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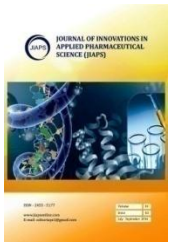

Review article

B2-R-bradykinin agonist-a novel approach in the treatment of cardiovascular diseases

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Key words: Bradykinin, cardiac heart failure, coronary artery disease, cardio vascular disorders.

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Abstract

Bradykinins are the most potent biologically active peptides located in vascular smooth muscle. The continuous advances in the characteristics of bradykinin receptors through development of selective receptor and molecular biology techniques aids to the rational design of drug effective in the treatment of cardiovascular diseases. BK B(2) receptor is not only implicated in the pathogenesis of inflammation, pain and tissue injury that also in powerful cardio protective mechanisms to treat and prevent various CV disorders such as hypertension, CHF, venous thrombosis, ventricular hypertrophy, ischemic heart disease. Several preclinical studies have been conducted using pharmacological agonist by which it was found that B(1)R have noxious effects whereas B(2)R have an important role in the process of coronary artery disease(CAD) and ischemic post conducting that limits the ischemia/reperfusion injury of the myocardium. However, none of the currently potent selective and non peptide agonists of BK B(2) receptors-JMV 1116(Fournier), RMP-7(lobradamil), FR-190997(Fujisawa) have been selected for the clinical assessment in cardiovascular indications. We therefore conclude that the treatment with potent and highly selective B2 receptor agonist, initiated immediately after the occurrence of acute ischemic event, should be explored as a potent therapeutic option in these circumstances .One of the major challenge is still an unanswered question that which of the mechanisms cardio protective (or) inflammation is extensively shown by BK B (2) receptor agonist. The following review will throw light on this discussion.

Introduction

Bradykinin is a nonapeptide (an oligo peptide with 9 amino acyl residues) which was first recognized by Rocha e Silva [1] from its effects on intestinal smooth muscle. It is a member of a family of vasodilatory peptides, the 'kinins'. These are of two types B1 and B2 receptors. They produce their pharmacological effects by acing on G protein coupled receptors.

Circulatory homeostasis is the result of a constant equilibrium between vasoconstrictors (e.g., pressor neurohormonal factors like angiotensin II, catecholamines, vasopressin, endothelin) and vasodilators (like kinins, prostaglandins, NO, etc.).Bradykinin, a tissue hormone that regulates the regional blood flows of vital organs [2]. In addition, the cardio protective properties of the ACEIs treatment is mediated and modulated by BK release. Evidence in recent years indicates that part of the cardio protective benefits of ACE inhibition is attributable to the diminished degradation and accumulation of BK.

The Kallikrein-Kinin System

The kinin family mainly includes BK (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), Kallidin (Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and methionyl-lysyl-BK(Met-Lys-Arg-Pro-Pro-Gly-Phe-Arg) [3-5]. These are pharmacologically active polypeptides derived from circulating precursors (kininogens) by the action of serine proteases, called kallikreins [3-5]. Once released into the circulation, kinins are rapidly inactivated by enzymes called kininases [3-5]. Kininogens are multifunctional proteins derived mainly from α2 globulin [3-5]. In humans, two forms of kininogens are High molecular weight kininogen (HMWK) and low molecular weight Kininogen (LMWK). These kininogens vary from each other, in molecular weight, susceptibility to plasma and tissue kallikreins and their physiological properties [6].

