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REVIEW ARTICLE

The kinin system - bradykinin: biological effects and clinical implications. Multiple role of the kinin system - bradykinin

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Abstract
The present review article regarding the kinin system-bradykinin is dealing with the biological effects of the above-mentioned entity mediated by specific B_1 and B_2 receptors as well as with its clinical implications known nowadays. The activation of the kinin system-bradykinin is particularly important in blood pressure regulation and in inflammatory reactions, through bradykinin ability to elevate vascular permeability and to cause vasodilatation in some arteries and veins. Recent data on bradykinin formation and release, synergy with ligands, receptors for bradykinin as well as on bradykinin participation in the mitogenesis process, are given in detail. Therapeutic potentials and future applications in many clinical situations including respiratory allergic reactions, septic shock, hypertension and its treatment, hypotensive transfusion reactions, heart diseases, pancreatitis, hereditary and acquired angioedema, Alzheimer disease and liver cirrhosis with ascites, are discussed in brief. Its role as a neuromediator, regulator of several vascular and renal functions, and its participation in signaling pathways, is also discussed in some detail. *Hippokratia 2007; 11 (3): 124-128*

Key words: *kinin system, bradykinin biology, bradykinin manifestations*

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The discovery of the kinin system is not recent, but its study in clinical field has been done only in the last years. This system is composed by substrates (kininogens) and plasma and tissue kallikreins are the specific activators of these substrates producing two vasoactive peptides called bradykinin and kallidin. The biological effects of kinins are mediated by specific receptors called B_1 and B_2.The activation of this system is particularly important in blood pressure regulation and in inflammatory reactions, through bradykinin (BK) ability to elevate vascular permeability and to cause vasodilatation of arteries and veins of the gut, aorta, uterus and urethra. The kinin system is involved in many clinical situations including respiratory allergic reactions, septic shock, hypertension and its treatment, hypotensive transfusion reactions, heart diseases, pancreatitis, hereditary and acquired angioedema, Alzheimer disease and liver cirrhosis with ascites[1].

Kinins are peptide hormones that transmit their biological effects via G protein – coupled receptors. The kinins have been implicated in the regulation of blood pressure, pain sensation and cell growth[2].

Apart from being a pro-inflammatory mediator, bradykinin is now recognized as a neuromediator and regulator of several vascular and renal functions. New breakthroughs point to unusual and atypical signaling pathways for a G- protein coupled receptor that could explain the anti-proliferative and anti – fibrogenic effects of bradykinin. The availability of transgenic and knock out animal models for bradykinin receptors or bradykinin – synthesizing or – catabolic enzymes confirms these cardiac and renal protective roles for this peptide system[3]. Bradykinin (BK) has multiple pathophysiologic functions such as induction of vascular permeability and mitogenesis, and it triggers the release of other mediators such as nitric oxide in inflammatory and cancer tissues[4].

Bradykinin formation and Release

Biologically active kinins, including BK and Lys(0)-BK, are short – lived peptide mediators predominantly generated by the enzymatic action of kallikreins on kininogen precursors[5]. Studies have proved that the levels of kinin peptides in tissues were higher than in blood, confirming the primary tissue localization of the kallikrein – kinin system. Kallikreins are produced by the inactive precursors prekallikreins after activation in plasma mediated by Factor XII (Hageman factor) which is an enzyme part of the clotting mechanism. Kallidin is a product of the enzymatic action of kallikrein to kininogens. Kallidin then is transformed into bradykinin after enzymatic action of plasma aminopeptidase. Separate studies measuring bradykinin and kallidin peptides demonstrated the differential regulation of the plasma and tissue kallikrein – kinin systems providing different insights on understanding this complex system.

Moreover studies have demonstrated that kinin pep-

tide levels are increased in the heart of rats with myocardial infarction, in tissues of diabetic and spontaneously hypertensive rats, and in urine of patients with interstitial cystitis, suggesting a probable role for kinin peptides in the pathogenesis of these conditions. By contrast, blood levels of kallidin , but not bradykinin ,peptides were suppressed in patients with severe cardiac failure, suggesting that the activity of the tissue kallikrein – kinin system may be suppressed in this condition[6].

