The Medicinal Chemistry of Enalapril and its Effect of Cough and Angioedema

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Abstract

Nearly two-thirds of American adults are on medications to manage hypertension.[1] The focus of this project is the Angiotensin Converting Enzyme Inhibitor (ACEI), enalapril. Some patients experience "ACE cough" and angioedema after taking enalapril. These adverse effects of enalapril are most likely due to the buildup of bradykinin via inhibition of the kinin-kallikrein system (KKS).[2] Accumulation of bradykinin and its binding to bradykinin 2 (BK2) and neurokinin 1 (NK1) receptors causes vasodilation and edema in surrounding tissues, which may explain angioedema.[3] By identifying genetic predispositions and genotyping, it may be possible to accurately pinpoint patients susceptible to these adverse events in the future before initiating an ACEI like enalapril.

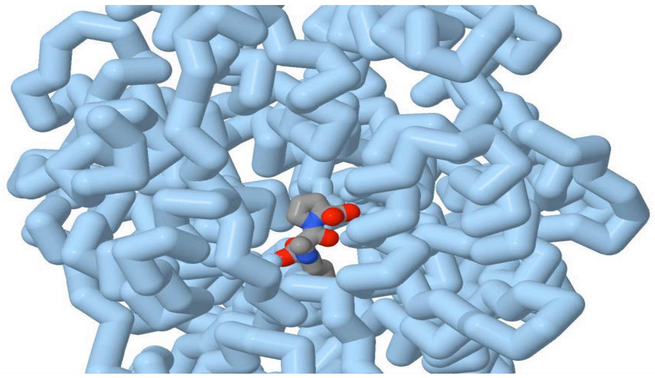

Figure 1: Enalapril inside the ACE. Rendered from 1UZE.pdb

Introduction

Enalapril was created via a rational drug design approach based on the inhibition of thermolysin, a zinc protease.[4] It is a prodrug metabolized to its active form, enalaprilat, via an esterase enzyme. Its antihypertensive mechanism of action revolves around the inhibition of ACE, a zinc metallopeptidase found throughout the body. It binds to ACE by mimicking the transition state of angiotensin I in the renin-angiotensin-aldosterone system (RAAS), with the aid of a zinc ion for stability.[5] The simultaneous off-target inhibition of the KKS is responsible for its adverse effects. This inhibits the breakdown of bradykinin, which potentiates vasodilatory effects of blood vessels.[2] This can lead to a dry, hacking cough and angioedema, a localized swelling of deeper layers of the dermis in the lips, tongue, cheeks and pharynx. KT, a 72 year-old overweight African American male, was recently started on enalapril for his hypertension and experienced both "ACE cough" and angioedema.

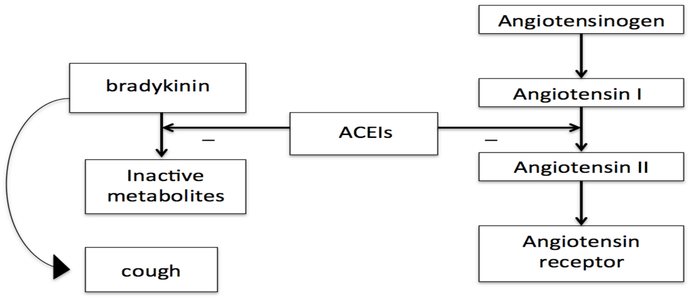

Figure 2: ACE Inhibitor Pathway. Medscape.com

Molecular Story

Enalaprilat is a dicarboxylate-containing ACEI that binds deep inside the ACE.[6] The most important bond of enalaprilat is its interaction with zinc at ACE[5] (shown alone in Figure 3, and with enalaprilat in Figure 5). A nucleophile attacks the carbonyl group on enalaprilat, which pushes electrons out and forms a stable tetrahedral structure. Zinc helps to stabilize this transition state by interacting with the oxygen molecules on the non-proline carboxylic acid.[6]

The proline moiety (bottom right of Figure 4) increases the drug's potency because it makes the molecule a dicarboxylate, which increases affinity to ACE. The phenylethyl group on the bottom left makes the molecule hydrophobic, increasing the potency of the drug in the active site.[7]

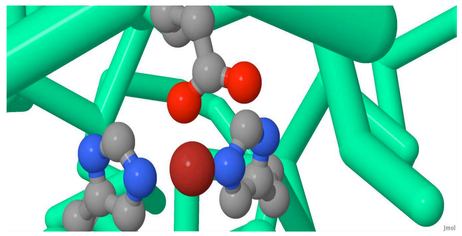

Figure 3: The ACE zinc atom in dark red, surrounded by two histidines and a glutamate, all of which use hydrogen bonding to help stabilize enalaprilat in the active site. Rendered from 1O8A.pdb

