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THE PLASMA KININS (BRADYKININ)-AN IMPORTANT CARDIOPROTECTIVE PEPTIDE WITH THERAPEUTIC POTENTIAL IN CARDIOVASCULAR DISEASES

Syeda Rashiq ul Ain[1], Ishrat Younus[*2], Tahmina Maqool[1], Areeba Khan[1]

[1]*Faculty of Pharmacy, Hamdard University, Karachi, Pakistan*
[2]*Faculty of Pharmacy, Hamdard University, Islamabad, Pakistan*

[*2]ishrat.imran@hamdard.edu.pk

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Corresponding Author: *
Ishrat Younus

Abstract
The plasma kallikrein-kinin system (KKS) is a network of enzymes, peptides, and receptors thatplayimportantrolesintheregulationofbloodpressure,inflammation,andcardiovascular disease. KKS deregulations are associated with many cardiovascular diseases such as hypertension, atherosclerosis and heart failure. This review aims to provide a comprehensive overview of the current understanding of KKS, including the synthesis of kinins, such as bradykininandtheireffectsonthecardiovascular system,presentingnewresearchresultsand therapeutic targets of specific kinin receptors and their therapeutic potential.

INTRODUCTION

Thereisincreasingevidencesuggestingthepresenceofthecomponentsofthekallikrein-kinin system(KKS)incardiacandvasculartissue,whichshape systemicandlocalKKS pathways,includingdifferentcelltypessuchasendothelialcells,cardiomyocytes,andvascular smooth muscle cells.(1)Perceptions from experimental models of hypertension, hypertrophy, ischemia,remodelling,andpreconditioningproposethatthebalanceoflocalKKSpathwaysis significant for endogenous cardio- and vasculo-protective components.Kinins are proven to playapartincontrollingthecardiovascularsysteminbothwell-beinganddiseaseindividuals, as well as in the pharmacological impacts of cardiovascular agents (1). Depending on the escalation of the stimulus, the activation of KKS leads to the activation of a few consecutive effector proenzymes, resulting in the induction of genes and activation of biomolecules involved in the mechanism of vasodilation, blood coagulation, and fibrinolysis (2).The kallikrein kinin system (KKS) produces a family of bioactive peptides. These include bradykinin andkallidin.Thoughbradykininand kallidin actbasically through the bradykinin receptor 2 (B2) (3). Kinins are strong vasodilators, advanced natriuretic and diuretic, and have advantageous cardiovascular impacts(1) .

KALLIKREIN-KININ SYSTEM:

The kallikrein-kinin system (KKS) is an endogenous proteolytic system that controls a wide rangeofphysiologicalactivitiesandcontributestothedevelopmentofmanyclinicaldisorders.
TheKKS is a complicated multienzyme cascade that generates manybioactive kinin peptides andtheirderivatives,includingbradykininandkallidin.Bradykininisanactivecomponentof kallikrein

activity. Its precursor, bradykinogen, can be found in the α2-globulin portion of normal mammalian plasma (4) Bradykinin is a powerful endothelial activator and vasodilator that works in conjunction with nitric oxide synthase (NOS), nitric oxide, Phospholipase A2 (PLA2), and its products, such as prostacyclin and hyperpolarizing eicosanoid components .

BRADYKININ:

Bradykinin activates NOS and PLA2 in artery endothelial cells, especially coronary arteries, resulting in the synthesis of many chemical and biological molecules, including nitric oxide, prostacyclin, andother eicosanoids,which relax vascularsmoothmuscle cellsviaparacrine action (3),(5),(6) . Platelet aggregation is also inhibited by these mediators at the endothelium surface and in the circulation. Furthermore, bradykinin induces the endothelium to release plasminogen activator, which promotes fibrinolysis. The significance of kinins in thrombosis is, however, poorly understood. Genetic and pharmacological investigations focused on components of the kallikrein-kinin system (3).

