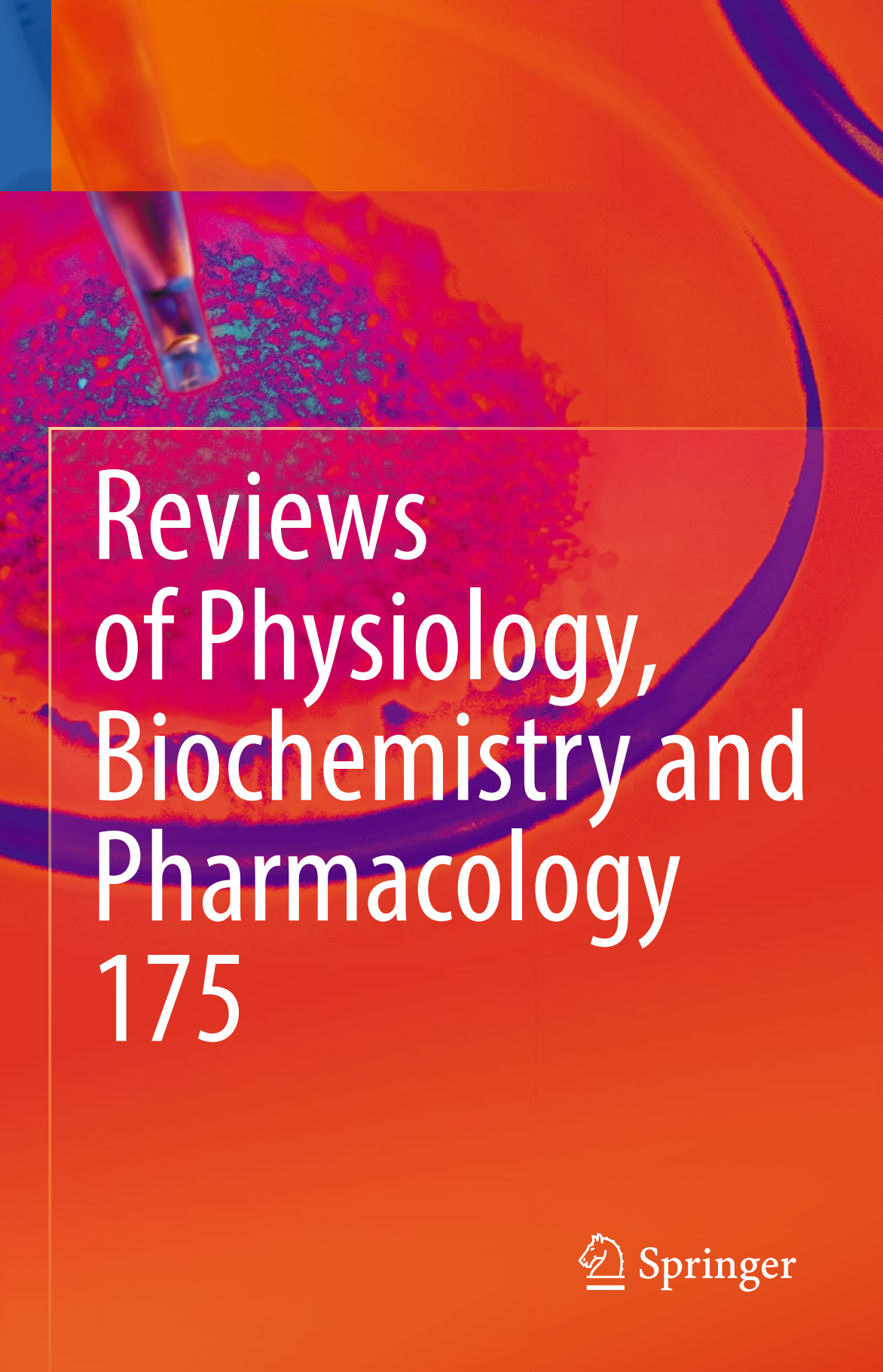
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Insulin-Like Growth Factor 1 in the Cardiovascular System

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Contents

Abstract Non-communicable diseases, such as cardiovascular diseases, are the leading cause of mortality worldwide. For this reason, a tremendous effort is being made worldwide to effectively circumvent these afflictions, where insulin-like growth factor 1 (IGF1) is being proposed both as a marker and as a central cornerstone in these diseases, making it an interesting molecule to focus on. Firstly, at the initiation of metabolic deregulation by overfeeding, IGF1 is decreased/inhibited. Secondly, such deficiency seems to be intimately related to the onset of MetS and establishment of vascular derangements leading to atherosclerosis and finally playing a definitive part in cerebrovascular and myocardial accidents, where IGF1 deficiency seems to render these organs vulnerable to oxidative and apoptotic/necrotic damage. Several human cohort correlations together with

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basic/translational experimental data seem to confirm deep IGF1 implication, albeit with controversy, which might, in part, be given by experimental design leading to blurred result interpretation.