Transduction of signals from BK receptors

Bradykinin interacts with its G protein coupled receptor at the cell surface. This interaction leads to specific changes in intracellular calcium (Ca^{2+}) involving several different mechanisms such as phospholipase C, prostagladins, protein kinase and phospholipase A_2. For example, t he addition of bradykinin to neural cells NG 108-15 results in a transient hyperpolarization followed by prolonged cell depolarization. Injection of inositol 1,4,5-trisphosphate or Ca2+ into the cytoplasm of NG108-15 cells also elicits cell hyperpolarization followed by depolarization. Tetraethylammonium ions inhibit the hyperpolarizing response of cells to bradykinin or inositol 1,4,5-trisphosphate. Thus, the hyperpolarizing phase of the cell response may be due to inositol 1,4,5-trisphosphate-dependent release of stored Ca2+ into the cytoplasm, which activates Ca2+-dependent K+ channels. The depolarizing phase of the cell response to bradykinin is due largely to inhibition of M channels, thereby decreasing the rate of K+ efflux from cells and, to a lesser extent, to activation of Ca2+-dependent ion channels and Ca2+ channels. In contrast, injection of inositol 1,4,5-trisphosphate or Ca2+ into the cytosol did not alter M channel activity[7].

Investigating the role of protein kinase C (PKC) and phosphatidyl inositol 3-kinase (PI3-K) in the signaling mechanism of cardio protection afforded by bradykinin brought us to the conclusion that BK B2 receptors can precondition guinea pig hearts via the dual activation of PKC and PI3-K. The mitochondrial ATP-sensitive K^+ channels act as downstream targets of PKC, whereas PI3-K is not associated with mitoK (ATP) channels[8].

Synergy with other

A variety of signals have been reported to synergise with bradykinin. Elevated levels of several cytokines including interleukin 1beta (IL-1beta) have been detected in airway fluid of asthmatic patients. Therefore studies have investigated the effect of IL-1beta on bradykinin –induced inositol phosphate accumulation and Ca^{2+} mobilization and up regulation of bradykinin receptor density in canine tracheal smooth muscle cells (TSMCs). The conclusions suggest that the augmentation of BK-induced responses produced by IL-1beta might be at least in part, mediated through activation of the Ras/Raf/MEK/MAPK (mitogen-activated protein kinase) pathway in TSMCs[9]. Another study, investigating the fact that inhalation of tumour necrosis factor-alpha (TNFa) induces a bronchial hyperreactivity to contractile agonists, reached to the same conclusions.[10] Recent studies demonstrate that bradykinin, via the B_2 receptor, induces IL-6 expression in airway smooth muscles cells by involving activation of extracellular-signal regulated kinase (ERK1/2) and p38mitogen mitogen –activated protein kinases signaling pathways. Moreover at the same study IL-6 secretion by BK proved to be sensitive to corticosteroids and was regulated by Thi2-cytokines.[11] Since the involvement of growth factors such as insulin-like growth factor(IGF-I) has been implicated in the early steps of diabetic nephropathy studies have investigated the effect of BK on Erk-1 and 2 activation and cell proliferation by IGF-I. They concluded that, a new inhibitory pathway of the early steps of IGF-I signaling by the B_2 receptor is found both in cultured mesangial cells and in isolated glomeruli, which involves a calcium-dependent tyrosine phosphatase activity[12]. Synergies between mechanisms of mitogen-activated protein kinase (MAPK) activation and bradykinin have been extensively reported. One study has illustrated the signal transduction pathway leading to MAPK activation in response to bradykinin in vascular smooth muscles. These findings provide evidence that activation of the B_2-kinin receptor in vascular smooth muscle cells (VSMC) leads to generation of multiple second messengers that converge to activate MAPK. The activation of this crucial kinase by BK provides a strong rationale to investigate the mitogenic actions of BK on VSMC proliferation in disease states of vascular injury[13].

Receptors for Bradykinin

Bradykinin action and intracellular response initiation is mediated through specific cell surface receptors. Bradykinin receptors are cell surface, G-protein coupled receptors of the seven-transmembrane domain family. The existence of two subtypes of bradykinin receptor, B_1 and B_2, has been confirmed through the use of high affinity peptide and nonpeptide receptor antagonists, radioligand binding studies and, recently, receptor cloning and expression studies. Differences in the affinities of B_2 receptor antagonists, including those of the [D-Phe7]-bradykinin series, D-Arg-[Hyp3, Thi5, D-Tic7, Oic8]-bradykinin (Hoe140, Icatibant) and the non-peptide, WIN64338, have led to the speculation that further subtypes of bradykinin receptor (including a tracheal B_3 receptor), and/or of species homologues of the B_2 receptor[14].

