Is Dipeptidylpeptidase IV the Missing Link in Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema?

Eric Grouzmann, Thierry Buclin

Approximately 40 million people worldwide are currently treated with angiotensin-converting enzyme (ACE) inhibitors (ACEIs) for hypertension, congestive heart failure, coronary diseases, and diabetic nephropathy. The primary mechanism of action of ACEIs is blocking of the renin angiotensin system by inhibiting the conversion of angiotensin I to the vasoconstrictor angiotensin II. Few serious adverse events specific to ACE inhibition were initially reported, because they are actually rare. However, ≤0.68 of every 100 patients seem to experience angioedema with ACEI, sometimes months and even years after the start of medication.[1] The pathophysiology of ACEI-induced angioedema is presently thought to result from the role of ACE in the degradation of other peptides including bradykinin (BK) and substance P (SP).[2] These proinflammatory peptides are released by sensory nerves during inflammation.[3] Both peptides elicit plasma exudation from postcapillary venules, leading to interstitial edema and affecting tissue function.[3]

What Do We Know About BK and SP Degradation?

The metabolism of BK and SP by proteases is redundant, with several enzymes available to terminate their biological action. Both ACE and neutral endopeptidase (NEP) play major roles in inactivating BK and SP.[2] BK is also processed by aminopeptidase P, but a contribution of this peptidase in angioedema during ACEI is unlikely, despite a downregulation of its activity reported in some cases.[4] BK is also a substrate of kininase I, capable of cleaving the last residue off its C-terminal end to generate des-Arg^9-BK, a fragment without affinity for the B2 receptor but an agonist on the inducible B1 receptor expressed during inflammation.[4] On the other hand, SP is sequentially truncated by dipeptidylpeptidase IV (DPPIV) into SP3-11 and then SP5-11, which is 1000-fold less potent than the native peptide.[5] However, the physiological importance of DPPIV in the inactivation of SP and the role of a reduction of DPPIV activity in ACEI-induced angioedema had not been evaluated before the article by Byrd et al,[6] published in this issue of *Hypertension*.

ACE Inhibition and Angioedema

The incidence of ACEI-induced angioedema ranges from 0.1% in patients treated with short-acting drugs such as captopril to 0.68% in patients treated with more potent inhibitors such as enalapril, as reported in the Omapatrilat Cardiovascular Treatment Versus Enalapril Study.[7] Recently, dual vasopeptidase inhibition seemed very promising by blocking NEP, thereby increasing circulating concentrations of natriuretic peptides, and ACE, thus hampering angiotensin II generation. Omapatrilat was the first dual inhibitor in this new class of drugs that was highly active in hypertension.[7] Unfortunately, vasopeptidase inhibitors caused up to a 2.1% rate of angioedema after a short period of treatment. Interestingly, smoking was associated with an even higher 3.9% occurrence of angioedema in omapatrilat-treated patients.[7] In contrast, diabetic patients seem less prone to develop angioedema during ACE or ACE/NEP blockade.[5] In this context, the new drug application for omapatrilat has been withdrawn pending safety reassessment. The increased rate of angioedema induced by dual ACE/NEP inhibitors strengthens the hypothesis that BK and/or SP are involved in the pathophysiology of this distressing condition. Indeed, under omapatrilat treatment, BK may still be degraded by aminopeptidase P and kininase I, whereas DPPIV remains the sole protease capable to degrade SP.

In their article, Byrd et al[6] found that BK half-life correlated inversely with ACE activity, whether the patients received ACEIs. This important finding confirms that BK concentrations are strongly under the control of ACE expression. To corroborate their idea that BK plays a less important role in the pathogenesis of ACEI-induced angioedema than expected, the authors report endogenous BK concentrations comparable in sera collected from ACEI-induced angioedema and ACEI-treated patients without angioedema. However, these observations are in contradiction with those of Pellacani et al,[8] who assessed that ACEI alone increased plasma kinin concentrations and that plasma BK concentrations raised >10-fold during acute attacks of angioedema associated with an ACEI.[9] Indeed, BK concentrations in tissues may better reflect the actual pathophysiological events linked with angioedema than circulating BK concentrations, because BK has a plasma half-life of 15 to 30 seconds because of its extremely rapid degradation by peptidases. Other than this, the fact that both aminopeptidase P and APN activities and plasma BK or des-Arg^9-BK half-lives are similar attenuates

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(*Hypertension*. 2008;51:45-47.)

