Kinin system

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Introduction

- The kallikrein kinin system is complex with several bioactive peptides that are formed in vascular smooth muscles as well as in the heart.

- The main constituents of this system are enzymes such as kallikreins, protein precursors which are kininogens and the potent vasoactive peptide kinin.

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- Kallikreins are serine proteases found in glandular cell, neutrophils and biological fluids.
- They are divided into two groups: tissue kallikrein and plasma kallikrein.
- Both differ in molecular weight, amino acid composition, type of kinin released and the functions.
- Kinin is the vasoactive component in this system which is released through the actions of kallikreins on kininogens.

In humans, kinin refers to the bradykinin (BK), kallidinin

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- Kinins, bradykinin and kallidinin or lysylbradykinin are important mediators of inflammatory responses.
- They are librated from precursor molecule kininogen by various proteases known as kininogenases.
- There are three types of kininogens; high (HMW) and low (LMW) molecular weight kininogen and T-kininogen.
- These molecules are synthesized by hepatocytes and released into plasma. They play a role in releasing kinin.

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- Bradykinin (BK) and kallidin or lysylbradykinin are two peptides referred as kinins.
- BK is a nonapeptide usually found in all secretions of the body such as urine, saliva and sweat.
- Also it is found in several tissues such as heart, vasculature, blood, kidney, colon and liver.
- BK is produced by plasma kallikrein and also it can be produced from kallidin by several aminopeptidases through cleavage of amino terminal lysine.
- On the other hand, kallidin is a decapeptide found in the heart, urine and circulation .
- Kallidin is produced by tissue kallikrein and it is rapidly converted to BK by the enzyme aminopeptidase N.

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Formation of bradykinin (BK)

- BK is a vasoactive peptide that is formed during inflammatory response from either HMW or LMW kininogen by action of enzyme called kallikreins.
- Three proteins are involved in BK formation; Hageman factor, prekallikrein and HMW kininogen.
- Plasma prekallikrein circulates in a complex form with HMW kininogen.
- This complex together with Hageman factor binds to negatively charged surface including basement membrane components and proteoglycans such as heparin.

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- Once they are exposed by tissue damage, prekallikrein is rapidly converted to plasma kallikrein by the enzyme prolylcarboxypeptidase.

- Kallikreins are the enzymes that break down kininogen (the precursors of kinin).

- There are two forms of kallikreins; plasma kallikrein which converts HMW kininogen to BK and tissue kallikrein which converts LMW kininogen to lysyl-bradykinin (kallidin) which is rapidly converted to BK by the enzyme aminopeptidase N.

