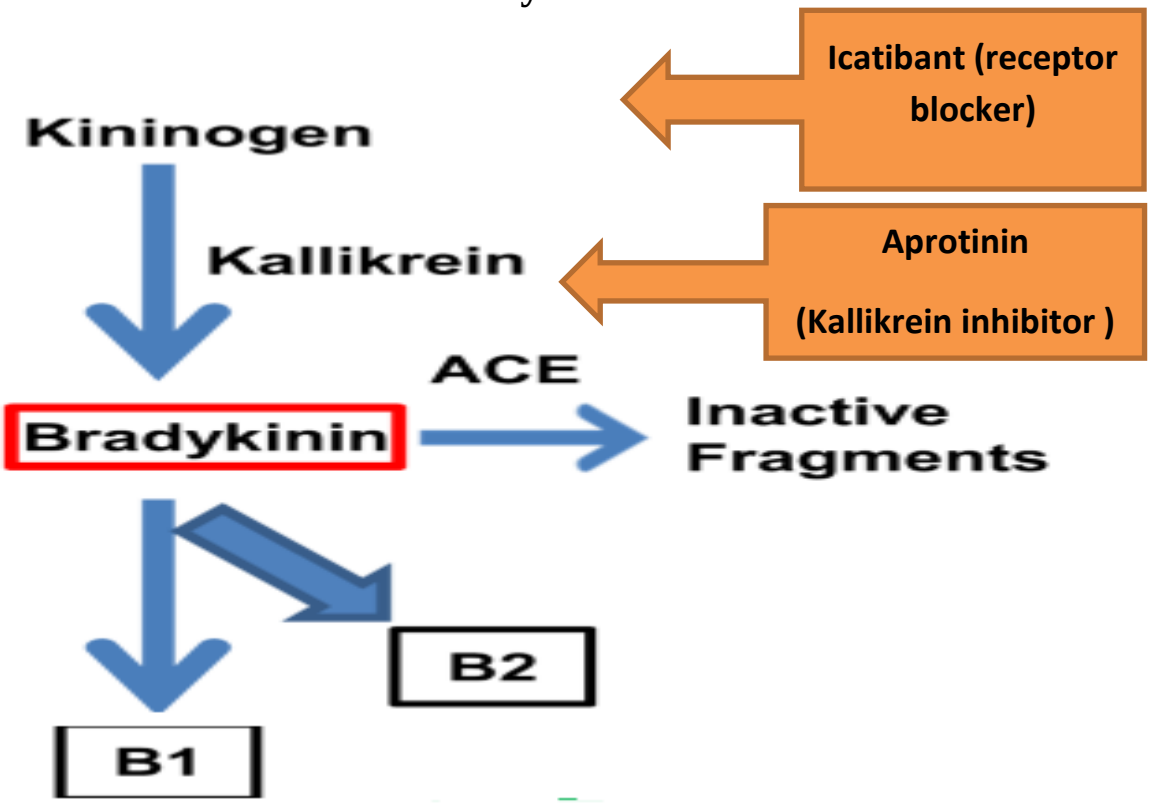
Lecture title: Kinins

Lecturer Affiliation: College of Veterinary Medicine

Summary:

The kinins: bradykinin and kallidin



Bradykinin is a potent vasodilator.

a. Two enzymes (one from plasma and the other from tissue) called kallikreins catalyze the formation of two polypeptides: **bradykinin**, and **kallidin**

b. kininogen serve as the precursor for the synthesis of the two peptides.

c. Proteases inactivate both bradykinin and kallidin. The major peptidase is ACE.

ACE inhibitors prolong the duration of action of both peptides and this contributes to their blood pressure lowering activity as well as bronchoconstriction.

Mechanism of action. **Bradykinin acts on bradykinin-1 (BK1) and bradykinin-2 (BK2)**

receptors.

