**ABSTRACT**

Angiotensin-converting enzyme (ACE) is a membrane-anchored carboxypeptidase enzyme that cleaves both angiotensin I and bradykinin. Cleavage of angiotensin I yields angiotensin II, and ultimately results in potent vasoconstriction and high blood pressure. Bradykinin acts as a vasodilator, and cleavage of bradykinin blocks this vasodilation, and also leads to a buildup of bradykinin in the tissues. The ACE inhibitor lisinopril binds irreversibly to the active site of ACE, and prevents cleavage of both angiotensin I and bradykinin. Lisinopril successfully reduces blood pressure by blocking the conversion of angiotensin I into angiotensin II. However, the buildup of bradykinin that occurs leads to the development of a dry cough in about 10% of users.

**MOLECULAR STORY**

- There are 2 isoforms of ACE: TACE and sACE.
- The larger, somatic isoform, sACE, is a polypeptide chain 1,277 amino acids long.
- sACE is found on the surface of vascular endothelial, epithelial, and neuroepithelial cells, with concentrations in pulmonary and renal endothelial.
- The larger sACE is comprised of two domains, the N-terminus and the C-terminus; within each domain is a zinc binding site.
- The active site contains several water molecules important for substrate binding.
- Within the active site, His-Glu-x-x-His hold zinc in place.

**HISTORICAL PERSPECTIVE OF DRUG DEVELOPMENT**

- ACE plays a dual role in stimulating vasoconstriction in the body by:
  - Catalyzing the cleavage of angiotensin I to angiotensin II, a potent vasoconstrictor
  - Cleaving bradykinin, a vasodilator, into inactive small peptides
- Blocking ACE would serve to reduce vasoconstriction and thereby reduce hypertension
- Exact structure of ACE was unknown but researchers knew it was similar to that of carboxypeptidase A, which binds substrate by:
  - Binding negative carboxylic terminal with a positive Arg145
  - A hydrophobic pocket that stabilizes an aromatic or non-polar residue on the C-terminus
  - A zinc moiety that stabilizes transition state
- Using the structure of carboxypeptidase A as a guide, researchers developed the first pharmacophore to target ACE, succinyl-L-proline.

**CASE STUDY**

Patient presents to the pharmacy with a dry cough keeping him up at night.

**Medication History:** Lisinopril for high blood pressure

OTC supplements

After reviewing the medication history, the pharmacist explains that dry cough is a side effect of lisinopril, resulting from the structure of lisinopril binding to the protein target. The pharmacist also explains that potassium should be avoided because of concern with the common side effect of high potassium levels in the body associated with taking lisinopril.

**FUTURE WORK**

- Explore molecular interactions between bradykinin and the receptors on which it acts to produce dry cough
- Identify genetic markers that determine susceptibility to dry cough
- Reformulate lisinopril to prevent buildup of bradykinin

**SUMMARY**

- Lisinopril uses many moieties that bind to ACE, some of which include hydrogen bonds and Van der Waals interactions. Zinc also plays a key role in lisinopril binding.
- Build-up of bradykinin causes dry cough in up to 10% of patients.
- Bradykinin may stimulate proinflammatory responses in the lungs.
- May also increase lung prostaglandin levels.

**REFERENCES**