BRADYKININ FORMATIONFROM K A L L I K R I N - K I N I N SYSTEM:

TheKKSconsistsoftissueandplasmakallikreinsthatacton low-andhigh-molecularweight kininogens (LMWK and HMWK, respectively) to create bioactive kinins, including Bradykinin and kallidin. Tissue kallikrein (Kallidin) is found ina varietyof organs, including the kidney, heart, and synovial tissue. It is generated as a precursor and transformed into an active form by cleaving an amino-terminal peptide.

Kallidin is released when active tissue kallikrein interacts with LMWK. Tissue and plasma kallikreins have different molecular weights, biological activities, and immunological characteristics. Pre-kallikrein is the inactive version of plasma kallikrein that circulates in the blood. This inactive pre-kallikrein is transformed to active kallikrein by activated Hageman factor(XIIa),which,togetherwithfactorXI,circulatesboundwithHMWK.Finally,factorXI can be transformed into XIa, which participates in the intrinsic coagulation cascade. Remarkably, earlier data suggest that the kinins may be produced in conjunction with the generation of thrombin at inflammatory sites, because dormant plasma kallikrein can be activated by the coagulant Hageman factor (2, 4, 7). This phenomenon can be easily understood by the schematic diagram in Figure 1(8), which illustrates the plasma and tissue kinin–kallikrein systems.

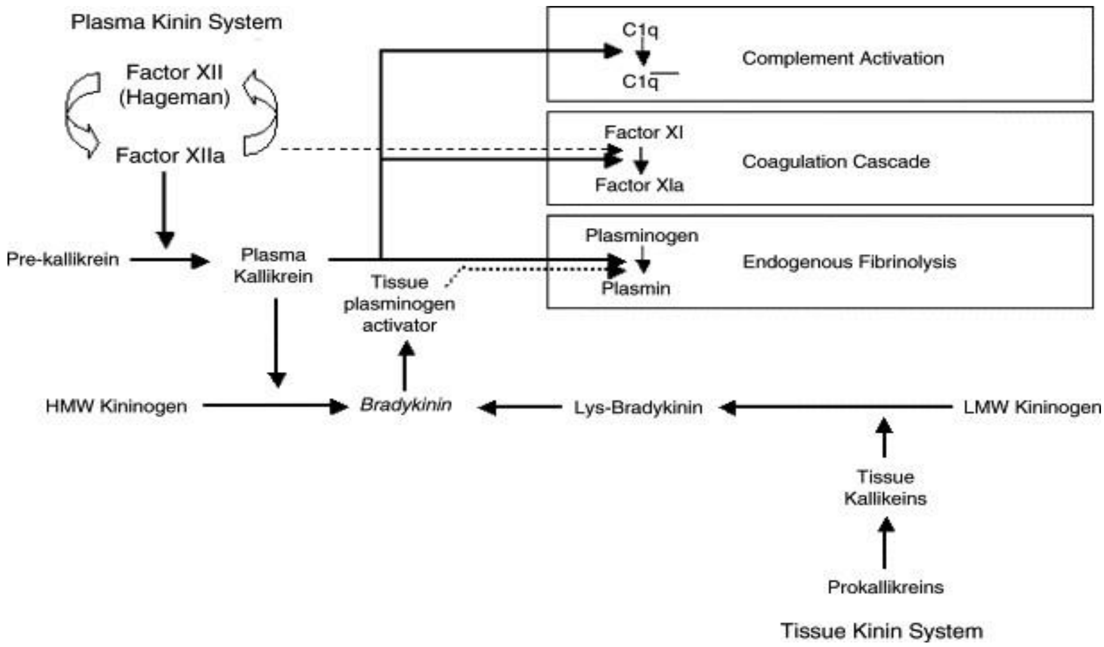

Figure01:Schematicdiagramofplasmaandtissuekinin–kallikreinsystems.HMW:high molecular weight; LMW: low molecular weight(8)

Kininases are enzymes that metabolize kinins at various cleavage sites. They include angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), carboxypeptidase N, carboxypeptidase M, cathepsin X, and aminopeptidase P. Thus, kallidin and methionyl-lysyl-Bradykinin are transformed into Bradykinin(BK) by aminopeptidases found in plasma and urine. After C-terminal arginine removal by circulating and/or tissue kininases, Bradykinin is transformedintodes-Arg9-BK,anotherpowerfulpeptide,orinertpeptides.These bradykinins have a short half-life in plasma, less than 30 seconds (2, 4).

