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Neuroprotection of bradykinin/bradykinin B2 receptor system in cerebral ischemia

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ABSTRACT

Bradykinin B2 receptor (B2R) activated by its endogenous ligand bradykinin participates in various physiological processes including neurogenesis, neuronal differentiation, and control of inflammation and blood pressure. Besides these effects, B2R has been demonstrated to protect neurons from ischemia/reperfusion (I/R) injury. Here, we highlight the mechanisms of BK/B2R-mediated neuroprotective effects in the peripheral and central nervous systems. Moreover, this review article summarizes some of the signaling pathways of B2R in cerebral ischemia, leading to a better understanding of its neuroprotection.

Contents

Abbreviations: GPCR, G-protein-coupled receptor; B2R, bradykinin B2 receptor; B1R, bradykinin B1 receptor; BK, bradykinin; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; KKS, kallikrein-kinin system; eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase; iNOS, inducible nitric oxide synthase; I/R, ischemia/reperfusion; H/R, hypoxia/reoxygenation; ROS, reactive oxygen species; OGD/R, oxygen and glucose deprivation/reoxygenation; MCAO, middle cerebral artery occlusion; CNS, central nervous system; VEGF, vascular endothelial growth factor; TK, tissue kallikrein; CHO, Chinese hamster ovary; HUK, human urinary kallidinogenase; APJ, apelin receptor; NADPH, nicotinamide adenine dinucleotide phosphate; ERK1/2, extracellular regulated protein kinases1/2; Akt, protein kinase B; GSK3β, glycogen synthase kinase 3β; Ang-(1–7), angiotensin-(1–7); ACE, angiotensin converting enzyme; NMDA, *N*-methyl-D-aspartate; PI3K, phosphatidylinositol 3 kinase; MAPK, mitogen-activated protein kinase; Raf, rapidly accelerated fibrosarcoma; JNK, c-Jun N-terminal Kinase; p38, p38 MAPK; NF-κB, nuclear factor κB; MnSOD, manganese superoxide dismutase; CA1, *cornu Ammon*; GFAP, glial fibrillary acidic protein; Bcl-2, B cell lymphoma 2; Bax, Bcl-2 associated X Protein; PC12 cell, pheochromocytoma 12 cell; iPS cell, induced pluripotent stem cell; AMPK, AMP-activated protein kinaseis; mTOR, mammalian target of rapamycinby; TSC2, tuberous sclerosis complex 2; AT1R, angiotensin II type 1 receptor; AT2R, angiotensin II type 2 receptor; CsA, Cyclosporine-A; PD, Parkinson's disease; BBB, blood brain barrier; PAM, Pralidoxime; KOR, kappa opioid receptor; PKC, protein kinase C; PKG, protein kinase G; cGMP, cyclic guanosine monophosphate; Pyk2, proline-rich tyrosine kinase2; Src, short for sarcoma member of the src family tyrosine kinases; DFP, diisopropylfluorophosphate; HOE140, D-Arg-L-Arg-L-Pro-L-Hyp-Gly-L-(2-Thienyl)Ala-L-Ser-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2α,3β,7aβ)-octahydro-1H-indole-2-carbonyl-L-Arg Icatibant acetate.

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1. Introduction

The kallikrein-kinin system (KKS) is a complex multi-enzyme system which is composed of the serine proteases tissue and plasma kallikreins. It has been well established that KKS is widespread across various tissues and shows diverse physiological and pathophysiological activities, such as control of arterial pressure, hypotension, edema formation, inflammation, stroke, smooth muscle contraction, and cardiovascular and renal homeostasis [1]. The peptides bradykinin (BK) and kallidin (Lys-BK) cleaved from kininogen precursors by plasma or tissue kallikrein (TK) specifically activate the bradykinin B2 receptors (B2R), while their bioactive metabolites des-Arg^{9}-BK and des-Arg^{10}-kallidin stimulate the bradykinin B1 receptors (B1R) [2]. Furthermore, B2R can be directly activated by TK which induces its redistribution on plasma membrane independent of kininogen and kinin release in cultured CHO cells [3]. Typically, the B2R is constitutively expressed in a wide variety of tissues, whereas B1R is inducible and overexpressed in inflammatory and injury conditions [4,5]. B1R and B2R both belong to the G protein coupled receptor (GPCR) family, but B2R mediates most of the physiological functions of kinin [6]. After activation, the two receptors trigger many physiological and pathological processes including regulation of blood pressure, immune cell invasion, smooth muscle cell contraction or relaxation, chloride release, vascular permeability increase and cell proliferation [7].

