Biochemical Pharmacology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Research update

The insulin-like growth factor I system: Physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome

Jun Ren [a,b,*], Piero Anversa [c]

[a] Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[b] Center for Cardiovascular Research and Alternative Medicine, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA
[c] Departments of Anesthesia and Medicine and Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 4 September 2014
Accepted 11 December 2014
Available online xxx

Keywords:
IGF-1
Metabolic syndrome
Obesity
Heart diseases

ABSTRACT

Metabolic syndrome is a cluster of risk factors including obesity, dyslipidemia, hypertension, and insulin resistance. A number of theories have been speculated for the pathogenesis of metabolic syndrome including impaired glucose and lipid metabolism, lipotoxicity, oxidative stress, interrupted neurohormonal regulation and compromised intracellular Ca^{2+} handling. Recent evidence has revealed that adults with severe growth hormone (GH) and insulin-like growth factor I (IGF-1) deficiency such as Laron syndrome display increased risk of stroke and cardiovascular diseases. IGF-1 signaling may regulate contractility, metabolism, hypertrophy, apoptosis, autophagy, stem cell regeneration and senescence in the heart to maintain cardiac homeostasis. An inverse relationship between plasma IGF-1 levels and prevalence of metabolic syndrome as well as associated cardiovascular complications has been identified, suggesting the clinical promises of IGF-1 analogues or IGF-1 receptor activation in the management of metabolic and cardiovascular diseases. However, the underlying pathophysiological mechanisms between IGF-1 and metabolic syndrome are still poorly understood. This mini-review will discuss the role of IGF-1 signaling cascade in the prevalence of metabolic syndrome in particular the susceptibility to overnutrition and sedentary life style-induced obesity, dyslipidemia, insulin resistance and other features of metabolic syndrome. Special attention will be dedicated in IGF-1-associated changes in cardiac responses in various metabolic syndrome components such as insulin resistance, obesity, hypertension and dyslipidemia. The potential risk of IGF-1 and IGF-1R stimulation such as tumorigenesis is discussed. Therapeutic promises of IGF-1 and IGF-1 analogues including mecasermin, mecasermin rinfabate and PEGylated IGF-1 will be discussed.

© 2014 Elsevier Inc. All rights reserved.

1. Metabolic syndrome and cardiovascular health

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. Epidemiological study has projected up to 23.3 million mortality in 2030 due to cardiovascular diseases because of the aging populations [1,2]. Despite the intensive management for cardiovascular diseases, many patients fail to achieve a satisfactory clinical outcome of managements and interventions against cardiovascular diseases. This may be attributed to, in part, the ever-rising prevalence of obesity and type 2 diabetes that undermine the effective management of cardiovascular diseases [3,4]. In fact, overweight/obesity, diabetes mellitus, dyslipidemia and hypertension often cluster together as the most significant risk factors for cardiovascular disease [3,5,6]. For example, even a modest increase in body weight may result in a rather significant rise in the overall risk of cardiovascular mortality. This cluster of risk factors of metabolic origin is collectively known as metabolic syndrome. Since its appearance in the medical vernacular a couple of decades ago, the cardiovascular sequelae of metabolic syndrome are recognized with a fast growing prevalence worldwide. The current criteria denote metabolic syndrome as a cluster of clinical symptoms including large waist circumference, hypertension, hyperglycemia, dyslipidemia and insulin resistance, all of which commonly associated with the increased prevalence of obesity and type 2 diabetes mellitus [6]. Patients with one or more metabolic

* Corresponding author.
E-mail addresses: ren.jun@zs-hospital.sh.cn, jren@uwyo.edu (J. Ren).

http://dx.doi.org/10.1016/j.bcp.2014.12.006
0006-2952/© 2014 Elsevier Inc. All rights reserved.

