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Review

Kinin-mediated inflammation in neurodegenerative disorders

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ABSTRACT

The mediatory role of kinins in both acute and chronic inflammation within nervous tissues has been widely described. Bradykinin, the major representative of these bioactive peptides, is one of a few mediators of inflammation that directly stimulates afferent nerves due to the broad expression of specific kinin receptors in cell types in these tissues. Moreover, kinins may be delivered to a site of injury not only after their production at the endothelium surface but also following their local production through the enzymatic degradation of kininogens at the surface of nerve cells. A strong correlation between inflammatory processes and neurodegeneration has been established. The activation of nerve cells, particularly microglia, in response to injury, trauma or infection initiates a number of reactions in the neuronal neighborhood that can lead to cell death after the prolonged action of inflammatory substances. In recent years, there has been a growing interest in the effects of kinins on neuronal destruction. In these studies, the overexpression of proteins involved in kinin generation or of kinin receptors has been observed in several neurologic disorders including neurodegenerative diseases such Alzheimer's disease and multiple sclerosis as well as disorders associated with a deficiency in cell communication such as epilepsy. This review is focused on recent findings that provide reliable evidence of the mediatory role of kinins in the inflammatory responses associated with different neurological disorders. A deeper understanding of the role of kinins in neurodegenerative diseases is likely to promote the future development of new therapeutic strategies for the control of these disorders. An example of this could be the prospective use of kinin receptor antagonists.

1. Introduction

Inflammation is considered to be the primary response of higher organisms to injury or to infection with the aim of repairing and healing the injured tissue. The activation of several regulatory cascades including the contact, complement and coagulation systems is fundamental processes in the inflammatory response (Cone, 2001; Huerre and Gounon, 1996; Keller et al., 2003; Lenz et al., 2007). Vascular permeability and blood flow increase in the first stages of inflammation, mainly owing to the local amplification of vasodilatation and endothelial cell contraction. The primary mediators of this step are substances produced by mast cells and platelets, such as histamine, bradykinin, leukotrienes and serotonin. Prostaglandins are also involved in these initial reactions. The increased vascular permeability causes stronger transport across the blood vessel wall, enriching the injured site in proteins and small molecules essential for the activation, recruitment and adhesion of leukocytes, the most important defence cells. At this stage, a decisive role has been attributed to pro-inflammatory cytokines and chemotactic factors. At the injured site, trauma-stopping processes such as coagulation or pathogen destruction also take place. Finally, a resolution of the inflammation follows and tissue repair is achieved. In this phase, anti-inflammatory cytokines are typically involved such as TGF-β, IL-4 or IL-10. A lack of control at any step of the inflammatory response can result in overproduction of toxic mediators, turning inflammation into a chronic state which may contribute to a development of serious disorders which can finally result in a total destruction of the organism (Huerre and Gounon, 1996; Lenz et al., 2007; Mariscalco, 2006).

Abbreviations: Aβ, amyloid peptide; ACE, angiotensin-converting enzyme; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; B1R and B2R, kinin receptor types 1 and 2; BBB, blood–brain barrier; BK, bradykinin; CPM and CPN, carboxypeptidase types M and N; CSF, cerebrospinal fluid; FTLD, frontotemporal lobular dementia; FXII, factor XII; HD, Huntington's disease; hK1, tissue kallikrein 1; HK, high molecular weight kininogen; Hsp 90, heat shock protein 90; KD, kallidin; LK, low molecular weight kininogen; MAPK, mitogen-activated protein kinase; MAPT, microtubule associated protein tau; Met-KD, Met-kallidin; MS, multiple sclerosis; NEP, neutral endopeptidase; PA, Parkinson's disease; PK, plasma kallikrein; PNS, peripheral nervous system; RNS, reactive nitric species; ROS, reactive oxygen species; PRCP, prolylcarboxypeptidase.

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2. The kinin-generating system and its association with inflammation

Among numerous modulators of inflammation there are many peptides that play particularly important roles in nervous tissues, including those belonging to the kinins' and tachykinins' families. The latter, especially substance P, regulate different functions in glial cells, the immune/inflammatory cells from these tissues (reviewed in Maggi, 1997). On the other hand, kinins, including bradykinin (BK) and kallidin (KD) are also potent regulators of inflammatory response both in central and peripheral nervous system (CNS and PNS, respectively). The inflammatory action of these two groups of peptides can proceed on different ways which can be related to the significant structural distinctness between their molecules. This review is focused on the kinin regulation of inflammation and their connection with neurological disorders including neurodegeneration. Kinins are dynamically produced and degraded under physiological conditions at the vessel wall, as well as at sites of focal infection or injury (Bhoola et al., 1992; Blais et al., 2000; Kaplan and Ghebrehiwet, 2010). These peptides are generated from proteinaceous precursors, high molecular weight kininogen (HK) and low molecular weight kininogen (LK) through the action of kallikreins, plasma kallikrein (PK) or tissue kallikrein (hK1) (Bhoola et al., 1992; Blais et al., 2000; Joseph and Kaplan, 2005; Sharma, 2006) (Fig. 1). However, the involvement of other endogenous proteinases has also been suggested (Kozik et al., 1998; Stuardo et al., 2004). Numerous research groups have studied the activation of the plasma contact system using endothelial cells which have thus become the best understood system that generates kinins (Colman and Schmaier, 1997; Joseph and Kaplan, 2005; Kaplan and Ghebrehiwet, 2010). To initiate this activation, the contact factors including HK, factor XII (FXII) and prekallikrein must bind to the endothelial cell surface to form a multiprotein complex with specific membrane receptors (Joseph and Kaplan, 2005). Numerous studies have now characterized the binding of these proteins to the surface of several types of human cells (smooth muscle cells, astrocytes, macrophages, neutrophils, neurons, epithelial cells) (Barbasz et al., 2008; Fernando et al., 2003, 2005; Guevara-Lora et al., 2011a; Herdenson et al., 1992; Varano Della Vergiliana et al., 2010, 2011) and pathogen microorganisms (Herwald et al., 1998; Karkowska-Kuleta et al., 2010; Rapala-Kozik et al., 2010, 2011; Sakata et al., 1996), resulting in subsequent kinin production (Barbasz and Kozik, 2009; Fernando et al., 2005; Guevara-Lora et al., 2011a; Karkowska-Kuleta et al., 2010; Rapala-Kozik et al., 2010; Varano Della Vergiliana et al., 2010). The other major type of kininogenase, tissue kallikrein, can produce KD in tissues in a cell surface binding-independent manner. Other cell proteins such as prolylcarboxypeptidase (PRCP) or heat-shock protein 90 (Hsp 90) are involved in kinin generation due to their ability to convert prekallikrein to active kallikrein at the cell surface (Joseph and Kaplan, 2005). Once formed, the kinins are subject to regulation of their concentration levels through degradation by kininases (Bhoola et al., 1992; Blais et al., 2000). Angiotensin-converting enzyme (ACE) degrades BK by first removing the dipeptide Phe^8–Arg^9 and next cleaving the Phe^5–Ser^6 bond. Neutral endopeptidase 24.11 (NEP, neprisylin, enkephalinase) preferentially cleaves the Pro^7–Phe^8 bond and prolonged incubation with this enzyme results in the hydrolysis of the Gly^4–Phe^5 bond. Others kininases, carboxypeptidase M and N (CPM and CPN) remove the arginine residue from the kinin C-terminus but the cleaved peptides remain active.