PLASMAKININ–BRADYKININ RECEPTORS:
Kinins exert their pharmacological activities by activating two cloned receptor types, B1 and B2, which are members of the seven-transmembrane G-protein-coupled receptor family. The bradykininB1receptorhasahighaffinityandselectivity forkininmetabolitesthatlacktheC- C-terminal arginine residue, such as des-Arg9-BK. The B1 receptor is infrequentlyexpressed in normal tissue, but it appears to be increased in pathological conditions linked with inflammation and tissue injury (2, 9).

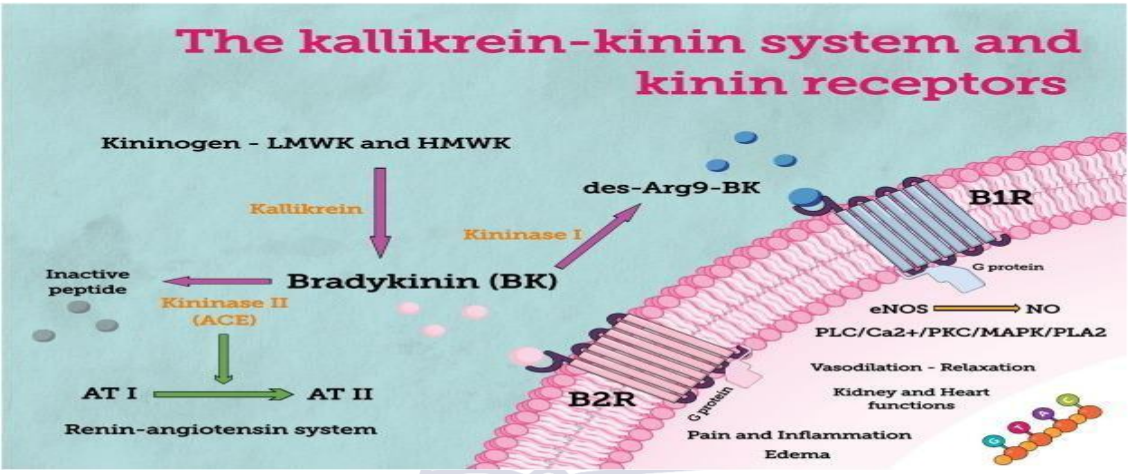

Figure02:Thekallikrein-kininsystemandkininreceptorpathway(11)

Activating both bradykinin receptors activates phospholipase C, which promotes intracellular calcium (Ca2+) mobilization by inositol 1,4,5-triphosphate, diacylglycerol generation, activation of several isoforms of protein kinase C (PKC), release of nitric oxide (NO) and prostaglandins,andactivationofmitogen-activatedproteinkinase(MAPK)andnuclearfactor-κB (NF-κB).(4, 7, 10) This process is illustrated schematically in Figure 2(11), which depicts the kallikrein–kinin system and kinin receptor pathway.

MECHANISM OF SIGNAL TRANSDUCTION:
The two bradykinin receptors, B1 and B2, are G-protein-coupled receptors that exert their activities through the activation of either Gq or Gi/o. In Endothelial cells, bradykinin binding to the B2-receptor enacts eNOS, cyclooxygenase, and cytochrome P450 epoxygenase(12).In expansion,laterstudiesproposethatB2-receptorsinVSMCsactivateNADPHoxidasetodeliver superoxide and specificallyenact charybdotoxin-sensitive K+ channels. B1 receptors enacted by bradykinin or kallidin metabolites, stimulate Phospholipase (PLC)-dependent elevation in intracellular Ca2+ andactivate eNOS and cyclooxygenase in endothelial cells(2),(12). In most vascular beds, arachidonic corrosive metabolites contribute enormously to the vasodilator activities of these receptors. B1 and B2 receptors can also elevate outline kinase to intercede inflammatory reactions, but the constrictor pathways enacted by the B1 and B2 receptors are poorly characterized (12)