Keywords Atherosclerosis · Cardiovascular disease · Cardiovascular system · IGF1 · Metabolic syndrome

1 Introduction

Non-communicable diseases such as diabetes, cardiovascular diseases, or cancer are the leading cause of mortality worldwide (Lee 2014). On the other hand, the term cardiovascular diseases (CVD), as defined by the World Health Organization, includes myocardial infarction and cerebrovascular disease. According to the World Economic Forum's 2009 report, these diseases have been postulated as endangering the world's economy, even being perceived as more threatening than economic crises, natural disasters, or pandemic influenza (Narayan et al. 2010). For this reason, a tremendous effort is being made worldwide to effectively circumvent these afflictions, where insulin-like growth factor 1 (IGF1) is being proposed both as a marker and as a central cornerstone in these diseases, making it an interesting molecule to focus on for reasons that will be thoroughly described along the following lines.

In the last decade, a prodigious amount of information concerning IGF1 arose regarding its newly discovered actions on every tissue. However, with no doubt, the area with the greatest amount of new data has been mitochondrial protection, metabolism, the cardiovascular system (CVS), and cytoprotection with antioxidant properties in several organs.

Herein we will present and integrate the most relevant findings regarding IGF1 actions in the cardiovascular system. Before getting into the matter, IGF1, its biochemistry, and physiology will be presented, with canonical and non-canonical pathways and receptor interactions. At first, it will be briefly presented the role that IGF1 plays in metabolism. This is an important fact to mention in order to understand its implication from before the onset of any cardiovascular complication and to introduce the idea that IGF1 might be implicated from the very early stages of metabolic deregulation all the way to cardiovascular recovery after an accident has occurred. However, no deep immersion will be made as this topic has been recently and thoroughly revised (Aguirre et al. 2016). In brief, IGF1 acts as a cornerstone in the growth hormone (GH)/IGF1/insulin axis, which can be deregulated by overfeeding and sedentary lifestyle. Such alteration ends up by downregulating or inhibiting IGF1 and eliciting insulin resistance, with its concomitant consequences that will be further discussed.

Thereafter, atherosclerosis will be reviewed integrating endothelial/vascular effects with immunologic ones, in the form of a progressive disease, and inserting, wherever it has been discovered, IGF1 actions in the vasculature and the immune system. Succinctly, IGF1 both acts as an anti-inflammatory agent and by regulating

the immune response. Then, IGF1 actions in the vasculature (regulating certain factors like eNOS and oxidative damage via Nrf2) and in the heart's development and homeostasis will coronate its implication in these pathologies.

After metabolic deregulation has led to metabolic syndrome (MetS) and atherosclerosis, clinical data of IGF1 in CVD will be reconciled, in which the majority sustain that IGF1 levels correlate with either prognosis, severity, or outcome, however, with a certain degree of controversy. Lastly, IGF1 as a treatment option will be debated, remarking its beneficial actions and unwanted effects from different trials for different diseases.

This review offers a new insight that brings together, firstly, a novel perspective of non-canonical IGF1 pathways. Thence after bringing simultaneously metabolic syndrome and atherosclerosis, describing vascular and immunologic effects. IGF1 implication in the system as a whole will be established. It also resumes novel findings of direct IGF1 actions in the heart (basic and translational) together with clinical data from CVD and stroke. Altogether it gives a novel and undivided approach to the totality of the pathophysiological CVD entity.