Receptors for bradykinin have been reported on many tissues. B_2 bradykinin receptors are present in neurones of the brain stem, basal nuclei, cerebral cortex, thalamus and hypothalamus. B_2 immunolabelling was also observed in the endothelial lining of the superior sagittal dural sinus and ependyma of the lateral and third ventricles. B_1 kinin receptors have been localised on neurones of the thalamus, spinal cord and hypothalamus[15]. Additionally, studies have demonstrated that BK B_2 receptors are present on renomedulary intersti-

tial cells both in vitro and in vivo. These properties are coupled to intracellular second messenger systems and in vitro, their stimulation results in cellular proliferation and synthesis of extra cellular matrix[16].

The bradykinin 1 and 2 receptors (B_1R, B_2R) are important mediators of cardiovascular homeostasis, inflammation, and nociception. While B_2R is constitutively expressed in many tissues, B_1R expression is thought to be absent, but induced under pro-inflammatory conditions. However, recent data from knockout mice have indicated that B_1R acts centrally to mediate nociception, a finding that suggests the constitutive presence of B_1R in brain and/or spinal cord. The presence of B_1R mRNA in the cerebral and entorhinal cortex, dentate gyrus, and pyramidal neurons of the hippocampus, in the thalamus, hypothalamus, amygdala, pontine nuclei, spinal cord, and dorsal root ganglion, demonstrates a basal level of expression in the primate nervous system and provides a foundation for understanding the central actions of kinins[17]. Receptors for bradykinin have been also reported to exist in tissues such as uterus, intestine, kidney, heart, and aorta.

Kinins are autacoid peptides and central neuromediators involved in cardiovascular regulation, inflammation and pain. Their effects are mediated by two transmembrane G-protein-coupled receptors denoted as B_1 and B_2 as we have already demonstrated. While the B_2 receptor is constitutive, the B_1 receptor is inducible and up regulated in the presence of cytokines, endotoxins or during tissue injury. The B_2 receptor is believed to play an important role in the beneficial effects of angiotensin-1 converting enzyme inhibitors used in the treatment of cardiovascular diseases, yet it is involved in the acute phase of inflammation and of somatic and visceral pain. Conversely, the B_1 receptor participates in the chronic phase of these responses and is likely to play a strategic role in diseases with a strong immune component such as rheumatoid arthritis, multiple sclerosis, septic shock and diabetes. A dual function for the B_1 receptor is also reported in some pathologies in which it can exert either a protective (multiple sclerosis and septic shock) or harmful (pain and inflammation) effect[18].

An additional role was introduced for B_2 BK receptor demonstrating its proliferative effects. The mitogenic signalling pathways used are "classical" pathways for GPCRs. Recent data show that bradykinin can also induce anti-mitogenic effects in proliferating cells using an "alternative" signal transduction pathway involving a protein tyrosine phosphatase[19].

Agonist/antagonist studies of bradykinin receptors

Kinin receptors have been characterized through studies on isolated organs in vitro and have been classified as B_1 and B_2. A careful analysis of B_2 receptors led to the identification of two subtypes, namely B2rb (in the rabbit) and B2gp (in the guinea-pig). The distinction between B2rb and B2gp receptors is primarily based on differences in the activity of selective agonists and particularly on differences in affinities of competitive antagonists, namely DArg[Hyp3,DPhe7,Leu8]BK and the non-peptide compound, WIN 64338. The non-competitive antagonist, HOE 140, has shown the same affinity on B2rb and B2gp. The potential role of B_1 and B_2 receptors in physiopathology is analysed on data obtained with specific and selective antagonists of the B_1 (desArg9 [Leu8] BK) and B_2 (HOE140) receptors[20]. Kinin B and B_2 receptor antagonists may be useful drugs endowed with analgesic and anti-inflammatory properties, with potential use in asthma, allergic rhinitis and other diseases. The first nonpeptide kinin B2 receptor antagonist, WIN 64338, was reported in 1993. Despite its low selectivity, the compound provided a reference for pharmacological and modeling studies. Several quinoline and imidazo[1,2-a]pyridine derivatives possess high affinity and selectivity for kinin B_2 receptors. Among them, FR 173657 displayed excellent in vitro and in vivo antagonistic activity, while FR 190997 emerged as the first nonpeptide agonist for B_2 receptor[21].