ROLESOFPLASMAKININ-BRADYKININ IN THE CARDIOVASCULAR SYSTEM:

1) TheRoleof Bradykininin Hypertension:A**RegulatoryMechanism**
Bradykinin is one of the most powerful vasodilators synthesized in the body, involved in the control of arterial blood pressure and inflammation. It is composed of nine amino acids,

they on are Arginine, Proline, Proline, Glycine, Phenylalanine, Serine, Proline, PhenylalanineandArginineandisrepresentedbythecodeRPPGFSPFR,andthemolecular weightofthispeptideis1060KDa(6).Itbelongstothegroupofthecirculatoryhormones, and it was described that it has been formed from high molecular weight kininogen (HMWK) by kallikrein as a part of the kinin-kallikrein system.(13-15) Once released, bradykinin exerts its effects through the activation of two G protein-coupled receptors. There are two types or subtypes of bradykinin receptors, namely the bradykinin B1 receptor and the bradykininB2receptor.(16).TheB2receptorisdeterminedtobeconstitutively expressed in different tissues, while the B1 receptor is found only in tissues that have undergone inflammation or become injured (6).

Bradykinin is an agent that leads to the dilation of arterioles through prostacyclin, nitric oxide, and endothelium-derived hyperpolarisingfactor, causing the ultimate lowering of blood pressure. It also has some weak diuretic function, contributing to the balance of fluids. Alteredkininmetabolismhasbeennotedinseveralhypertensiveconditionsinclinicaland experimental hypertensive subjects. It is also an active participant in the regulation of sodium balance; hemodynamics and blood pressure through the regulation of the vasoconstrictor renin angiotensin system and the vasodilators prostaglandin, prostacyclin and nitric oxide. Hypertension is treated using angiotensin-converting enzyme (ACE) inhibitors, and these compounds act, at least in part, by raising bradykinin concentration through inhibiting these enzymes' ability to degrade the substance, thereby augmenting its hypotensive effect. It is postulated that the hypotensive effect of ACE inhibitors is experienced with the help of bradykinin and nitric oxide (15, 17).

- **Bradykinin'srole inhypertension**

The therapeutic potential of bradykinin in hypertension is promising. Still, we need some targeted research for the targeted therapies of bradykinin, also we need to understand the impact of bradykinin on blood pressure management. In 21 century, we are still facing challenges in the management of hypertension. We need a more effective and tailored approach (6). As we know the bradykinin is the product of KKS (Kallikrein-kinin system),andthisproductplays a pivotalroleincardiovascularhealth,actsascardio-protective, regulates blood pressure and has an important role in the pathophysiology of hypertension (15). KKS acts as a compensatory mechanism in hypertension, it is counter counter-regulatorysystemagainstvasopressinandprotectsend-organdamageinhypertension,while targeted action is still under debate in the case of blood pressure regulation because the KKS system is complex in regulating blood flow in the heart and kidneys, also in vascular resistance (6, 18). Uncontrolled hypertension can lead to dangerous cardiovascular situations due to increasedpressureexertedonthebloodvessels,whichaffectstheheartnormalphysiology and causes heart failure, CAD, LVH, PAD, CKD, stroke (19). Hence, it is clear that hypertensionplays an importantrole in cardiovascular-relatedcomplications,and the kininsystem plays an importantroleinthemanagementofhypertension. Wecanconcludethatlower levels of kallikrein might be responsible for the hypertension(20)

- **Vasodilation and Sodium Excretion:** Bradykinin plays a pivotal part in controlling systemic blood pressure through vasodilation in most zones of circulation, diminishing add up to peripheral resistance, and directing sodium excretion from the kidney. This component is fundamental for maintaining healthy blood pressure levels (21)

- **Kidney Function and Sodium Reabsorption:** The kallikrein-kinin system within the kidney fundamentally suppresses sodium reabsorption along the collecting ducts. Bradykinin specifically restrains sodium chloride and water reabsorption by the distal nephron, which makes a difference in counteracting the hypertensinogenic activities of the renin-angiotensin system (17, 21).