2 IGF1 and IGFBP Physiology

IGF1 conforms a large protein of 70 amino acids with several structural and functional domains. This pleiotropic hormone possesses endocrine, paracrine, and autocrine effects. It also shares structural homology with IGF2 and proinsulin (over 60% homology) (Rinderknecht and Humbel 1978; Flier et al. 1997). IGF1 is synthesised in virtually every tissue (D'Ercole et al. 1984), yet mainly produced by the liver (responsible for ~75% of the circulating hormone) following GH stimulation. Conversely, IGF1 acts as a negative regulator for GH secretion in the hypothalamus via somatostatin production in the adrenal gland (Berelowitz et al. 1981; Böni-Schnetzler et al. 1991; Ohlsson et al. 2009). This inhibitory negative feedback mechanism is very important for metabolic coordination (Fig. 1). IGF1 is strongly regulated by the professed insulin-like growth factor-binding proteins (IGFBPs), which increase IGF1 half-life, from minutes to hours, most commonly by forming a heterotrimeric complex with acid-labile subunit and IGFBP3. However, binding to this complex hinders its attachment to the type 1 insulin-like growth factor 1 receptor (IGF1R) (Clemmons 1998; Rosenfeld et al. 2000; Rajpathak et al. 2009; Martín-Estal et al. 2015). For this reason, the ratio between IGF1 and IGFBP3 is considered the clinically relevant value to roughly estimate biologically active/available IGF1. Nevertheless, being vaguely precise as its regulation system goes beyond such simplicity. IGFBPs also operate by guiding IGF1 to tissues to inhibit or potentiate IGF1 actions. IGFBPs may as well act as independent substrates (without bound IGF1) for IGF1R and/or specific IGFBP membrane, intracellular, or nuclear receptors (Clemmons 1998; Rosenfeld et al. 2000; Rajpathak et al. 2009). Up until now, six high-affinity IGFBPs have been described (Clemmons 1998; Rosenfeld et al. 2000; Rajpathak et al. 2009). Likewise, insulin-like growth factor-binding