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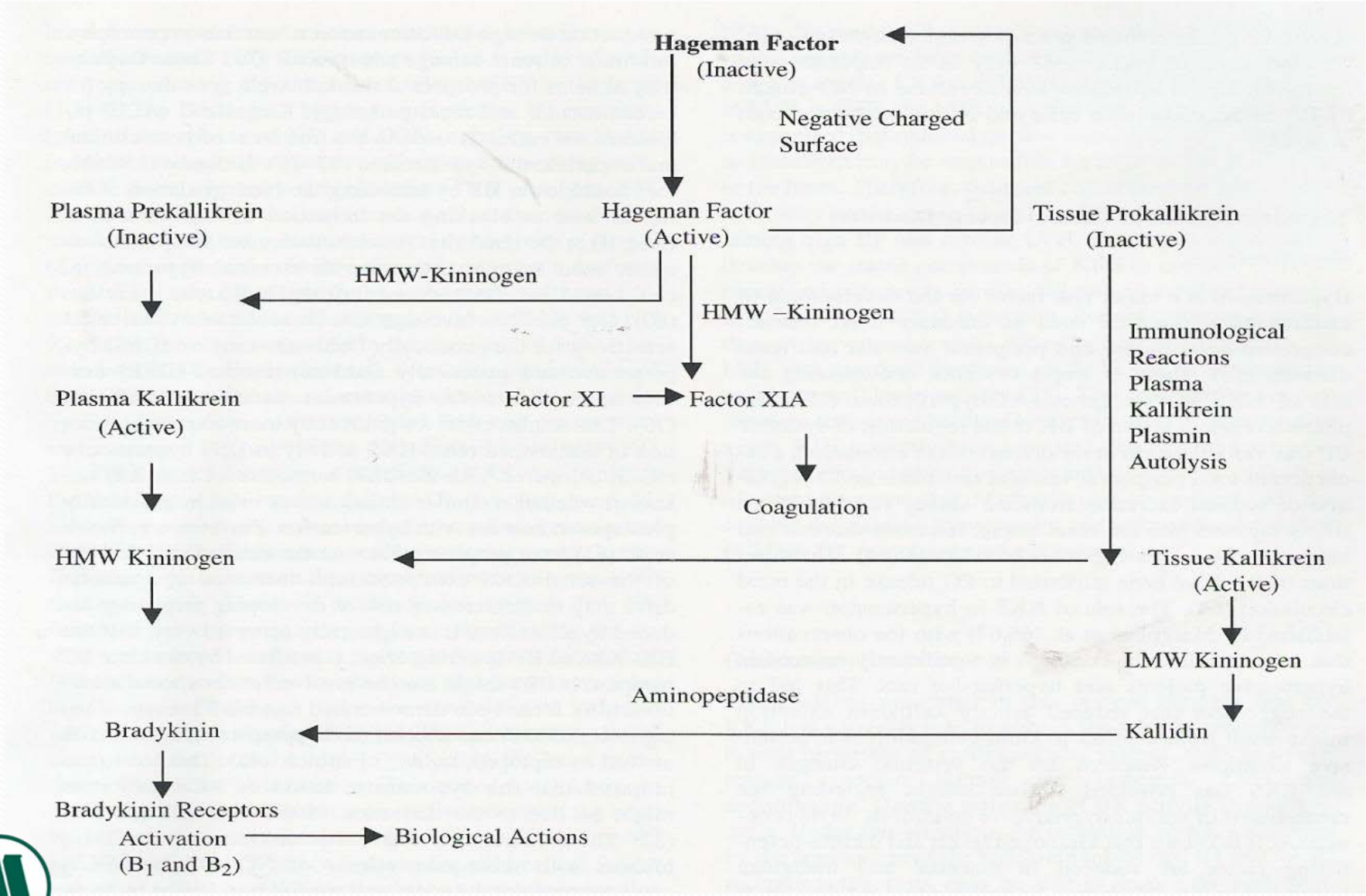
Hageman Factor
(Inactive)
Negative Charged
Surface
Plasma Prekallikrein
(Inactive)
Hageman Factor
(Active)
Tissue Prokallikrein
(Inactive)
HMW-Kininogen
HMW –Kininogen
Immunological
Reactions
Plasma
Kallikrein
Plasmin
Autolysis
Plasma Kallikrein
(Active)
Factor XI
Factor XIA
Coagulation
HMW Kininogen
Tissue Kallikrein
(Active)
LMW Kininogen
Aminopeptidase
Bradykinin
Kallidin
Bradykinin Receptors
Activation
(B1 and B2)
Biological Actions

