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Review article

Protective roles of bioactive peptides during ischemia-reperfusion injury: From bench to bedside

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ABSTRACT

Ischemia-reperfusion (I/R) is a well-known pathological condition which may lead to disability and mortality. I/R injury remains an unresolved and complicated situation in a number of clinical conditions, such as cardiac arrest with successful reanimation, as well as ischemic events in brain and heart. Peptides have many attractive advantages which make them suitable candidate drugs in treating I/R injury, such as low toxicity and immunogenicity, good solubility property, distinct tissue distribution pattern, and favorable pharmacokinetic profile. An increasing number of studies indicate that peptides could protect against I/R injury in many different organs and tissues. Peptides also face several therapeutic challenges that limit their clinical application. In this review, we present the mechanisms of action of peptides in reducing I/R injury, as well as further discuss modification strategies to improve the functional properties of bioactive peptides.

Contents

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1. Introduction

Ischemia-reperfusion (I/R) is considered a well-recognized pathological condition characterized by an initial restriction of blood flow to an area or organ followed by restoration of blood flow [1]. I/R injury is implicated in the pathophysiology of several clinical conditions such as hypertension, stroke, sepsis, major trauma, shock, and organ transplantation [2]. A number of mechanisms have been proposed as mediators of the damage induced by I/R, including activation of the complement system and leukocyte recruitment, increased free radical concentration, calcium overload, endothelial dysfunction, and endoplasmic reticulum stress [2–4]. I/R could activate the pathways of necrosis, apoptosis, necroptosis, and autophagy, which may lead to cell death [5]. There are three time frames in the protection against I/R injury: before (ischemic pre-conditioning) or after (ischemic per-conditioning) the onset of ischemia, or at the onset of reperfusion (ischemic post-conditioning) [6].

An increasing number of studies indicate that peptides have good solubility property, distinct tissue distribution, and favorable pharmacokinetic profile, which could result in high uptake into target tissues and rapid clearance from the blood and non-target tissues [7–9]. Some peptides exhibit low toxicity and immunogenicity, and they can be easily synthesized and modified to improve their stability and binding affinity [9,10]. These advantages make them suitable candidate drugs in treating I/R injury. Currently, a large variety of bioactive peptides that target specific receptors, activators, and the processes of angiogenesis, inflammation and apoptosis in I/R injury have been identified and characterized [11–15].

In this review, we highlight recent studies that provide new insight into the roles and mechanisms of peptides in reducing I/R injury, as well as further discuss modification strategies to improve the functional properties of bioactive peptides.

2. Peptides and I/R injury

2.1. Peptides and cerebral I/R injury

Cerebral I/R injury can be described as a deleterious, but potentially salvageable deterioration of an ischemic injury after reperfusion [16]. Cerebral I/R injury is a common pathophysiological process of stroke which may contribute to both death and disability in humans [17]. The major pathogenic mechanisms of cerebral I/R injury include glutamate-mediated excitotoxicity, oxidative stress, edema, inflammation, necrotic and apoptotic cell death, mitochondrial dysfunction, and breakdown of the blood-brain barrier [3,18]. These events usually occur in an overlapping manner and depend on the intensity and duration of the injury [18]. A growing body of evidence suggests that peptides could interfere with one or more of these mechanisms (Table 1), such as anti-inflammation [22,23,26], anti-oxidant [23,32,33], and anti-apoptotic effects [30,32], thus leading to the emergence of new therapeutic interventions in cerebral I/R injury. Identification of other peptides exerting inhibitory effects on oxidative stress, inflammation, and apoptosis, together with structure-function relationship study, will provide new opportunities to develop new safe drugs against cerebral I/R injury.