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Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.107.101329

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the role of circulating BK in angioedema induced by ACEIs. A clinical trial has been launched to evaluate the effectiveness of icatibant (also known as HOE-140), a specific antagonist on type 2 BK receptors, at reducing symptoms in patients developing ACEI-associated angioedema.[10]

DPPIV Activity and ACEI-Induced Angioedema

Byrd et al[6] hypothesized that an additional peptidase was involved in ACEI-induced angioedema. They actually found that plasma DPPIV activity was decreased in patients with a history of ACEI-induced angioedema compared with control subjects and that ACE and DPPIV activities were not correlated in those patients. DPPIV activities reduced in smokers and increased in diabetics have already been reported.[11,12] This correlates with observations in patients receiving ACEI and raises the question of whether the higher frequency of smoking subjects developing ACEI-induced angioedema may be a consequence of DPPIV decrease. Thus, the role of SP may be more prominent than suspected previously. Ex vivo studies performed by Byrd et al[6] on sera demonstrate that the degradation half-life of SP correlates inversely with the DPPIV antigen under ACEI. The importance of DPPIV to terminate the action of SP has also been emphasized by studies conducted in patients suffering from chronic rhinosinusitis. DPPIV activity was found inversely correlated with inflammation in nasal biopsy tissues collected from such patients.[5] Moreover, in an animal trial, the administration of recombinant DPPIV attenuated considerably the proinflammatory action of SP or of histamine and capsaicin that causes the release of SP.[5] Therefore, DPPIV may be considered as an important rescue enzyme to attenuate the proinflammatory effects of SP in a way similar to the role of NEP regarding BK. Because both SP and BK may be involved in cascade in the paroxysmal development of angioedema, it would not be surprising that conditions enhancing any of these 2 proinflammatory signals increase the risk for angioedema. Clinical trials investigating SP antagonists (also termed "NK_1 antagonists," such as aprepitant commercialized as an antiemetic) for the treatment of ACEI-associated angioedema have not yet been performed to our knowledge. The results of Byrd et al[6] clearly call for such investigations.

DPPIV Inhibitors

A new therapeutic area for the treatment of type 2 diabetes seems very promising with the DPPIV enzyme inhibitors that prevent glucagon-like peptide 1 degradation and thereby increase the incretin effect of this peptide. The first oral DPPIV inhibitor launched in the US market was sitaglitpin (MK-0431, Januvia) and has recently been approved by the European Agency for the Evaluation of Medicinal Products. Vildagliptin (LAF237, Galvus), saxagliptin (BMS-477118), and alogliptin (Syr-322, Takeda) have been filed for approval or are in advanced phase III development and are competing to conquer market shares of this new oral treatment modality for diabetes.[13] Data comparing the clinical efficacy and safety profiles of various compounds have been reported by Amori et al[14] in a recent meta-analysis, including 13 controlled double-blind trials of ≥12-week duration in 4780 subjects. They found an increased risk of nasopharyngitis, urinary tract infection, and headache.[14] However, no cases of angioedema were reported in this meta-analysis, but a history of angioedema represented a notable exclusion criterion in all of the trials. The Food and Drug Administration adverse event reporting system mentions 10 cases of angioedema during the first 8 months of postmarketing sitagliptin exposure. These results seem reassuring in comparison with the data submitted in the new drug application for omapatrilat, showing 44 instances of angioedema among ≈6000 patients.[15] Nevertheless, elderly patients with diabetes often have renal complications, making them candidates for ACEI therapy. The implications of the study by Byrd et al[6] may, thus, put them at higher risk of developing angioedema if their antidiabetic treatment includes a DPPIV inhibitor.

Perspectives and Remaining Questions

The metabolism of peptides by peptidases represents an important and still poorly studied issue in the assessment of their clinical properties. SP and BK functions are mainly regulated by ACE, NEP, and DPPIV. The merits of the study by Byrd et al[6] are that it draws attention on the high variability in DPPIV activity and on its impact on the metabolism of SP, which becomes critical during ACE inhibition.

We know that suppression of ACE activity causes an increase in the incidence of angioedema and that additional suppression of NEP activity further increases this risk. What will be the consequence of DPPIV pharmacological blockade for the pathogenesis of angioedema in patients receiving ACEIs? It is too early to answer the question, because angioedema is rare and may appear up to years after the onset of drug treatment. The simultaneous inhibition of ACE and DPPIV should, however, be prescribed with caution, because no available data suggest that such a combination is less hazardous than ACE/NEP dual inhibition regarding its impact on BK and SP degradation. As mentioned by the European Agency for the Evaluation of Medicinal Products, "conclusive studies to determine whether these in vitro substrates are regulated by DPPIV in vivo have not occurred largely." Therefore, although in vitro experiments show a wide variety of DPPIV substrates, the biological relevance in vivo remains uncertain.[16] Postmarketing monitoring will hopefully help to resolve this issue. Specific investigations might also be performed to compare the respective importance of NEP and DPPIV in degrading SP. In the meantime, the administration of short-acting DPPIV inhibitors may be safer with regard to the risk of angioedema, even perhaps in the absence of ACEI comedication. Indeed, glucagon-like peptide 1 is released during meals and needs to be protected from degradation by DPPIV for relatively short periods of time to maintain its glucoincretin activity.

Source of Funding

This correspondence is partially based on studies funded by the Swiss National Science Foundation No. 3100AO-101999.

Disclosures

E.G. has received an honorarium from Phenomix corporation. T.B. reports no conflicts.

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Hypertension
Journal of the American Heart Association

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Hypertension. 2008;51:45-47; originally published online November 19, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.101329
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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