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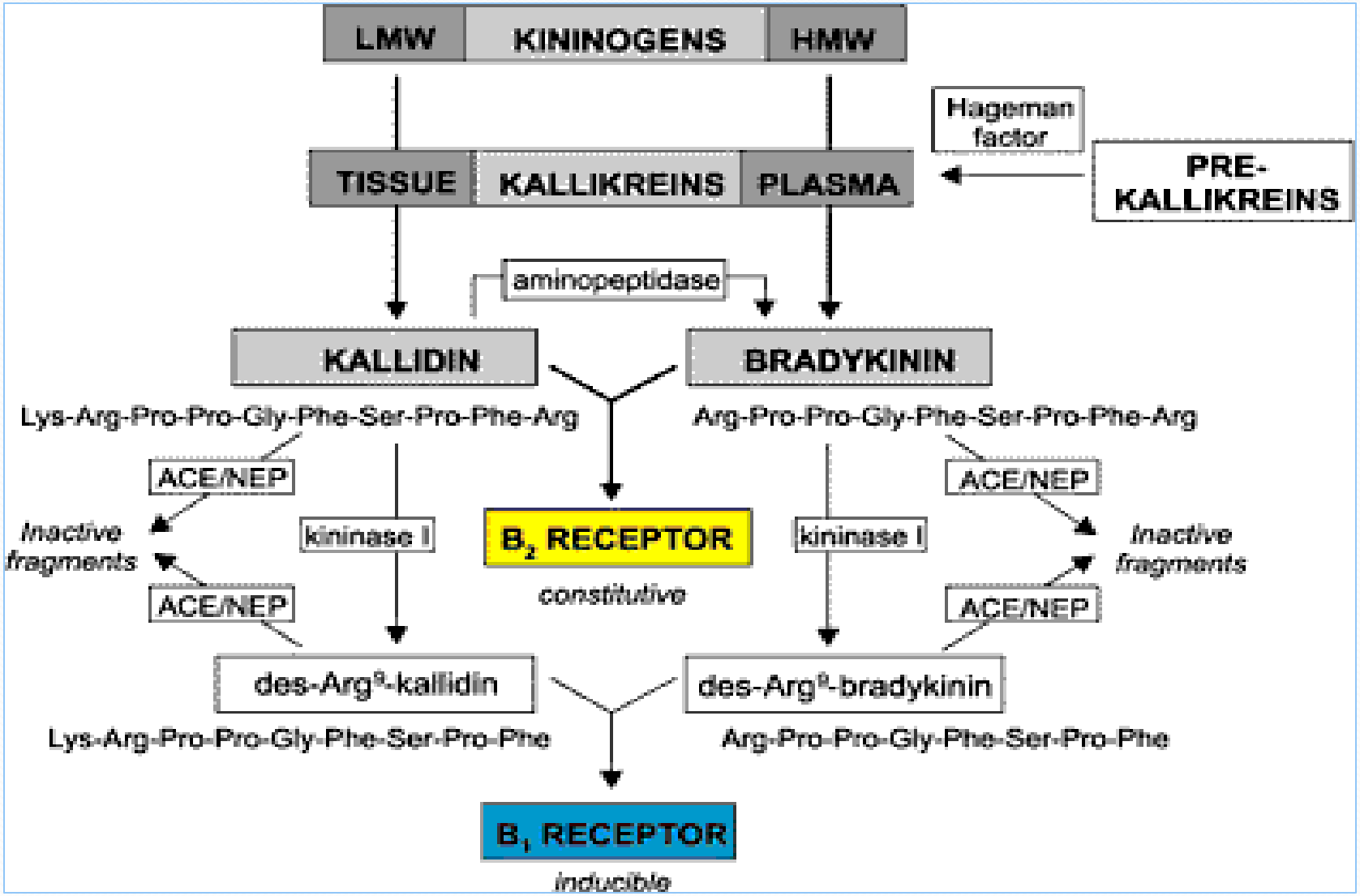
LMW
KININOGENS
HMW
Hagemen factor
PRE-KALLIKREINS
TISSUE
KALLIKREINS
PLASMA
aminopeptidase
KALLIDIN
BRADYKININ
Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
ACE/NEP
ACE/NEP
Inactive fragments
kininase I
B2 RECEPTOR
constitutive
kininase I
Inactive fragments
ACE/NEP
ACE/NEP
des-Arg9-kallidin
des-Arg9-bradykinin
Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe
Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe
B1 RECEPTOR
inducible

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The kinin interaction System

All the following physiological processes are activated in a cascade-like manner:

- Complement
- Kinin generation
- Blood coagulation
- Fibrinolytic system

They interact with one another and with various cell membrane proteins.