Moreover studies have focused on the pharmacological characteristics of the first nonpeptide bradykinin receptor agonist 8- [2,6 – dichloro – 3 - [N] - [(E) – 4 - (N-methylcarbamoyl) cinnamidoacetyl-N-methylamino] benzyloxy] – 2 – methyl – 4 - (2-pyridylmethoxy) quinolin e (FR190997). FR190997, whose structure is quite different from the natural peptide ligand, but is similar to the nonpeptide antagonists FR165649, FR167344 and FR173657, potently and selectively interacts with the human B_2 receptor and markedly stimulates inositol phosphate formation in transfected Chinese hamster ovary (CHO) cells. FR190997 induces concentration-dependent contraction of isolated guinea pig ileum. In vivo, FR190997 mimics the biological action of bradykinin and induces hypotensive responses in rats with prolonged duration, presumably as a consequence of its resistance to proteolytic degradation. Therefore, FR190997 is a highly potent and subtype-selective nonpeptide agonist, which displays high intrinsic activity at the bradykinin B_2 receptor[22]. Moreover, while BK acts as a full agonist in man, rabbit and pig, FR 190997 behaves as a full agonist on human, as partial agonist on rabbit, and as pure antagonist on pig B_2 receptors[23].

More antagonists like bradykinin B_2 receptor antagonist HOE-140 or bradykinin B_1 receptor R-954 successfully used to demonstrate the important modulatory effects of bradykinin B_1 and B_2 receptors on allergic lung inflammation[24]. Additionally it was proved that in certain tumour cell lines HOE-140 may act as mitogenic B_2 receptor agonist whereas the nonpeptide B_2 receptor antagonist FR 173657 does not. In H-69 small-cell lung cancer cells FR 173657 was found to exhibit properties of an inverse agonist[25].

Bradykinin and Mitogenesis

Exploring the pathophysiologic roles of BK in tumor, recent studies have examined the distribution of BK B_2 receptors in human adenocarcinoma (lung, stomach), lymphoma (lymph node), hepatoma, squamous cell car-

cinoma (lung) and carcinoid (duodenum), and in mouse colon adenocarcinoma 38 (C-38) and sarcoma 180 (S-180) tumor tissues. The results provided direct evidence that the BK B_2 receptor is expressed in human cancer and experimental murine tumors, which suggests a potential role for BK in inducing pathologic signal transduction in cancer growth and progression, nitric oxide production and vascular permeability enhancement in tumors. BK antagonists may thus have applications in the modulation of cancer growth and in paraneoplastic syndromes[5].

It has been suggested that bradykinin (BK) plays an important role in regulating neointimal formation after vascular injury. However, implication of BK in the growth of rat VSMCs is controversial. Therefore, by examining the mitogenic effect of BK on VSMCs associated with activation of MAPK we reach to specific conclusions. The mitogenic effect of BK is mediated through activation of the Ras/Raf/MEK/MAPK pathway similar to that of PDGF-BB. BK-mediated MAPK activation was modulated by Ca^{2+}, PKC, and tyrosine kinase all of which are associated with cell proliferation in rat cultured VSMCs[26].

MAPK pathway is a very important signal transduction cascade involved in controlling mitogenesis. It is now clear that both tyrosine kinase growth factor receptors and G protein-coupled receptors regulate this pathway[27]. Activation of the B_2 receptor by BK leads to the generation of multiple second messengers that converge to activate MAPK. Additionally, the same study provides cellular and molecular evidence for a potential role of BK in VSMC function. The significance of these findings to the in vivo actions of BK on the pathological progression initiated by vascular wall changes is unclear. Because the in vivo physiological actions of BK are modulated by various autacoids, such as eicosanoids and nitric oxide, the contribution of these second messenger systems to the signaling mechanisms initiated by BK in VSMC must be considered[28]. Better understanding of the molecular and cellular mechanisms by which kinins stimulate VSMC proliferation in vivo, a process obligatory to the development of vascular injury, could lead to the development of new strategies for intervention and treatment of vascular diseases.