Pharmacologic effects:

Blood vessels	1-Kinins on artery cause vasodilation which result from ▪ Direct inhibitory effect on vascular smooth muscle ▪ Release of nitric oxide ▪ Release of vasodilator PG 2-Kinin on veins cause vasoconstriction which result from ▪ Direct stimulatory effect on venous smooth muscle ▪ Release of vasoconstrictor PG 3- kinins cause increase capillary permeability ------oedema formation
Role in inflammation	Four classic symptoms ▪ Redness ▪ Local heat ▪ Swelling

	▪ Pain
Sensory nerve	Potent pain inducer

Drugs that on kinin-kallikrein system

1. The synthesis of kinins can be **stimulated** by ACE inhibitors
2. The synthesis of kinin can be **inhibited** by:

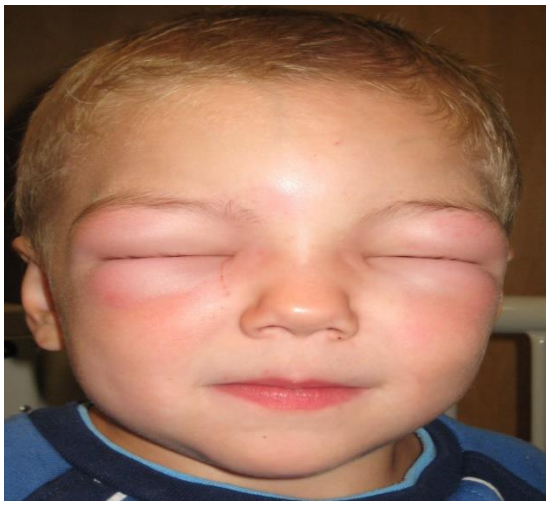
Kallikrein inhibitors: Aprotinin

Kinins receptor antagonist: icatibant

Icatibant

Mechanism of action: selective antagonism of B2 receptors

Clinical use: Treat the symptom of acute attacks of hereditary angioedema in patients with C1-esterase-inhibitor deficiency.



Endothelin:

It's an inflammatory mediator synthesized in the endothelium of blood vessels.

Types of Endothelin:

1.Endothelin 1

2.Endothelin 2

3.Endothelin 3

Pharmacological effects:

It has the same effects like previous autacoids plus sever vasoconstriction.

Receptors:

ET_A___ vasoconstriction

ET_B

Note: endothelin appears to be the causes of 95% of hypertension especially primary pulmonary hypertension (pulmonary artery). _____women.

Drugs

1. **Bosentan**: its non-selective ET receptor blocker.

2. **Ambrisentan**: its selective ET_A receptor blocker.

Uses: Pulmonary hypertension

Note: there are other drugs treat pulmonary hypertension, like sildenafil and prostacyclin.

Purines :

Nucleotides (Adenosine) and Nucleotides (ADP and ATP) are extracellular chemical mediators. ATP is stored in vesicles and released by exocytosis or through tissue damage.

Released ATP is rapidly converted to ADP and adenosine. The three purines act on three main families of purines receptors and exert a wide range of functions

Receptors	Endogenous ligand	Important sites	Pharmacological effect
A	Adenosine	Lung	Bronchoconstriction
		Conducting of the heart	Inhibit conduction
		Mast cells	Promote mediator release
		CNS	Complex inhibitory function
P2Y	ATP ADP	Platelets	Promote aggregation
		CNS	Complex neuropsychiatric effects
P2X	ATP		

Drugs act on purines receptors:

1. Adenosine:

It is a short acting purine **A receptor agonist**. It is given by i.v. route to inhibit AV conduction and converts supraventricular tachycardia to the sinus rhythm in non-asthmatic patients.

2. Methylxanthines:

Caffeine, aminophylline and theophylline are purine **A receptor antagonists**. They are used as **bronchodilators** and **CNS stimulants.**

3. Clopidogrel:

Clopidogrel is a platelet inhibitor that irreversibly binds to **P2Y** receptors on platelets. This binding prevents ADP binding to P2Y receptors and platelet aggregation.