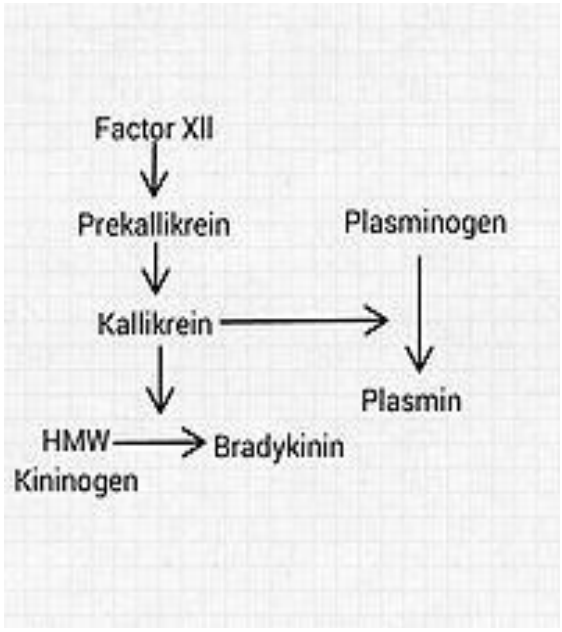


Figure 1. Synthesis of Bradykinin

They are synthesized in liver and circulate in the plasma and body fluids. Tissue kallikrein is found in various organs such as kidney, heart and synovial tissue [7].

These kallikreins are single chain acidic glycoprotiens [3-5]. Plasma kallikrein circulates in an inactive form also known as the pre-kallikrien or Fletcher factor. Inactive kallikrein can be activated to form kallikrein by inactivated to form kallikrein by activated Hageman factor or factor XIIa, which then liberate BK from the HMWK [3-5]. In addition plasma kallikrein is able to convert inactive factor XII to XIIa by positive feedback reaction [3]. Factor XIIa and factor XI circulate with HMWK in the bound form [3-5]. Inactive factor XI converted to active factor XIa through HMWK to participate in the intrinsic coagulation pathway [3-5].

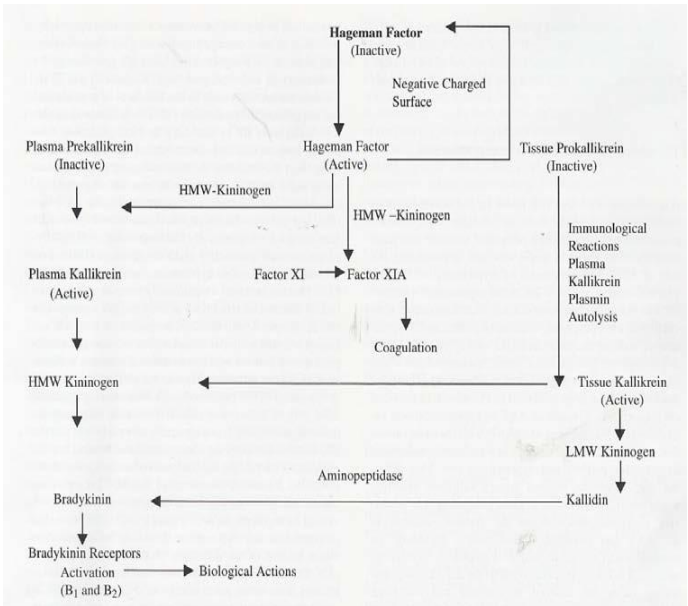


Figure 2. Metabolism of Bradykinin

Biological actions: contraction of muscles in bronchus and gut, increases vascular permeability and is also involved in the mechanism of pain [8], natriuresis, raises internal calcium levels in neocortical astrocytes causing release of glutamate [9], also thought to induce dry cough in some patients on ACE inhibitor drugs, also play a role in a rare disease known as Angio-neurotic edema [10], causes constriction and eventual atrophy of the ductus arteriosus.

In immunological reactions the tissue proteoglycone and mast cell heparin may act as an initiating surface for the initial activation of the Hageman factor. It seems that the kinins may be generated in parallel with the formation of the thrombin at inflammatory sites, since inactive plasma kallikrein can be activated by coagulant Hageman factor.

Kinin receptors classification

Kinins exert a variety of biological actions by acting through specific receptors that are wide spread and belong to 2 major categories B1 and B2 that have been defined pharmacologically using a variety of peptidergic agonist and antagonists. Recent pharmacological findings from various studies suggest the existence of new receptor types named B3, B4, B5. These receptors mediate the contractile and the relaxant response of the oesophagus to BK. However, B3, B4, and B5 receptors have not been sufficiently characterized either with agonists or with antagonists to be considered as new functional sites.

