of Ang A and alamandine seen *in-vivo*.

Conclusion

Notwithstanding these limitations, bacterial aspartate β-decarboxylase is a promising candidate enzyme for the biosynthesis of alamandine. This hypothesis could be tested by the recombinant production and purification of aspartate β-decarboxylases from multiple gut bacteria to evaluate their ability to decarboxylate the amino terminal aspartic acid of Ang II and Ang (1–7) to alanine, forming Ang A and alamandine, respectively. While there is good circumstantial evidence for synthesis of Ang A and alamandine in the intestinal tract, additional support for this hypothesis would be gained from direct measurements of Ang A and alamandine in the intestinal tract. As described above, another probable scenario could be the translocation of bacteria of the gut microbiome into the systemic circulation, wherein the starting metabolites (Ang II and Ang 1–7) necessary for formation of Ang A and alamandine are readily available. This could be achieved by giving faecal transplants to germ-free mice and determining the presence of bacteria in the circulation.

The addition of alamandine and its receptor *MrgD* to the RAS pathway amplifies the counter-regulatory arm of the RAS that antagonizes the pathogenic ACE/Ang II/AT1R arm. The relevance of alamandine in the context of the RAS and its importance in human physiology and disease is not yet fully established. To our knowledge, no study specifically delineating the enzymatic pathways of formation of endogenous Ang A or alamandine biosynthesis has been reported. These studies are essential to elucidate the mechanism and regulation of Ang A and alamandine production, and to assess the physiological significance of the specific cell signaling mechanisms of *MrgD* and other Mas related G protein-coupled receptors. Getting fresh information on novel RAS metabolites offer novel opportunities for treatment and prevention of hypertension and associated renal and cardiovascular disorders.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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