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Bradykinin Pathway and Pathological States: Potential Therapeutic Agents against Such States

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Editorial

Bradykinin is one of the two kinins that are present in human body. It is a biologically active nonapeptide hormone released following the breakdown of kallidin (decapeptide lysyl-bradykinin) by aminopeptidase [1]. Kallidin is generated from low molecular weight kininogen by the action of kininogenases. Kininogenases include plasma kallikrein and tissue kallikrein. Kininogen is found in the α2-globulin fraction of normal mammalian plasma [2]. Bradykinin is very effectively removed during passage through the lung and other vascular beds. It is degraded by peptidases. The cellular effects of bradykinin are mediated by two bradykinin G-protein-coupled receptors namely Bradykinin Receptor B_1 (B_1BKR) and Bradykinin Receptor B_2 (B_2BKR) respectively [3]. Bradykinin receptor B_2 is constitutively expressed in numerous tissues and after ligand binding becomes promptly desensitized. The low expression of bradykinin receptor B1 in healthy conditions however becomes increased during inflammation, infection, or injury [4,5].

The mechanism of action may involve (i) stimulation of the membrane phospholipid metabolism by activating phospholipase C, (ii) promotion of intracellular calcium mobilization by inositol 1,4,5-triphosphate, (iii) release of Nitric Oxide (NO) and prostaglandins [4].

The disruption or loss of homeostasis associated with bradykinin activation may result in disease states such as (i) inflammation-arising from vasodilation, increased vascular permeability, stimulating prostaglandins synthesis [6] (ii) spinal cord injury [7] (iii) central and peripheral nervous systems ischemia [8] (iv) plasma extravasation [9] (v) bronchoconstriction-linked to asthma and rhinitis [10] (vi) pain and irritation in skin, muscle, joints, vasculature, and all visceral organs [11,12]. Pain arises from direct stimulation of primary sensory neurons and provoking the release of substance P, neurokinin. (vii) natriuresis-arising from inhibition of sodium reabsorption [13], (viii) the biphasic disruptions of the blood-spinal cord barrier [14], (ix) subarachnoid and intraparenchymal hemorrhage and secondary ischemia [15], (x) immune cell invasion leading to cytokines release [16], (xi) pancreatitis [17] (xii) cancer growth and progression [18].

In order to effectively reduce disruption or loss of homeostasis triggered by bradykinin activation, scientists have developed a number of bradykinin receptor antagonists [19].

Bradykinin receptor antagonists have also been found to play vital role as potential endogenous cardioprotective substances and have contributed to the effects of angiotensin converting enzyme inhibitors [20]. Structurally, bradykinin B_2 antagonists typically possess a constrained peptide backbone due to the inclusion of bulky non-natural amino acids. Some of these antagonists include:

(i) Icatibant (HOE 140) is a competitive (surmountable) selective peptide antagonist for B2 receptors in humans and a noncompetitive, selective antagonist for B_2 receptors in other mammalian species [21,22]. It is currently approved for the management of hereditary angioedema attacks [23].

(ii) Anatibant, a selective non-peptide bradykinin B_2 receptor antagonist [24]. It has been used in a clinical trial for the prevention of brain edema after head injury [25].

(iii) WIN 64338, chemically defined (S)-4-[2-[*Bis*(cyclohexylamino)methyleneamino]-3-(2-naphthalenyl)-1-oxopropylamino]benzyl tributyl phosphonium chloride hydrochloride is the first nonpeptide kinin B_2 receptor antagonist but with low selectivity [26].

(iv) FR 173657, a quinoline and imidazo[1,2-a]pyridine derivative chemically defined (E)-3-{(6-acetamido-3-pyridyl)-N-2,4-dichloro-3-[(2-methyl-8-quinolinyl)oxymethyl]-phenyl}-N-methylaminocarbonylmethyl]acrylamide is a bradykinin B_2 receptor antagonist and has high affinity and selectivity for the receptor [27].

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(v) R-954, chemically defined (AcOrn[Oic(2),(αMe) Phe(5),dβNal(7),Ile(8)]desArg(9)-bradykinin) is a bradykinin B1 receptor peptide antagonist [28] and its antitumoral activity has been reported [29,30].

(vi) Sodium cromoglycate and nedocromil sodium-reported to inhibit the respiratory airways [31].

(vii) Cyclooxygenase inhibitors have been reported as bradykinin anatagonists because bradykinin has been implicated in cough induced by angiotensin converting enzyme inhibitors [32].

Conclusion

Kinins (including bradykinin) have emerged as inflammatory mediators implicated in the development of the vital signs of inflammation that are dependent on vascular responses (vasodilation, increased microvascular permeability). Bradykinin B_1 and B_2 receptor antagonists may be useful drugs endowed with analgesic and anti-inflammatory properties and with potential use in asthma, allergic rhinitis and other diseases. Finally, despite efforts by scientists aimed at developing chemical substances that antagonize the bradykinin receptors, clinical applications remain limited.

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