2.2. Peptides and myocardial I/R injury

During myocardial ischemia, the deprivation of oxygen and nutrient supply could result in a series of abrupt metabolic and biochemical changes within the myocardium, such as the production of lactate and a drop in intracellular pH [37]. The damaged myocardial structure and decreased heart function induced by ischemia can be alleviated by timely myocardial reperfusion [3,38]. However, myocardial reperfusion can lead to irreversible cell damage as well as endothelial and microvascular injury [39]. Therefore, effective cardioprotective strategies that target the ischemic and reperfusion components of myocardial injury should be developed [6]. Recently, an increasing number of studies indicate that peptides exert cardioprotection against myocardial I/R injury (MIRI) in intact animals, isolated hearts, and cardiac myocytes (Table 2) mainly through reduction of oxidative stress [40,43,46,50,56,59,60], pro-survival/anti-apoptotic action [40,47,48,49,51,52,54,57,58,60,61,64,65], enhanced release of endothelial NO [45], metabolic changes [62], prostaglandin release [41], conversion to ET-1 by ECE [53], activation of the Na^+/H^+ exchanger [42], and prevention of specific IgM binding to ischaemic antigens in the heart [66]. Considering these peptides have showed cardioprotective role against MIRI mainly in animals, further investigations are needed to carry out at the clinical level.

2.3. Peptides and renal I/R injury

Acute renal failure induced by I/R injury remains one of the most common causes of morbidity and mortality worldwide [68]. Renal I/R

Table 1
Protective effects of peptides in cerebral I/R injury.

Peptides	Experimental models	Proposed mechanisms	Refs.
Apelin-13	Cerebral I/R *in vivo* (Mouse)	Up-regulation of AMPKα phosphorylation level	[19]
C19	Cerebral I/R *in vivo* (Rat)	Unknown	[20]
CGRP	Cerebral I/R *in vivo* (Rat)	*Via* the action of vasodilation and indirectly by improvement of the BBB dysfunction	[21]
COG1410	Cerebral I/R *in vivo* (Mouse)	Reduction of early inflammation	[22]
Cordymin	Cerebral I/R *in vivo* (Rat)	Anti-inflammation and antioxidant effect	[23]
CART	Cerebral I/R *in vivo* (Rat)	Facilitation of the transcription, synthesis and secretion of BDNF in a CREB-dependent way	[17]
Exendin-4	Cerebral I/R *in vivo* (Mouse)	Probably through increased intracellular cAMP levels	[24]
Humanin	Cerebral I/R *in vivo* (Mouse)	Activation of PI3K/Akt pathway	[25]
IKK-NBD peptide	Cerebral I/R *in vivo* (Rat)	Partly through reduction of inflammation	[26]
SS31	Cerebral I/R *in vivo* (Mouse)	Down-regulation of CD36	[27]
DADLE	Cerebral I/R *in vivo* (Rat)	Possibly through increase of GDNF expression	[28]
Hepcidin	Cerebral I/R *in vivo* (Rat)	Induction of FPN1 internalized degradation and iron accumulation, and reduction of the efflux of iron	[29]
Glutathione	Cerebral I/R *in vivo* (Rat)	Activation of the PI3K/Akt pathway, inactivation of FOXO3, and expression of Bcl2	[30]
Bradykinin	Cerebral I/R *in vivo* (Rat)	Unknown	[31]
Ghrelin	Cerebral I/R *in vivo* (Rat)	Inhibition of apoptosis and oxidative stress	[32]
Liraglutide	Cerebral I/R *in vivo* (Rat)	Anti-oxidative effects and VEGF upregulation	[33]
Orexin-A	Cerebral I/R *in vivo* (Rat)	Probably through the HIF-1α pathway	[34]
Leptin	Cerebral I/R *in vivo* (Mouse)	Through the PI3K/Akt pathway	[35]
Adiponectin	Cerebral I/R *in vivo* (Mouse)	Through an endothelial nitric oxide synthase–dependent mechanism	[36]

AMPK: AMP-activated protein kinase; CGRP: calcitonin gene-related peptide; BBB: blood-brain barrier; CART: cocaine and amphetamine regulated transcript; BDNF: brain derived neurotrophic factor; CREB: cAMP-response element binding protein; cAMP: cyclic adenosine monophosphate; PI3K: phosphatidylinositol 3-kinase; Akt (PKB): protein kinase B; IKK: IκB kinase; NBD: NF-κB essential modulator binding domain; DADLE: [D-Ala2,D-Leu5] enkephalin; GDNF: glial cell line-derived neurotrophic factor; FPN1: ferroportin 1; FOXO3: forkhead box O3; VEGF: vascular endothelial growth factor; HIF-1α: hypoxia-inducible factor-1α.