B1 Receptors

The B1 receptors (also called bradykinin receptor B1) are expressed only as a result of tissue injury and are presumed to play a role in chronic pain. This receptor has been also described to play a role in inflammation[11]. Most recently, it has been shown that the kinin B1 receptor recruits neutrophil via chemokine CXCL5 production. Moreover, endothelial cells have been described as a potential source for this B1 receptor-CXCL5 pathway[12].

B2 Receptors

The B2 receptor is constitutively expressed and participates in bradykinin's vasodilatory role.

The mechanism of action of bradykinin

The BK receptor stimulation in the intact cells or in tissues appears to initiate the second-messenger systems. The BK receptor stimulation in the intact cells or in tissues appears to initiate the second –messenger pathways such as arachidonic acid products and the activation of calcium-sensitive systems [13]. The elevation of cellular inositol phosphates by BK involves G-protein coupled action of phospholipase. A2 and C that are used in the synthesis of eicosanoids [14]. It is of noted that indomethacin, a cyclooxygenase inhibitor, was able to initiate potentiation of BK-induced contractions [15]. It was demonstrated that B2 receptor stimulation causes production of cyclic guanosine monophosphate (cyclic GMP) in aortic endothelial cells [16]. The formation

of cyclic GMP may be an important step for the biological actions as well as release of nitric oxide evoked by BK in the endothelial cells and in the vascular smooth muscle.

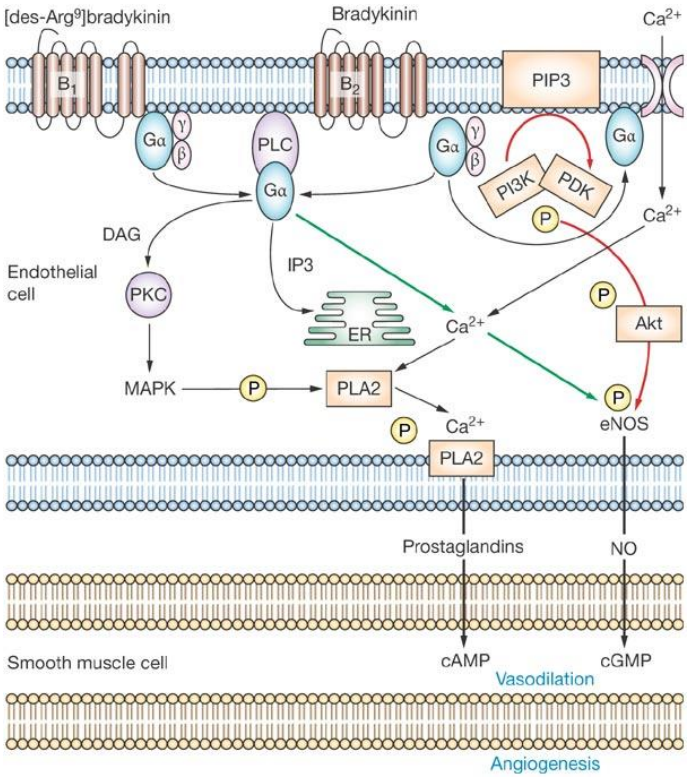


Figure 3. Mechanism of action of Bradykinin

Pharmacological actions [17]

On CVS [17]

- It is potent vasodilator.
- They release histamine and other mediators from mast cells and markedly increase capillary permeability.
- They cause flushing, throbbing, head ache and fall in BP.

On Smooth Muscle [17]

- Contraction of intestine is slow.
- They cause bronchoconstriction in asthmatic patients.

On Neurons [17]

- Stimulate nerve ending that transmit pain and produce pain and causes inflammation.

On Kidney [17]

- Increase renal blood flow and facilitate salt,
- Water excretion by action on tubules.

Adverse Drug Reactions [18]:

- Swelling,
- Angiogenesis,
- Pain induction,
- Edema [19].

