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ACE phenotyping as a first step toward personalized medicine for ACE inhibitors. Why does ACE genotyping not predict the therapeutic efficacy of ACE inhibition?

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Abstract

Angiotensin (Ang)-converting enzyme (ACE) inhibitors are widely used for the treatment of cardiovascular diseases. Not all patients respond to ACE inhibitors, and it has been suggested that genetic variation might be a useful marker to predict the therapeutic efficacy of these drugs. In particular, the ACE insertion (I)/deletion (D) polymorphism has been investigated in this regard. Despite a decade of intensive research involving the genotyping of thousands of patients, we still do not know whether ACE genotyping helps in predicting the success of ACE inhibition. This review critically addresses the concept that predictive information on therapeutic efficacy of ACE inhibitors might be obtained based on ACE genotyping. It answers the following questions: Do higher ACE levels really result in higher Ang II levels? Is ACE the only converting enzyme in humans? Does ACE inhibition affect ACE expression? Why does ACE have 2 catalytically active domains? What is the relevance of ACE inhibitor-induced signaling through membrane-bound ACE? The review ends with the proposal that ACE phenotyping may prove to be a better first step toward personalized medicine for ACE inhibitors than ACE genotyping.

Keywords: Angiotensin; ACE inhibitors; Bradykinin; Genotyping; Hypertension; I/D polymorphism; Signaling

Abbreviations: ACE, angiotensin-converting enzyme; Ang, angiotensin; AT_1, Ang II type 1 receptor; D, deletion; CK2, casein kinase 2; COX-2, cyclooxygenase-2; I, insertion; JNK, c-Jun N-terminal kinase.

Contents

1. Introduction . . . 608
2. ACE variation and Ang II generation . . . 608
3. Role of alternative Ang II-generating enzymes . . . 609
4. ACE upregulation following ACE inhibition? . . . 610
5. ACE C-domain versus N-domain . . . 611
6. ACE inhibitor-induced signaling . . . 612
7. ACE I/D polymorphism and the response to ACE inhibition . . . 612
8. Conclusions: ACE phenotyping instead of genotyping? . . . 613
References . . . 614

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1. Introduction

Angiotensin (Ang)-converting enzyme (ACE) inhibitors are widely used for the treatment of cardiovascular diseases. However, their mechanism of action is not completely understood. In general, it is believed that these drugs block Ang II generation at tissue sites rather than Ang II generation in circulating blood (Dzau, 1988; van den Meiracker et al., 1992; Campbell et al., 1994; van Kats et al., 2000, 2005). In addition, interference with the metabolism of ACE substrates other than Ang I (e.g., bradykinin and *N*-acetyl-Ser-Asp-Lys-Pro) may contribute to their beneficial effects (Gainer et al., 1998; Azizi et al., 2002; Peng et al., 2005).

Not all patients respond to ACE inhibitors (Dickerson et al., 1999; Struthers et al., 2001), and it has been suggested that genetic variation might be a useful marker to predict the therapeutic efficacy of these drugs (Turner et al., 2001). In particular, the ACE insertion (I)/deletion (D) polymorphism has been investigated in this regard, although no conclusive data have been obtained. This polymorphism, corresponding with a 287-base pair insert in intron 16 of the gene, associates with the ACE concentration in blood and tissues, subjects with 1 or 2 D alleles having approximately 30% and 60% higher ACE levels, respectively, than subjects with the II genotype (Rigat et al., 1990). Subjects with the DD genotype are assumed to display increased Ang II generation and require higher doses of ACE inhibitors to fully suppress ACE.

This review critically addresses the idea that predictive information on therapeutic efficacy of ACE inhibitors can be obtained based on ACE genotyping. It will also answer the following questions: Do higher ACE levels really result in higher Ang II levels? Is ACE the only converting enzyme in humans? Does ACE inhibition affect ACE expression? Why does ACE have 2 catalytically active domains? What is the relevance of ACE inhibitor-induced signaling through membrane-bound ACE? The review ends with the proposal that ACE phenotyping may prove to be a better first step toward personalized medicine for ACE inhibitors than ACE genotyping. Moreover, given the equieffectiveness of ACE inhibitors and Ang II type 1 (AT_1) receptor blockers, such phenotyping might also be of use to determine the response to AT_1 receptor blockers.