In early 1990s, Kamiya and coworkers found that BK-mediated the progression of cerebral edema and the lactate accumulation could be suppressed by inhibiting BK synthesis [8]. For example, BK levels are elevated after focal cerebral ischemia in mice [9]. Tissue BK levels show a marked correlation with brain swelling and tissue injury. Similar study also show high BK levels in human ischemic stroke, where kallikrein levels are increased at 24 h and remain elevated for several weeks. In another study, an early administration of B2R specific antagonist LF16-0687 Ms reduces postischemic brain swelling, and improves neurological recovery after focal cerebral I/R [10]. BK can not only induce depolarization of astrocytes and neurons, but increase intracellular Ca^{2+} concentration after acute ischemic stroke. However, the effects of BK were inhibited by natriuretic peptides [11]. Dobrivojević M et al. also found that urodilatin, a kind of atrial natriuretic peptide, decreased the size of the lesions and brain edema through inhibiting the BK/B2R signaling pathway *in vivo* middle cerebral artery occlusion (MCAO) experiments [11].

It has been increasingly appreciated that BK and Lys-BK could act as a “double-edged sword”. By inhibiting oxidative stress and apoptosis, systemic or local delivery of human TK protects against mouse myocardial ischemia/reperfusion (I/R) injury *via* B2R [12,13]. Besides protection in myocardial I/R injury [14–16], B2R has also been found to be neuroprotective in brain ischemic insults, and enhance migration of glial cells *via* activation of B2R [17,18]. In addition, kallikrein gene overexpression induces lessening of ischemic injury in MCAO mice and in rat epilepsy model *via* B2R [12,13,19]. Indeed, B2R expression is neither limited to cells directly involved in immune responses nor endothelial cells of blood vessels in the heart, but is expressed in superficial laminae of the spinal cord and dorsal root ganglia associated with the sensory nervous system [4]. In the central nervous system (CNS), BK regulates synaptic function, and promotes neurogenesis and neuroprotection against acidosis-mediated neurotoxicity *in vitro* [20–23]. Additionaly, BK protects against both hypoxia/reoxygenation(H/R)-induced injury in rat cortical neurons and glutamate-induced neurotoxicity in rat retinal neurons [17,24]. With overexpression of Homer1b/c, BK shows the neuroprotection against oxygen and glucose deprivation/reoxygenation (OGD/R)-induced cell injury by enhancing cell survival, reducing lactate dehydrogenase release, caspase-3 activity and cell apoptosis [25].

Here, we review the neuroprotective of B2R in the models of ischemic stroke *in vitro* and *in vivo,* and its possible mechanism and signaling pathways.

2. Mechanisms of BK/B2R-induced neuroprotection

Ischemic damage can increase activity of NAD(P)H oxidase and glutamatergic receptors, superoxide formation, neuronal apoptosis, and the levels of proinflammatory cytokine and intracellular calcium [26,27].The neuroprotection of BK can counter the deleterious effects following cerebral ischemic injury and promotes cell survival through attenuating the progression of the disease and secondary brain damage. Thus, BK participates in neuroprotection through activation of B2R in cerebral injury.

2.1. BK/B2R mediates vascular effects and angiogenesis in ischemic stroke

Angiogenesis is required for a variety of normal and pathological processes, which can enhance nutrient supply and oxygen to the injured tissue, especially for the ischemic boundary zone. So the neovascularization facilitates synaptogenesis and neurogenesis, resulting in functional recovery [28,29]. As a tissue kallikrein extracted from urine, human urinary kallidinogenase (HUK) promotes angiogenesis after I/R *via* activation of B2R, which is potentially due to increased the expression of VEGF and apelin/APJ in ERK1/2 dependent way in MCAO mice [30], consistenting with the findings of our previous studies [31,32]. It has been demonstrated that BK protects against I/R-induced cardiomyocyte apoptosis through Akt-GSK-3β-caspase-3 signaling pathway [33,34]. The neuroprotective effect of BK *via* the B2R in ischemic stroke has also been revealed by several studies [13,35–37]. For example, kallikrein gene transfer significantly increased capillary density in the ischemic brain after cerebral I/R, which was mediated by the B2R and accompanied by increasing Akt activation and NO production [13]. In the early period after I/R, kallikrein could promote the angiogenesis through enhancing the expression of vascular endothelial growth factor (VEGF) [37]. In addition, kallikrein gene transfer also promoted the proliferation of some neuronal cells in the ischemic penumbra and primary cultured neuronal cells[13], while these effects were significantly attenuated by the B2R antagonist icatibant.In addition to direct neuroprotection, BK can also promote neuroprotective by the interaction between this nonapeptide and angiotensin-(1–7) [Ang-(1–7)]. Multiple groups have found that Ang-(1–7) induced upregulation of endothelial nitric oxide synthase (eNOS) and NO production in stroke [38,39], and improved endothelial function [40]. These studies indicate that Ang-(1–7) may have a vasodilatory effect to increase cerebral blood flow, which might contribute to its neuroprotective efficacy [41]. Intrestingly, Tom et al. revealed that Ang-(1–7) was able to inhibit the proteolytic function of angiotensin converting enzyme (ACE) by binding with ACE at the COOH-terminal domain, thus promoting BK function. Moreover, lateral