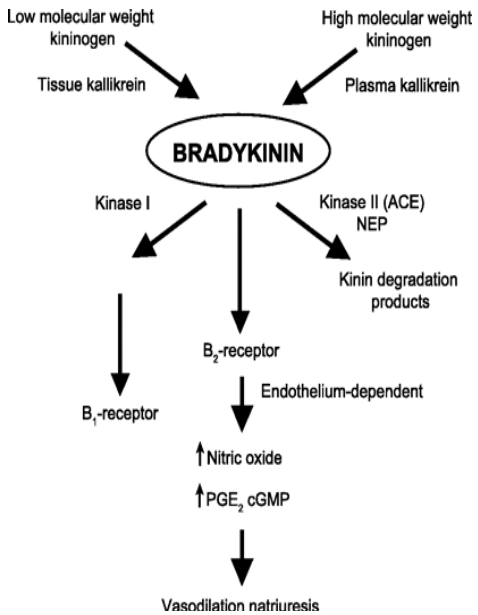
Role of bradykinin in cardioprotection

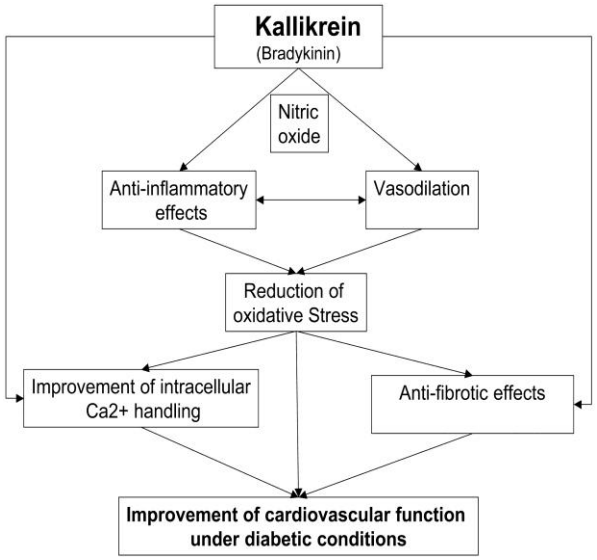
The kinin system is known to have a prime role in the regulation of systemic blood pressure. BK is able to produce vasodilatation, diuresis, natriuresis and reduction in the total vascular peripheral resistance. There is ample evidence documenting the reduced activities of kinin system in the genesis of hypertension. Hypertension is a major risk factor for the development of cardiovascular diseases, such as coronary heart disease, congestive heart failure and peripheral vascular and renal diseases.

The pharmacological action of BK in the regulation of systemic BP was vasodilatation in most areas of the circulation, a reduction of total peripheral vascular resistance and aregulation of sodium excretion from the kidney. When BK is injected into the renal artery, it causes diuresis and natiuresis by increasing the renal blood flow. These actions of BK have been attributed to prostaglandin release in the renal circulation. The role of kinin system in hypertension was established by Morgolius [20].

The development of a compound having renal kallikrein-like activity may serve the purpose of excreting excessive sodium from kidney. This action may be useful for the treatment of hypertension. Also it has studied that patients over expressing renal tissue kallikrien were hypotensive and that the administration of (aprotinin), a tissue kallikrein inhibitor, restored the BP in the patients. It is known that the hypertension may lead to coronary heart disease, congestive heart failure etc. and renal diseases also.

The suppression of the hypotensive responses of ACE inhibitors by a tissue kallikrein in hypertensive patients supports the view that tissue kallikrein may have a role in the regulation of BP [21]. In this regard it has been proposed that tissue kallikrein gene delivery into various hypertensive models exhibits protection against high BP, cardiac hypertrophy and renal damage [22].





Bradykinin B2 Agonists

R-838(sar-[D-phe4]des-arg-BK)

Uses

Hypertension, stimulation of vascular formation following ischemia.

Aprotinin

Uses

Treatment of acute pancreatitis, prevent blood loss during open heart surgery, treatment of hemorrhages.

Future Prospectives

Potent nonapeptide BK B2 agonist has been discovered recently but the oral efficacy of this agonist is very limited due to their in adequate pharmacokinetic property. This excludes their development as potential therapeutic agents for the treatment of all CV indications. However, tests have been performed on animals (in vivo) but not in vitro which may give more beneficial effects in future if performed.

Conclusion

We therefore conclude that treatment with a potent and highly selective B2 agonist, initiated immediately after the occurrence of an acute ischemic event, should be further explored as a potential therapeutic option in these circumstances.

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