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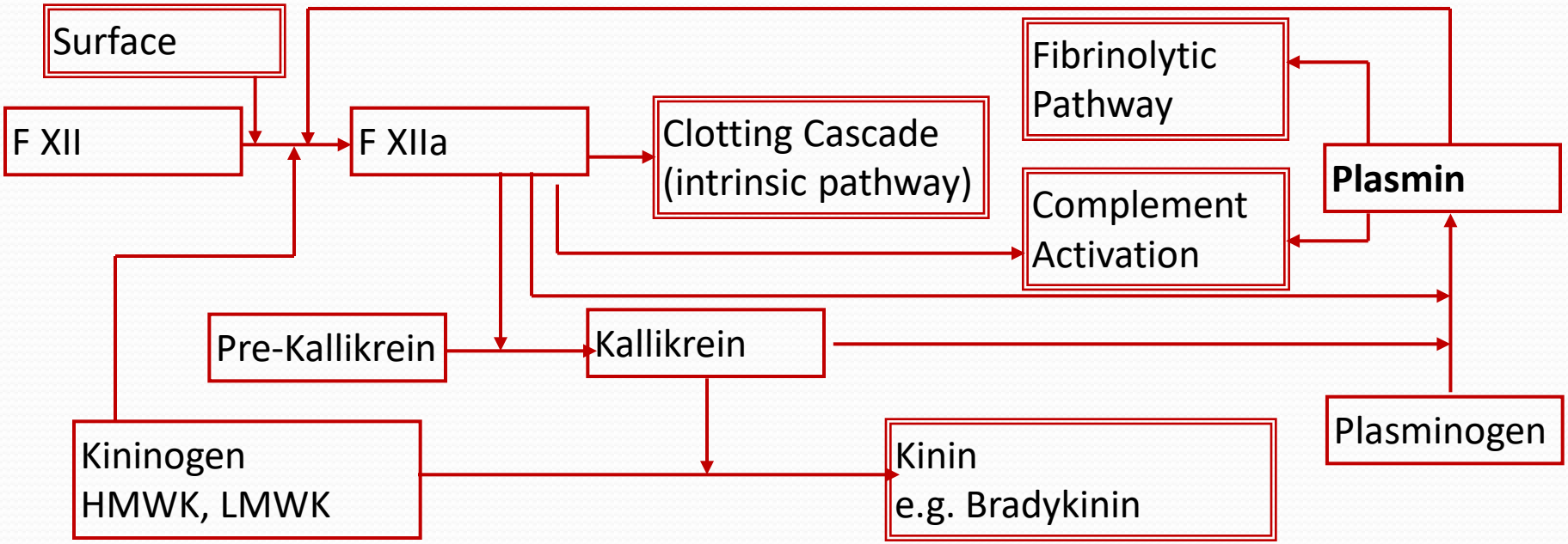
The kinin interaction System



Effects

- vascular smooth muscle relaxation
- Increased permeability of blood vessels → Oedema
- Pain
- Interaction with clotting cascade
- Interaction with fibrinolytic cascade
- Interaction with complement cascade

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Degradation of bradykinin

- Degradation of BK peptides are done by enzymes called kininases.
- Kininases cleave BK at either their aminoterminal or carboxyterminal end.
- Enzymes that cleave at aminoterminal are: aminopeptidase M (APM), which can degrade kallidin into BK3, and aminopeptidase P (APP), which cleaves the first amino acid of BK to give BK-(2-9).
- On the other hand, there are four major enzymes responsible for carboxyterminal degradation of BK, which are:
- angiotensin converting enzyme ACE, carboxypeptidase N and M (CPN, CPM) and neutral endopeptidase NEP.

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Receptors for bradykinin

- There are two subtypes of BK receptors; B1 and B2 receptors.

- These two receptors have similar structures with seven transmembrane domain coupled to G-protein. Also, B3 and B4 receptors have been proposed as additional receptors.

- B1 & B2 receptors that present on the membrane of many cell types including:
- Vessel endothelial cells
- Smooth muscle
- Nerve cells
- Synovial lining cells
- Bradykinin interaction with receptor causes the release of a variety of cytokines that alter cellular function.

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Physiological effects of B1 receptors

- BK B1 receptors have role in different systems.
- In the circulation B1 receptors stimulation can cause vasodilatation in the vessels.
- In cardiovascular system B1 receptors have been shown to precondition the heart against ischemic events and protect the heart from arrhythmias.
- Involved in renal functions by affecting both natriuresis and glomerular filtration. Also, they involve in the pathogenesis of diabetes.

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- In inflammation, B1 receptors involve in leucocytes recruitment and in the initiation of inflammatory responses as well as in the physiology of pain.