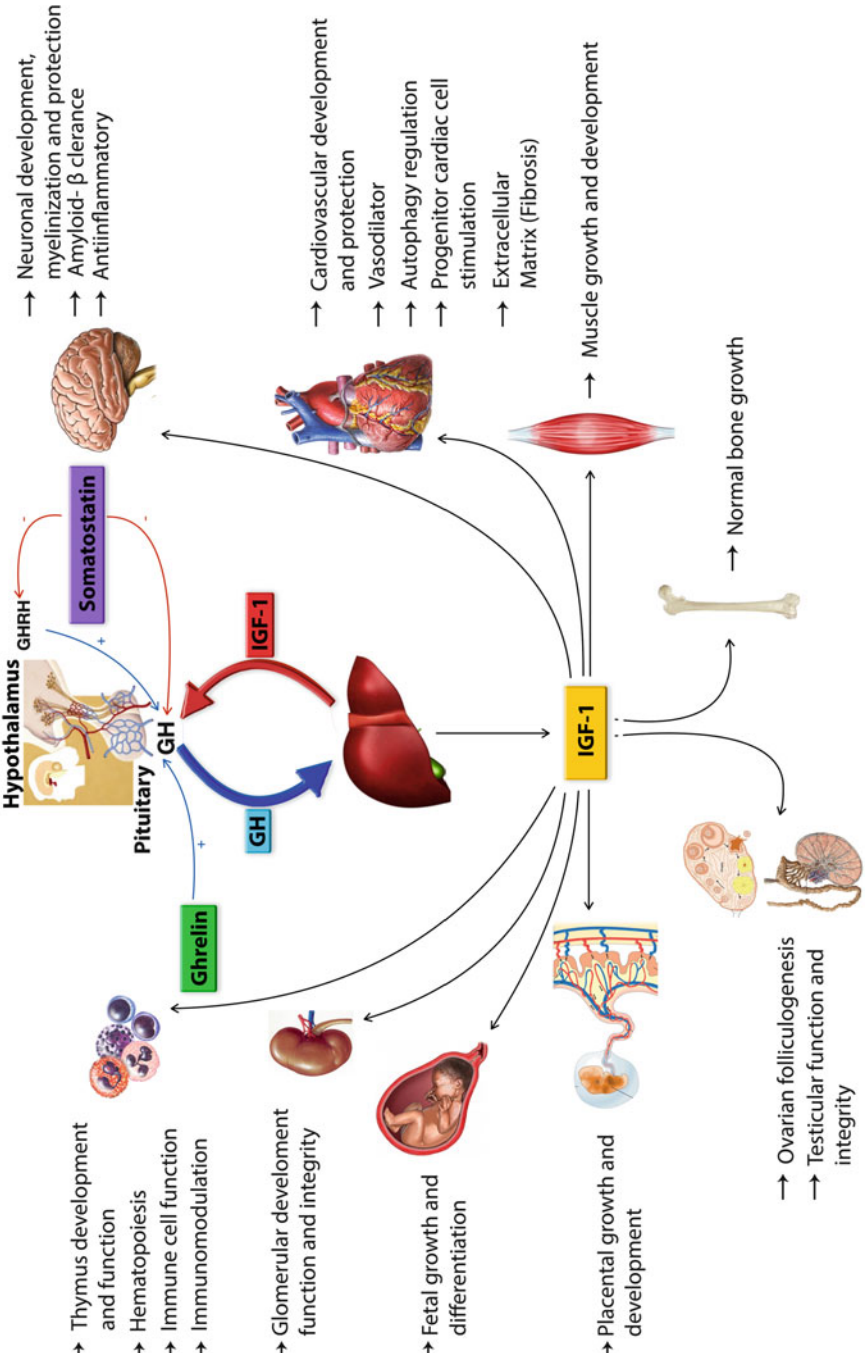

Fig. 1 Model of GH/IGF1 axis regulation and IGF1 target organs. Negative feedback mechanism induced by IGF1 regulates the GH/IGF1 axis: IGF1 inhibits GH gene expression by stimulating somatostatin secretion. GH secretion stimulates IGF1 secretion in the liver. GHRH (growth hormone-releasing hormone) stimulates GH secretion, which stimulates IGF1 secretion

protein-related proteins (IGFBPrPs) have been proposed, which assist IGF1, but still, exactly how is not yet completely understood (Liu et al. 2002; López-Bermejo et al. 2003).

Nonetheless, it is worth mentioning that IGF1 has a complex post-transcriptional and post-translational modification process. Six exons make up the IGF1 gene, which undergoes alternative splicing, dependent upon transcription starting sites, and post-translational modification, leading to several isoforms in different organs (Temmerman et al. 2010). For what is known today, two classes of post-transcriptional modification can occur. One that alters the 5′ end of the transcript and another altering 3′ ends. For the former, affecting the N-terminal signal peptide, if the transcription initiates at exon 1, it then skips exon 2 which results in removal of a 186-base long sequence. These transcripts are termed as Class 1 transcripts. On the other hand, transcripts that have exon 2 and usually lack exon 1 are known as Class 2 transcripts (Shavlakadze et al. 2005). Conversely, 3′ alternative splicing affecting the C-terminal peptide extension adds further complexity. For example, when a Class 1 transcript undergoes partial splicing of exon 4 and skips exons 5–6, 19 amino acids are added to the common 16 amino acids encoded by exon 4, thus generating a 35-amino acid long E-peptide in humans, termed Class 1 Ea-peptide. This peptide is the common IGF1 isoform mainly expressed by the liver (circulating isoform) and skeletal muscle; however, virtually every tissue makes this isoform (Shavlakadze et al. 2005; Stavropoulou and Halapas 2009; Temmerman et al. 2010). Moreover, human Eb-peptide contains additional 61 amino acids encoded by exon 5 and a nucleus-nucleolus import sequence, and Ec (also called mechano growth factor, MGF, Eb in mice) expresses full exon 4, 49 bp of exon 5, and then exon 6 (exons 4–6) yielding an extension peptide with a total predicted length of 41 amino acids. Eb and Ec (MGF) peptides both were found to be expressed in the liver; however Ec (MGF) is highly expressed in injured muscles (Shavlakadze et al. 2005). Of recent discovery, the mIGF1 isoform, comprising a Class 1 signal peptide and a C-terminal Ea extension peptide, is highly expressed in neonatal tissues and in the adult liver but decreases during ageing in extrahepatic tissues. However its expression is reactivated in response to damage and has been attributed dramatic cell survival and renewal actions in senescent muscle (Santini et al. 2006). Then, post-translational modifications (protease cleavage) give rise to additional isoforms of the unprocessed (precursor) IGF1, which differ by the length of the amino-terminal signal peptide and structure of the so-called extension peptide (E-peptide) on the carboxy-terminal end, which are both cleaved to yield a 70-amino-acid-long single-chain mature IGF1 polypeptide with three intrachain disulphide bridges. IGF1 contains a B amino-terminal domain, an A domain, and a C domain. However, unlike proinsulin, IGF1 polypeptides also contain a D-carboxy-terminal domain (Shavlakadze et al. 2005).

IGF2 physiological role is still unclear. But, still, important functions have been characterised for foetus development and cerebral protection (Castilla-Cortázar et al. 2011; Garcia-Fernandez et al. 2011). IGF2 can act over its own receptor (IGF2 receptor – IGF2R), which is a manose-6-phosphate transmembrane protein with undetermined actions, or it can bind to and activate IGF1R, despite with less affinity