Please cite this article in press as: Ren J, Anversa P. The insulin-like growth factor I system: Physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. Biochem Pharmacol (2015), http://dx.doi.org/10.1016/j.bcp.2014.12.006

syndrome components may display certain non-specific clinical symptoms, obesity and a sedentary lifestyle. A plethora of epidemiological and clinical evidence has depicted an important role of glucose and lipid metabolism, insulin resistance and central obesity as the most predominant factors for the occurrence of metabolic syndrome [6,7]. Insulin, a cardinal player in glucose and lipid metabolism, promotes glucose uptake and lipid oxidation, as well as suppresses glucose production. Insulin-resistant individuals exhibit much higher risk of developing hypertension, type 2 diabetes and the overall risk of cardiovascular diseases [5,8]. However, it is noteworthy that even confirmed metabolic syndrome has little clinical therapeutic value other than treating each individual component of metabolic syndrome such as hypertension and insulin resistance [5], which may or may not lower cardiovascular risks affiliated with metabolic syndrome. In an effort to better address the health care issues associated with metabolic syndrome, intensive effort has been engaged to better elucidate the mechanism of action behind contributing cardiovascular risk factors for metabolic syndrome including factors predisposing metabolic syndrome and the associated complications. Recent evidence has depicted, although sometimes controversially, a pivotal role for insulin-like growth factor I (IGF-1) in the prevalence of insulin resistance and metabolic syndrome [9–11]. IGF-1 is an anabolic growth hormone with an essential role in cell proliferation, growth, and metabolism, and is associated with the prevalence of pathological conditions such as obesity and aging [2,12–17]. Circulating IGF-1 levels are reported to be inversely correlated with the risk of cardiovascular diseases [2]. For example, elderly patients with low circulating IGF-1 levels are at a much higher risk of ischemic stroke and congestive heart failure [2,18]. Not surprisingly, recent evidence has revealed promising therapeutic benefits of IGF-1 or its analogues such as mecasermin, mecasermin rinfabate and polyethylene glycol modified IGF-1 (PEG-IGF-1) in certain pathological conditions including muscular dystrophies and heart failure [2,19–21].

Insulin and IGF-1 share structural homology and interact with the same membrane receptors, albeit with different affinities. Insulin and IGF-1 exert complementary biological actions, which are pathologically important when levels of one hormone drops significantly [11]. One recent large scale community-based Framingham Heart Study suggested that lower IGF-1 levels are associated with insulin resistance and metabolic syndrome [10]. This is in line with the observation of reduced IGF-1 levels in individuals with metabolic syndrome and its various components, in a manner reminiscent of ischemic cardio- and cerebrovascular diseases [11]. Both free IGF-1 and IGF-1/IGFBP-3 ratio, a rough estimate of free IGF-1 levels, are significantly decreased in obesity [22]. Further evidence revealed the clinical value of IGF-1/IGFBP-3 ratio. After adjusting for age and ethnic background, men and women in the lowest quartile of the IGF-1/IGFBP-3 ratio are 3-fold more likely to meet the Adult Treatment Panel III (ATP-III) definition for metabolic syndrome and twice as likely to be insulin-resistant (<0.760). IGF-1/IGFBP-3 ratio decreases significantly as the number of metabolic syndrome components increases [23]. In addition, visceral adipose tissue mass is inversely correlated with circulating IGF-1 levels [22]. Consistently, increased metabolic syndrome prevalence is also consolidated in patients with growth hormone (GH) deficiency, which is partially reversed by GH replacement therapy [11]. Patients with abdominal obesity display a favorable response to GH therapy in body composition, lipid and glucose homeostasis, suggesting the therapeutic potentials of recombinant GH or activation of endogenous GH production for metabolic disorders in obesity [22,24]. Moreover, IGF-1 binding capacity may also contribute to the altered IGF-1 levels in metabolic syndrome although controversy exists for the use of IGF-1 and its binding proteins in clinics [10,11]. Nonetheless, the precise mechanism(s) behind the apparent inverse relationship between circulating IGF-1 level and metabolic syndrome prevalence remains elusive. Given the essential role of IGF-1 in the maintenance of cardiac geometry and function [11,25], it may be speculated that IGF-1 and IGF-1 signaling cascade play an essential role in the maintenance of cardiac function and structure in various metabolic disorders although convincing evidence is still lacking. Given the complexity of metabolic syndrome and IGF-1 system, this review will attempt to address the following questions based on the currently available clinical and experimental findings: [1] Is there evidence for changes in IGF-1 levels in individuals with metabolic syndrome? [2] What are the mechanisms responsible for the connection between IGF-1 and metabolic syndrome prevalence? [3] Will experimental and clinical findings for IGF-1 in metabolic syndrome provide useful information or guidance in designing novel therapeutic approaches for prevention, treatment, and possible prognosis of metabolic syndrome or its complications? We hope to provide a landscape of molecular mechanisms involved in heart diseases in patients and animal models of metabolic syndrome component, and to address the therapeutic benefit, if any, of IGF-1 analogue in the management of metabolic syndrome.