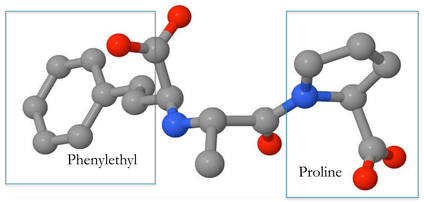

Figure 4: Enalaprilat. Rendered from 1UZE.pdb

Enalaprilat's ability to mimic the transition state of angiotensin I hydrolysis is thought to be the reason for its strong binding ability. The secondary amine, the carboxylic acid, and phenylethyl groups all contribute to the overall binding of the compound to ACE[7]:

- The secondary amine is located at the same position as the labile amide nitrogen
- The ionized carboxylic acid can form an ionic bond with the zinc atom
- The phenylethyl group mimics the hydrophobic side chain of the Phe amino acid, which is present in angiotensin I

Ala354, Glu384, His353, and Tyr amino acid residues also help to stabilize to enalaprilat via electrostatic interactions in the ACE binding site.[6] A water molecule also binds to Glu384, which results in a polarization between the glutamate carboxylate group and the zinc ion.[4] The zinc can then attack the carbonyl group on enalaprilat, forming the tetrahedral intermediate.

Hydrogen bonding interactions between Ala354 and the amide on His353 help to stabilize the structure. Chloride ions aid in stabilizing the C-domain active site by creating electrostatic interactions with the tyrosine and arginine amino acids surrounding them.[4]

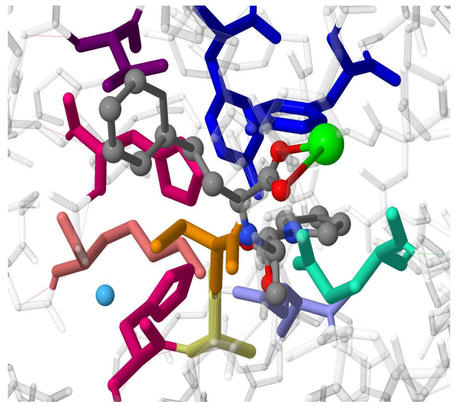

Figure 5: Enalaprilat (grey) in the binding pocket of ACE along with the important amino acid interactions. The most important interaction is with the Zinc atom. Rendered from 1UZE.pdb

	ALA 354 = YELLOW		LYS 511 = SALMON
	CL 703 = LIGHT BLUE		SER 355 = ORANGE
	GLN 281 = PERIWINKLE PURPLE		TYR 520 & 523 = DARK BLUE
	GLU 384 = TURQUOISE		VAL 518 = DARK PURPLE
	HIS 315 & 353 = MAGENTA		ZN 701 = LIME GREEN

Further Drug Design

As a prodrug, enalapril must bind to two proteins in order to elicit its effect. The oral bioavailability of enalapril is currently around 60%, so there remains room for improvement. One proposed mechanism to increase bioavailability would be to increase affinity for the carboxylesterase that cleaves enalapril. Currently, enalapril only has one ester that is hydrolyzed in the active site of carboxylesterase. By increasing the number of esters, we can increase affinity for enalapril in the active site. One place that we can add an additional ester is on the proline carboxylic acid (marked by star in Figure 6). This addition would not only increase affinity, but also decrease polarity, making the drug more easily transported across the intestinal lumen. An addition of electron withdrawing groups such as a hydroxyl, a halogen, or an aryl to the R groups attached to the esters would also allow them to hydrolyze more readily. Because these groups are sometimes polar, it would be necessary to test absorption to ensure the drug reaches the carboxylesterase enzyme. We believe that these molecular changes may lead to an increase in bioavailability, thus improving patient outcomes.

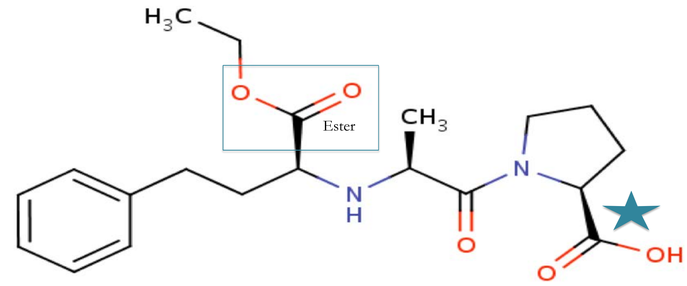

Figure 6: Enalapril

Summary

The vasodilatory effect of bradykinin is manifested through binding of BK2 receptor, a G-protein coupled receptor associated with isolated hypertension. It has been speculated that polymorphisms in the genes coding for BK2 receptors could explain why certain people are more susceptible to adverse effects like angioedema when taking an ACEI or non-steroidal anti-inflammatory drug (NSAID). It is also known that certain factors increase the likelihood of angioedema, including advanced age, African descent, and being overweight.[8] KT had all of these risk factors. In the future, it might be likely that people with genetic risk factors could be screened for relevant BK2 polymorphisms. Another option for these patients could be the introduction of bradykinin inhibitors, such as icatibant, to treat acute angioedema attacks.

References

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