European Journal of Pharmacology 768 (2015) 58–70

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Bradykinin in ischemic conditioning-induced tissue protection: Evidences and possible mechanisms

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ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form
15 October 2015
Accepted 15 October 2015
Available online 21 October 2015

Keywords:
Bradykinin
Remote ischemic preconditioning
Myocardium
Postconditioning
Cardioprotection

ABSTRACT

Ischemic conditioning is an intrinsic protective mechanism in which repeated short episodes of reversible ischemia protects the tissue and increases its tolerance against a subsequent longer period of ischemia (index ischemia). Bradykinin is a physiologically and pharmacologically active peptide of the kallikrein–kinin system. Besides the involvement of bradykinin in a variety of physiological and pathological responses such as pain, inflammation and in cardiovascular system as a potent vasodilator, it also acts as an endogenous cytoprotective mediator in the ischemic tissue. Pretreatment with various pharmacological modulators of bradykinin has confirmed the involvement of bradykinin in ischemic conditioning-induced protection. The protective actions of bradykinin in three major paradigms of ischemic conditioning i.e. ischemic preconditioning, ischemic postconditioning and remote ischemic preconditioning involves activation and regulation of various endogenous signaling cascades to render the heart resistant to infarction. In ischemic preconditioning, bradykinin exerts cardioprotective effect via activation of PI3K/Akt/eNOS signaling pathway and regulation of redox state via NO release. The role of bradykinin and its B_2 receptors in ischemic-postconditioning induced neuroprotection has been described mainly due to its increased redox signaling cascade and activation of mitochondrial anti-apoptotic pathway. Furthermore, its cardioprotective role during remote ischemic preconditioning has been associated with activation of B_2 receptors mediated neurogenic pathway and internalization of B_2 receptors along with the formation of signalosomes that activates intracellular cytoprotective transduction pathways. The present review focuses on the potential role of bradykinin in mediating different forms of ischemic conditioning (pre/post/remote)-induced cardioprotection and neuroprotection along with the possible mechanisms.

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http://dx.doi.org/10.1016/j.ejphar.2015.10.029
0014-2999/

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1. Introduction

Ischemia is a condition in which there is an inadequate supply of blood, oxygen and vital nutrients to a portion of tissue, which typically occurs when there is an imbalance between oxygen supply and demand. However, restoration of blood flow to the ischemic region in the form of reperfusion also leads to some detrimental changes due to release of oxygen free radicals, cytokines and increased expression of adhesion molecules which ultimately results in ischemia/reperfusion injury (Eltzschig and Eckle, 2011). Ischemic conditioning is an endogenous protective strategy in which brief episodes of ischemia and reperfusion to a tissue alleviates the deleterious effects of sustained ischemia (index ischemia). On the basis of time and site of application of ischemic stimulus, ischemic conditioning has been classified into ischemic preconditioning (stimulus delivered to heart before sustained ischemic insult) (Murray et al., 1986), ischemic postconditioning (stimulus delivered to heart at the onset of reperfusion) (Lee et al., 2013), remote ischemic preconditioning (stimulus delivered to distant tissue before sustained ischemia) (Randhawa and Jaggi, 2015; Randhawa et al., 2015; Przyklenk et al., 1993, 2013) and remote ischemic postconditioning (stimulus delivered to distant tissue at onset of reperfusion) (Gao et al., 2015).

Bradykinin, an endogenous nonapeptide, is a principal active agent of kallikrein–kinin system. It is generated in the plasma during binding of inactive Hageman factor (Factor VII) to the negative surfaces such as damaged endothelial cells by dissociation of high molecular weight kininogen by plasma-kallikrein. It is also synthesized locally within tissues during tissue injury such as ischemia–reperfusion injury (Sainz et al., 2007) and during acute inflammation due to release of cellular proteases from the mast cells and basophils. Bradykinin is rapidly degraded by the endopeptidases mainly angiotensin converting enzyme, carboxypeptidase N and neutral endopeptidase, which cleave bradykinin into inactive form inside the tissues (Ahmad et al., 2006). Bradykinin has been found to exert its physiological effects via two types of G-protein coupled receptors known as bradykinin receptor type 1 (B_1R) and bradykinin receptor type 2 (B_2R) (Hall, 1997). B_1 receptors are mainly expressed under pathophysiological conditions while B_2 receptors are is wide-spread and expressed mainly on the heart, brain and spinal cord tissues in normal as well as in pathological conditions (Baxter and Ebrahim, 2002).