- **Impaired Kallikrein-Kinin System and Hypertension:** A decreased movement of the kallikrein-kinin system can lead to an impaired ability of the kidneys to respond to an elevationindietarysaltintake,resultinginincreasedarteriolarsensitivityto Vasoconstrictivesubstancesandeventually,highbloodweight.Typicallyfrequentlyseen in salt-sensitive hypertension (17).

- **ReceptorB1andVascularDisease:**Researchrecommendsthatreceptor B1mayplaya defensive role in vascular disease states, such as hypertension or ischemic organ disorders. However, its work in controlling blood pressure remains somewhat questionable. Studies have appeared that when B2 is repressed or absent, receptor B1 is upregulated and may develop a few B2 hemodynamic properties, showing that both receptors play a part in keeping up ordinary vasoregulation and the development of hypertension (15, 17, 21).

- **Bradykinin Receptors and Vasoregulation:** Historically, it was accepted that bradykininactsprimarilythroughB2toexertitsphysiologicalimpacts.Inanycase,later researchproposesthatbothB1andB2receptorsareincludedwithinthecontrolofblood pressure and vasoregulation(21).

2) Roleof in Pathophysiologyof HeartFailureandHypertrophy:
Bradykinin (BK) is a circulating peptide that acts on endothelial cells in the peripheral and coronary vasculature. There are two BK receptor subtypes: B1R (inducible, expressed after tissue damage) and B2R (constitutively expressed in endothelial cells)
B1R Signaling: Induces calcium-dependent iNOs activation, promotes local tissue inflammation, neutrophil recruitment, and capillary dilation, and Contracts venous outflow (22)
B2RSignaling:Increasesintracellularcalcium,activatingeNOS,causesvasodilationthrough NOreleasetoVSMC,leadingtocGMPproductionand relaxation.NegativelyregulatesVSMC and cardiomyocyte proliferation and growth, countering hypertrophy and blood vessels (22).

3) InflammatoryEffect:
Bradykinin plays a noticeable part in inflammation. In conjunction with prostaglandins and histamine,Bradykinin is arevasodilatormediatorinwhichthearteriolarsmooth musclerelaxes and,inturn,elevatesbloodflow.Bradykinin,alongwith prostaglandinE2(PGE2),playsapart in the sensitization of sensory nerve endings, which causes the dolour, or pain, a component oftheinflammationprocess.Inthiswaywithintheprocessofinflammation,bradykinincauses an increase in vasodilation, an increase in permeability, and an increase in pain.

4) Cardio-protective Effects:
Pharmacologicalstudiesreportthemyocardialdefensivepartof the BDKRB1andBDKRB2genes in diabetic and non-diabetic patients, individually, in intense coronary disorder. Cardio- protectivedrug-mediatedincreaseofkinins'half-lives,includingbradykinin,hasdefensiveparts in cardiac remodeling, apoptosis and fibrosis, through BDKRB2-NO.(23)

5) Rolein EndothelialCellsand Neovascularization:
Bradykinin has a proliferative impact on endothelial cells. Locally incorporated bradykinin takes part in neovascularization and helps repair vascular walls and remodelling after acute ischemia. It signals through BDKRB2/PI3K/eNOS intervened work of circulating progenitor cells having the regenerating capacity to the damage site.(24)

6) RoleinCardiacConditioning Mechanisms:
Bradykinin has a key function in all cardiac conditioning mechanisms. Bradykinin represses myocardial apoptosis through Akt and GSK-3Î² phosphorylation, progresses antiapoptotic protein profile and plays a part in ventricular remodelling.(25)[20],(26)

7) Anti-FibroticEffects:
Bradykinincanhaveanti-fibroticimpactsinpathogenicremodellingthatencompasses cardiomyocytes, driving to left ventricular broadening and dysfunction.(27)