Therapeutic potentials – Future applications

The continuing advances in our knowledge of the characteristics of the bradykinin receptors through the further development of the selective receptor antagonists and molecular biology techniques, aids to the rational design of drugs effective in the therapeutic manipulation of inflammatory processes and in the control of inflammatory disease. It has been proved that receptor antagonists play an important role as potential endogenous cardioprotective substances also contributing to the effects of angiotensin converting enzyme inhibitors[29] are discussed and analysed in Many recent studies in conjuction with the therapeutic potential of B_1 and B_2 receptor antagonists discuss and analyse the therapeutic potential of endogenous kinins as mediators of the therapeutic beneficial effects of the angiotensin-converting enzyme inhibitors or the potential of the use of exogenous kinins in the vascular permeability[19].

In various animal models and in humans it has been shown that the stimulation of BK B (2) receptors is not only implicated in the pathogenesis of inflammation, pain and tissue injury but also in powerful cardioprotective mechanisms. Either exogenous administration of BK or locally increased BK concentrations as a consequence of the inhibition of its metabolic breakdown by angiotensin converting enzyme inhibitors, reveal the significant contribution of BK in powerful cardioprotective mechanisms[30]. These are mainly triggered by the syntehesis and release of the vasorelaxant, anti-hypertrophic and anti-atherosclerotic endothelial mediators nitric oxide, prostaglandins and tissue-type plasminogen activator, by ischaemic preconditioning and by an increase in insulin sensitivity. Consequently, BK B(2) receptor agonists may have important clinical value in the treatment and prevention of various cardiovascular disorders such as hypertension, ischaemic heart disease, left ventricular hypertrophy, ventricular remodelling and congestive heart failure as well as diabetic disorders by mimicking the reported beneficial effects of BK. However, none of the currently known potent and selective peptide and non-peptide agonists of BK B2 receptors RMP-7, JMV-1116, FR-190997 and FR-191413 have been selected for a clinical assessment in cardiovascular indications. One major challenge of this approach is the still unanswered question of whether there is a sufficient safe therapeutic window between potential cardioprotective and pro-inflammatory effects following BK B(2) receptor agonism[30].

The investigation of therapeutic actions of angiotensin type 1 (AT1) receptor antagonists and ACE inhibitors (ACEI) demonstrated complex interactions between the renin-angiotensin system and the kallikrein-kinin system in several experimental and clinical studies. They are evidenced by the fact that ACE efficiently catabolizes kinins, angiotensin-derivatives such as ANG-(1-7) exert kininlike effects; and kallikrein probably serves as a prorenin-activating enzyme[31]. Several authors have demonstrated experimentally that the protective effects of ACEI are at least partly mediated by a direct potentiation of kinin receptor response on BK stimulation. Furthermore, studies on AT1 antagonists, which do not directly influence kinin degradation and studies on angiotensin-receptor transgenic mice have revealed additional interactions between the rennin-angiotensin system and the kallikrein-kinin system[31,32]. One study demonstrated for the first time that B1R contributes to the cardio-beneficial effects of AT1 blockade. To investigate the role of the bradykinin B1 receptor (B1R) on the angiotensin receptor AT1 blockade-dependent cardioprotective effects, we studied the B1R regulation in wild-type rats treated with the AT1 antagonist, irbesartan (IRB), and also in transgenic rats with cardiac overexpression of the human AT1 (TGR-alphaMHCAT1)

after induction of myocardial infarction (MI). In addition, we treated wild-type rats with IRB and/or the B1R antagonist, B9958, and determined the left ventricular (LV) function. Wild type rats were treated with IRB and/or the B1R antagonist, B9958, and the left ventricular (LV) function was determined. The results were important demonstrating that LV function had improved by almost 50% after treatment with IRB but remained unchanged in TGR-alphaMHCAT1 after induction of MI compared to their untreated controls. The beneficial effect of IRB was reversed by co-treatment with B9958. The B1R antagonist treatment alone had no effect. A cross-talk between AT1 and B1R was also indicated by an up-regulation of B1R after treatment with IRB on protein and RNA level, while AT1 overexpression reduced B1R expression after induction of MI[32].

Although it is widely accepted that the blockade of kinin receptors with specific antagonists could be of benefit in the treatment of somatic and visceral inflammation and pain, recent molecular and functional evidence suggests that the activation of B_1 receptors with an agonist may afford a novel therapeutic approach in the CNS inflammatory demyelinating disorder encountered in multiple sclerosis by reducing immune cell infiltration (T- lymphocytes) into the brain. Hence, the B_1 receptor may exert either a protective or detrimental effect depending on the inflammatory disease[33]. The function of B receptors and their agonists and antagonists deserve to be investigated further.

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