- Finally, it has been shown that B1 receptors are mitogenic in fibrotic tissues

- B2 receptors involve in the physiology and pathophysiology of pain, inflammation and hyperalgesia.

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Pathophysiological role of bradykinin

Pain and neurology:

- Pain producing effect of BK is due to stimulation of afferent nerve terminals.
- This is caused by the presence of B2 receptors on neural elements as in nonmylinated nerve terminals, sensory ganglia and dorsal layer of the spinal cord, thus BK is both algesic and hyperalgesic.
- Although these effects are mediated mainly by B2 receptors, B1 receptors are also involved in the process of pain perception since B1 receptor agonist exacerbate the pain.

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Allergy:

- BK is involved in the pathogenesis of allergic asthma and bronchitis.
- Earlier reports indicated that injecting skin with BK may cause Lewis's triple response which is similar to that caused by histamine.
- BK either released with the air way tissue or derived from blood stream can stimulate sensory nerves to release tachykinin.
- Tachykinins cause bronchoconstriction and plasma exudation during the anaphylactic response.

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Rhinitis:

- There is a lot of evidence showing that BK is involved in the symptoms of different types of rhinitis.
- Specific binding to B2 receptors are found in the nasal turbinate of guinea pigs and man.
- Also by using a sensitive lavage method elevated BK levels have been detected in the nasal cavity of man.
- The receptors involved in these effects are mainly B2 receptors type; since selective B1 receptor agonist (des Arg9 BK) does not produce such effects.
- Moreover, the effects of BK on nasal cavity and lower airway are mediated partly by platelet activating factor (PAF).

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GI diseases

- BK receptors are involved in many gastrointestinal diseases.
- First, dumping syndrome which results as a complication of gastric surgery is characterized by flushing and hypotension with excessive release of BK and tryptophan 5-hydroxylase from the gut.
- Moreover, carcinoid syndrome results in excessive production of kallikrein and tryptophan 5-hydroxylase in enterochromaffin cells caused by intestinal tumors and hepatic metastases.

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Cardioprotective effects of bradykinin

- BK has multiple effects on cardiovascular system.
- These effects are produced through vasodilatation and plasma extravasation properties which lead to inflammation.
- Vasodilatation is mainly mediated by B2 receptor; however under inflammatory conditions B1 receptor upregulation mediates BK induced vasodilatation and hypotension.
- BK is a potent vasodilator; it acts through stimulation of endothelial cell causing release of secondary mediators which affect the vascular smooth muscle.
- These mediators are nitric oxide (NO) and prostaglandin I2 (PGI2).

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Involvement of the kinin system in the regulation of renin system

- The first recognized important link between these two systems was angiotensin-converting enzyme (ACE).
- This enzyme has the bifunctional activities of being one of the degrading peptidases (kininase II) of BK and converting the inactive 10-amino acid angiotensin I to the biologically active 8-amino acid angiotensin II.
- which induces local vasoconstriction and increases blood pressure.

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Cancer

- The role of BK receptor in human cancer has been studied, as BK can stimulate growth and increase vascular permeability of tumors.
- Also, increased generation of BK has been reported in several types of cancers.
- Cervical cancer tissue as well as cervical cancer metastatic lesions showed higher expression of both B1 and B2 receptors than normal cervical tissues.
- In contrast, prostate cancer tissue has been found to express high level of B1 receptor compared with normal prostate tissue, as B1 receptor promote cell growth and stimulate migration as well as invasion in a prostate cell line

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Hypertension

- Is a major risk factor for the development of cardiovascular diseases like coronary heart disease, congestive heart failure, peripheral vascular and renal diseases.

- It has been shown that the kallikrein kinin system exert a fine control on vascular smooth muscle tone, arterial blood pressure and play a significant cardioprotective effect.

- Moreover, BK has a vasodilator action on peripheral blood vessels and has potent diuretic and natriuretic effects that regulate sodium excretion from the kidney

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Diabetes

- Type 1 diabetes (insulin dependent diabetes mellitus) is an inflammatory autoimmune disease associated with vascular permeability changes leading to many complications.

- Recently, it was reported that BK B1 receptors were found to be up regulated in type 1 diabetes.

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