8) Rolein AnginaandCardiac Nociception:
Bradykinin is included in dead tissue-activated chest pain (angina), intervened through 12-lipoxygenase items, IP3 and TRPV1 channels. Bradykinin acts as a cardiac nociceptor, which stimulates BDKRB2 in upper thoracic spinal (sympathetic) sensory neurons.(28),(29). ThromboxaneA2,alipidfamilypartwithpro-thromboticproperties,correspondinglyinteracts with bradykinin during myocardial ischemia, fortifying cardiac spinal afferent. (29),(30) Bradykinin agonists can be used to treat Bradykinin deficit, which appears to support endogenous bradykinin-BDKRB2-mediated cardiac protection. However, determining the appropriatedosage,therapeuticwindow,andmedicationperiodwillbecriticaltomaintaining the balance.

ADVANCES IN BRADYKININ RECEPTORS AND THEIR THERAPEUTIC POTENTIALS:
Recentadvancesinunderstandingthecharacteristicsofbradykininreceptors,facilitatedbythe developmentofselectivereceptorantagonistsandmolecularbiologytechniques,haveenabled therationaldesignofdrugseffectiveinthetherapeutic manipulationofinflammatoryprocesses and control of cardiovascular diseases.(2),(3)

- **ReceptorAntagonistsandCardio-protection:**

Receptor antagonists have been shown to play a crucial role as potential endogenous cardio-protective substances, contributing to the effects of angiotensin-converting enzyme (ACE) inhibitors. The therapeutic potential of Bradykinin B1 and B2 receptor antagonists has been extensivelydiscussed and analyzed in recent studies, highlighting their potential in mediating thebeneficialeffectsofACEinhibitorsortheuseofexogenouskininsinvascularpermeability.
(6). ACE inhibitors, initially designed to lower blood pressure, have been shown to increase kinin levels in blood and tissues, leading to beneficial effects in heart failure, diabetic nephropathy, andperipheral ischemia. Kininsare notinvolvedintheblood pressure-lowering effectsofACEinhibitorsbutareessentialfortheirbeneficialeffectsincardiacischemia,post-ischemic heart disease, and peripheral ischemia.(3)

- **BradykininB2ReceptorsandCardio-protection:**

StimulationofBKB2receptorshasbeenimplicatedinthepathogenesisofinflammation,pain, andtissueinjury,aswellaspowerfulcardio-protectivemechanisms.Exogenousadministration ofBKorlocallyincreasedBKconcentrations,resultingfromACEinhibition,hasbeenshown to contribute significantly to cardio-protective mechanisms. These mechanisms are triggered by the synthesis and release of vaso-relaxant, anti-hypertrophic, and anti-atherosclerotic endothelial mediators, such as nitric oxide, prostaglandins, and tissue-type plasminogen activators. (2),(3)

- **TherapeuticPotentialofBKB2ReceptorAgonists:**

BKB2 receptoragonists mayhaveimportant clinicalvalueinthetreatment andpreventionof various cardiovascular disorders, including hypertension, ischemic heart disease, left ventricular hypertrophy, ventricular remodelling, and congestive heart failure, as well as diabetic disorders. However, the challenge remains to identify a sufficiently safe therapeutic window between potential cardioprotective and pro-inflammatory effects following BK B2 receptor agonism.(2),(3)

- **InteractionsbetweentheRenin-AngiotensinSystemandtheKallikrein-KininSystem:**

The investigation of therapeutic actions of angiotensin type 1 (AT1) receptor antagonists and ACE inhibitors has demonstrated complex interactions between the renin-angiotensin system and the kallikrein-kinin system. These interactions are evidenced by the fact that ACE efficiently catabolizes kinins, angiotensin-derivatives exert kinin-like effects, and kallikrein probably serves as a prorenin-activating enzyme.(2),(3)

- **Roleof B1ReceptorsinCardiovascularProtection:**

StudieshavedemonstratedthatB1receptorscontributetothecardio-beneficialeffectsofAT1 blockade. The regulation of B1 receptors in wild-type rats treated with the AT1 antagonist, irbesartan(IRB),andintransgenicratswithcardiacoverexpressionofthehumanAT1(TGR- TGR-alphaMHCAT1) was investigated. The results showed that LV function improved by almost 50%aftertreatmentwithIRB,butremainedunchangedinTGR-alphaMHCAT1afterinduction of MI compared to their untreated controls.