2. Insulin-like growth factor 1 (IGF-1)

IGF-1 is primarily produced in the liver from GH metabolism, prior to secretion into circulation. IGF-1 possesses insulin-like metabolic action (short-term) and growth factor-like long-term effects on cell proliferation and differentiation [2,26,27]. IGF-1 activity is regulated by IGF binding proteins (IGFBP), with IGFBP-3 carrying majority (>80%) of circulating IGF-1. At least six IGFBPs are identified to regulate the levels and biological activities of IGF-1 through IGF-1 receptor (known as the type 1 IGF receptor, IGF-1R) [28]. IGF-1R consists of a $\alpha_2\beta_2$ heterotetrameric complex of ~400 kDa with two extracellular α-subunits that contain ligand-binding sites. Each α-subunit of IGF-1R may couple to one of two membrane-spanning β-subunits containing domains with intrinsic tyrosine kinase activity [2]. Tyrosine kinase phosphorylation of the IGF-1R as well as the proximal cytosolic substrate collagen-homology (SHC) leads to the phosphorylation of IGF-IR substrates, insulin receptor substrate (IRS)-1 or -2 and generates the docking site for the Src homologue 2 (SH2) domain of the growth factor receptor-binding protein 2 (Grb2). Upon phosphorylation of IGF-1R and/or SHC, a ternary complex is formed including SHC, Grb2 and the Ras guanylnucleotide exchange factor SOS to target SOS to the plasma membrane location of Ras. With the exchange of GDP for GTP on Ras facilitated by SOS, the mitogenic Ras/Raf/mitogen-activated protein kinase (MAPK) cascade is turned on to promote cell growth, survival and proliferation. Meanwhile, the p85 regulatory subunit of PI3-kinase serves as an essential SH2 domain-containing protein. Binding of tyrosine-phosphorylated IRS-1 with p85 activates the catalytic function of the 110-kDa subunit of phosphatidylinositol 3′ kinase (PI3K), a seminal player for cardiac survival, metabolism and function including glucose transport, anti-lipolysis, protein and glycogen synthesis, inhibition of apoptosis, and contractile function [29]. Activated Akt inhibits pro-apoptotic signaling including Bad and Caspase-9 while facilitating nuclear factor-κB (NF-κB) transcriptional activity and mammalian target of rapamycin (mTOR), which serves as a main mediator of mitogenic stimuli transduced by PI3K/Akt [30]. Activation of the MAPK pathway is deemed essential for the mitogenic action of IGF-1 whereas the PI3K pathway is important for mediating the metabolic and anti-apoptotic signals of IGF-1. Further evidence revealed that phosphatase and the Tensin homolog gene deleted on chromosome 10 (PTEN) may serve as an essential lipid phosphatase to oppose IGF-IR-Akt signaling

Please cite this article in press as: Ren J, Anversa P. The insulin-like growth factor I system: Physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. Biochem Pharmacol (2015), http://dx.doi.org/10.1016/j.bcp.2014.12.006

Download English Version:

https://daneshyari.com/en/article/5823380

Download Persian Version:

https://daneshyari.com/article/5823380

Daneshyari.com