Bradykinin is among those important mediators that have been explored in mediating cardioprotection and neuroprotection in various forms of ischemic conditioning including preconditioning (Dong et al., 2013), postconditioning (Danielisová et al., 2008, 2009) and remote ischemic preconditioning (Gross et al., 2011; Saxena et al., 2011, 2013). Various studies described that pretreatment with different bradykinin receptor antagonists such as B_2 receptor antagonist HOE-140, non-competitive antagonist noscapine and lys [Leu^8]Des-Arg^9-bradykinin, a B_1 receptor antagonist completely abrogate the protective effect of bradykinin indicating the role of bradykinin in mediating protection in various forms of ischemic conditioning (Gross et al., 2011; Wall et al., 1994; Yang et al., 2004; Danielisova et al., 2014). Bradykinin has been reported to mimic the ischemic preconditioning through various preconditioning mediators such as reactive oxygen species, nitric oxide (NO), cyclic guananyl monophosphate (cGMP), protein kinase-G (PKG) and mitoK_{ATP} channels (Cohen et al., 2001; Oldenburg et al., 2004). Bradykinin preconditioning has been found to protect the neurons from degeneration by regulating the levels of antioxidant enzymes in spinal cord ischemia (Mechírová et al., 2014). Bradykinin is also involved in remote ischemic preconditioning (RIPC) induced cardioprotection via B_2 receptors that further lead to activation of transduction pathways in mitochondria (Saxena et al., 2011). Bradykinin has been found to act as a central mediator of a nociceptive preconditioning known as remote preconditioning of trauma (RPCT) and exerts cardioprotection via neurogenic activation of protein kinase C (PKC) (Jones et al., 2009). Furthermore the role of bradykinin in reducing the infarct size and ameliorating the focal cerebral ischemia is also documented (Danielisova et al., 2014). The present review emphasizes the cardioprotective and neuroprotective actions of bradykinin in different forms of ischemic conditioning along with the possible mechanisms.

2. Bradykinin and ischemic preconditioning

2.1. Evidences

Bradykinin is an important endogenous peptide that mediates ischemic preconditioning-induced cardioprotection via activation of a unique signal transduction cascade that rapidly results in acquisition of tolerance, when exposed to sustained ischemic conditions. Bradykinin preconditioning elicits cardioprotective effects against postischaemic contractile dysfunction similar to that of ischemic preconditioning (Starkopf et al., 1997). It has been shown that cardiac interstitial concentration of bradykinin is increased during ischemic preconditioning in left anterior descending coronary artery occlusion model of myocardial ischemia in anesthetized cats suggesting the possible role of bradykinin in ischemic preconditioning-induced cardioprotection (Pan et al., 2000). Wall and coworkers demonstrated the key role of bradykinin in ischemic preconditioning-induced cardioprotective effects in an open-chest rabbit model of acute coronary occlusion. Intra-atrial infusion of bradykinin (250 μg/kg/min) mimicked the cardioprotective effects of ischemic preconditioning. Furthermore, pretreatment with HOE 140 (B_2 receptor antagonist, 1 μg/kg) abolished the cardioprotective effect of bradykinin as well as of ischemic preconditioning indicating that endogenously generated bradykinin may mediate the cardioprotective events associated with ischemic preconditioning (Wall et al., 1994). Kositprapa and coworkers demonstrated that administration of HOE-140 (1 μg/kg i.v. bolus) abolished the cardioprotective effects of late phase of ischemic preconditioning as well as of intra-arterial bradykinin in open chest rabbit model of ischemia reperfusion injury (Kositprapa et al., 2001).