METHODOLOGY

A thorough literature search was performed using electronic databases such as PubMed, Science hub, Science direct, National Library of Medicine. The following keyword searches were used: "plasma kinin system", "bradykinin", "kallidin", "cardiovascular disease", "hypertension", "heart failure", and "cardioprotective peptides".
Thesearchfocusedonpaperspublishedinthepastthree decades. Studies investigating the involvement of the plasma kinin system in cardiovascular diseases were considered. Plasma Kinin-related studies on cardiovascular function were included, and studiesthatdidnotfocusontheroleofplasmakinininca rdiovasculardiseaseswereexcluded.

RESULTANDCONCLUSION

Thiscomprehensivereviewconcludedthatthekallikrein-kininsystem(KKS)demonstratesan important role in the cardiovascular system. The normal regulation of the KKS pathway is important for the normal functioning of cardiac and vaso-protective components. Bradykinin is the peptide produced by KKS and is a potent vasodilator and cardio-protective peptide. It alsoplaysaroleinthepathophysiologyofheartfailureandhypertrophy,andalsohas apivotal role in cardiac condition processes, antifibrotic effects, and cardiac nociception and blood pressureregulation.Thetherapeuticpotentialofbradykininreceptors,especiallyB1andB2 Receptors,has been broadlydiscussed. The stimulation of BK B2 receptors has been involved in cardio-protective mechanisms, and BK B2 receptor agonists may have vital clinical value within the treatment and prevention of different cardiovascular disorders. The KKS system and its peptide bradykinin have played a significant role in the cardiovascular system, and furtherin-depthresearchisneededtofullyunderstandthemechanismsandtodiscoverthenew therapeutic potentials which can lead to the discovery of new treatment approaches for cardiovascular diseases.

DISCUSSION

The kallikrein-kinin system (KKS) is an endogenous proteolytic system that controls a wide rangeofphysiologicalactivitiesandcontributestothedevelopmentofmanyclinicaldisorders. TheKKS is a complicated multienzymecascadethat generates manybioactivekinin peptides and their derivatives, including bradykinin and kallidin. Bradykinin is secreted through these stepsfromtheKallikrein-KininSystem(KKS);Tissuekallikreincleaveslow-molecular-weight kininogen (LMWK) to secrete kallidin. Kallidin is converted by aminopeptidases in plasma and urine to bradykinin and then released into the blood stream. The two bradykinin receptors, B1andB2,areG-protein-coupledreceptorsthatexerttheiractivitiesthroughthe enactmentof either Gq or Gi/o. Activating both bradykinin receptors activates phospholipase C, which promotes intracellular calcium (Ca2+) mobilization by inositol 1,4,5-triphosphate, diacylglycerolgeneration,activationofseveralisoformsofproteinkinaseC(PKC),releaseof nitric oxide (NO) and prostaglandins, and activation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB). Bradykinin plays an important role in controlling blood pressure through vasodilation, sodium excretion and kidney function. Bradykinin is involved in inflammation, causing vasodilation, increased permeability and inflammation. Bradykinin has cardio-protective effects, including reducing heart failure, apoptosis and fibrosis. Bradykinin can prevent cardiomyocyte apoptosis, promote an anti-apoptotic protein profile,and playarolein ventricularrestructuring. Bradykininhas an antifibroticeffectinthe treatmentofdiseasesthatcause leftventricular enlargement anddysfunction.BK B2 receptor agonists and antagonists mayhave important clinical value in the treatment and prevention of various cardiovascular disorders, including hypertension, ischemic heart disease, left ventricular hypertrophy, ventricular remodelling, and congestive heart failure, as well as diabetic disorders. The function of Bradykinin receptors and their agonists and antagonists deservestobeinvestigatedfurther.The studyofbradykininreceptorsandtheir antagonistshas Opened up new avenuesfor the development of therapeutic strategies for the treatment andprevention of cardiovascular disorders.

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