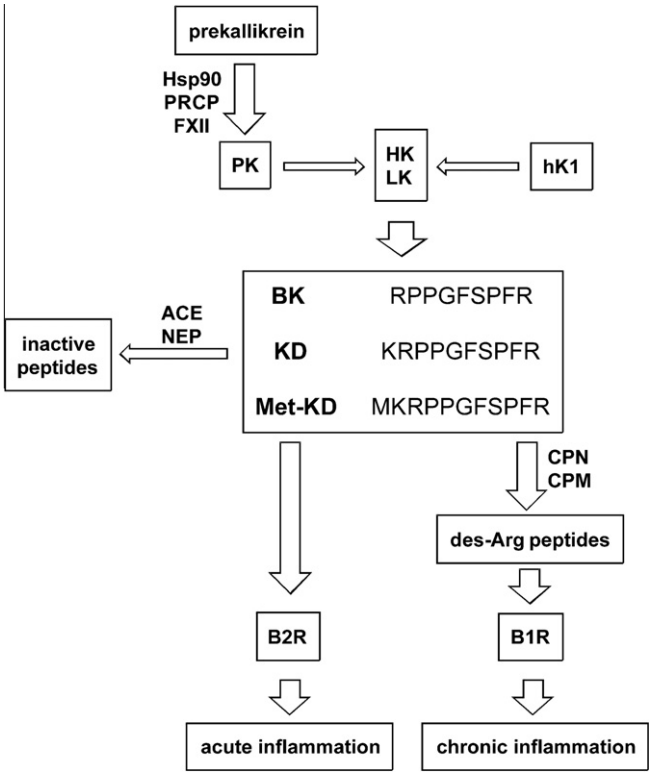

Fig. 1. A scheme of the plasma and tissue kinin generation systems. Kinins (BK, KD, Met-KD) produced from kininogens (HK, LK) by the enzymatic action of kallikreins (PK, hK1) are then degraded by kininases (ACE, NEP, CPM, CPN), leading inactive peptides or des-Arg peptides active toward B1R. Other abbreviations are explained in the text.

B1R and B2R are two types of receptors involved in kinin recognition. B1R binds only the des-Arg kinin peptides whereas B2R recognizes BK and KD. Both receptor types are involved in inflammatory processes. The use of animal models and specific antagonists against these receptors has assisted in the determination of their role during acute or chronic inflammation. The B2 receptor is ubiquitous in mammals and its expression has been demonstrated also in other vertebrates. B1R on the other hand is not expressed constitutively but certain stimuli such as inflammation, infection or trauma can up-regulate its expression (Calixto et al., 2000; Campos et al., 2006; Leeb-Lundberg et al., 2005; Marceau et al., 2002). The activation of these G protein-coupled receptors initiates a signal transduction cascade through phospholipase C, leading to inositol 3-phosphate formation, intracellular Ca^{2+} mobilization and nitric oxide production. Another BK-dependent signalling pathway involves phospholipase A_2 activation causing arachidonic acid release with subsequent production of prostaglandins and nitric oxide (Calixto et al., 2000; Leeb-Lundberg et al., 2005; Marceau et al., 2002; Yu et al., 2002). Other signalling molecules activated by the kinin action are associated with a number of protein kinases, such as tyrosine-kinases, mitogen-activated protein kinases (MAPK) or phosphatidylinositol-3-kinase. The kinin-induced activation of several transcription factors (NFκB, STATs, AP-1, Elk-1) has also been demonstrated. Given that the two kinin receptors engage similar signalling pathways, the end-signal for each is the most likely point of difference and may at least partially underlie the significant differences in the desensitization and internalization of these receptors. For this reason, the acute phase of the inflammatory process is attributed mainly to B2R which is quickly desensitized after agonist binding and chronic inflammation is mainly attributed to B1R, which can be desensitized only partially. In addition, B2R may internalize with the agonist into the cell thereby regulating its surface expression whilst B1R is not internalized in response to agonists.