2. ACE variation and Ang II generation

Ang II generation depends on renin, angiotensinogen, and ACE. Renin cleaves angiotensinogen to generate Ang I, and Ang I is subsequently converted to Ang II by ACE. The renin–Ang system is a feedback-regulated system, and compensatory mechanisms will rapidly neutralize alterations of one of the components. For instance, Ang II inhibits renin release; thus, a rise in Ang II will immediately be counteracted by a reduction in renin release.

Circulating ACE levels, although stable within 1 healthy individual (Alhenc-Gelas et al., 1991), differ up to ≈5–10-fold between individuals (Fig. 1). The ACE I/D polymorphism was originally proposed to account for 47% of the total phenotypic variance of circulating ACE (Rigat et al., 1990). More recent investigations suggest that this percentage is much lower (Tiret et al., 1992; Danilov et al., 1996; Rossi et al., 1999), possibly even close to 10% (Rice et al., 2006). Thus, it is now estimated that <20% of ACE variability can be accounted for the I/D polymorphism.

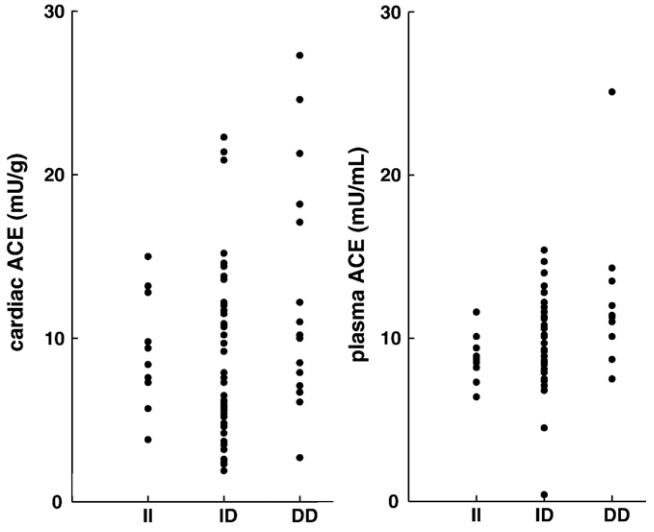

Fig. 1. ACE concentration in human cardiac tissue (left panel) and blood plasma (right panel) for individuals with the II, ID, and DD genotypes, respectively. Data taken from Danser et al. (1995) and Osterop et al. (1998). According to these data, the I/D polymorphism accounts for 22% and 31%, respectively, of the ACE variation.

The majority of ACE is expressed on the surface of (endothelial) cells. Circulating (extracellular) ACE is derived from ACE-expressing cells by proteolytic cleavage at the juxtamembrane stalk region (Wei et al., 1991b). An unidentified membrane-bound secretase catalyzes the cleavage/secretion process (Parkin et al., 2004). This process is greatly enhanced in subjects with a point mutation in the stalk region (Kramers et al., 2001). As a consequence, subjects with this mutation display serum ACE levels exceeding 4 times the upper limit of normal. Yet the amount of cell-associated ACE in these subjects was unaltered, and they exhibited no clinical abnormalities nor elevated circulating Ang II levels. This is in full agreement with the idea that the main, if not the only, site of Ang II generation is the cell surface (i.e., that Ang II generation involves "tissue ACE" rather than circulating ACE; Dzau, 1988; Danser et al., 1992a,1992 b; Admiraal et al., 1993; Neri Serneri et al., 1996).

ACE I/D polymorphism affects tissue ACE to approximately the same degree as circulating ACE (Danser et al., 1995; Mizuiri et al., 2001; Fig. 1); thus, subjects with 1 or 2 D alleles will respectively have 30% and 60% higher tissue ACE levels than subjects with the II genotype. Not surprisingly in serum, the percentage of Ang I that is metabolized by ACE to Ang II correlates directly with the concentration of ACE (Fig. 2). Theoretically, one would expect that a 30–60% rise in ACE in vivo results in a 30–60% increase in Ang II formation. Indeed, *ACE* gene titration studies in mice fully confirm this concept: changes in ACE were effectively compensated by renin feedback (Takahashi et al., 2003; Alexiou et al., 2005). Accordingly