Mechanisms of Ageing and Development xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

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

GH/IGF-I/insulin system in centenarians

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ARTICLE INFO

Article history:
Received 14 October 2016
Received in revised form
10 November 2016
Accepted 3 December 2016
Available online xxx

Keywords:
IGF-I
Insulin
Centenarians
Longevity
Ageing

ABSTRACT

The endocrine system plays a major role in the regulation of several biological activity and in the ageing process. Evolutionary conservation of GH/IGF-I/insulin pathway from worms to mice and similarities in this system between mice and humans raised expectations that downregulated activity of the GH/IGF-I/insulin pathway could be beneficial for the extension of human life span.

Centenarians represent the best example of successful ageing having reached the very extremes of the human life span, escaping and delaying the occurrence of several fatal age-related diseases, such as cancer and cardiovascular diseases.

This review describes the endocrine profile of centenarians concerning the GH/IGF-I/insulin system, focusing on the relevance of this pathway on the modulation of ageing and longevity.

Contents

1. Introduction

Over the last two decades several reports have underlined the pivotal role of insulin/insulin-like growth factor type I (IGF-I) signaling in the control of ageing in organisms ranging from unicellular yeast to more complex mammals (Bartke et al., 2016).

While lower species have a single insulin/IGF signaling, it diverged into two different hormonal pathways in mammals: the growth hormone (GH)/IGF axis and the glucose/insulin system. Both pathways have overlapping functions and strict interactions (Bartke et al., 2016).

The GH/IGF axis represents the main regulator of postnatal growth and modulate several other physiological processes such as metabolism. This system involves several hormones (GH, IGF-I and IGF type II) (Vottero et al., 2013; Vitale et al., 2013).

GH is a 191 amino acid peptide hormone, which is produced by somatotroph cells of the adenohypophysis and secreted in a pulsatile manner. Its secretion is stimulated by GH releasing hormone, ghrelin and dietary factors, such as proteins and hypoglycemia. GH secretion is negatively regulated by somatostatin. GH exerts its effects by interaction with GH receptor and activates a cascade of signaling events, most relevant of which is the JAK-STAT pathway. In humans, the extracellular GH-binding domain of the GH recep-

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http://dx.doi.org/10.1016/j.mad.2016.12.001
0047-6374/

tor is proteolytically cleaved from the mature form and circulates in plasma as a GH-binding protein (Rosenfeld et al., 2009; Giustina et al., 2008).

IGF-I is a small polypeptide hormone, consisting of 70 amino acid residues, mainly produced by the liver under GH control. However, local production of IGF-I has been also described in bone, muscle, brain, vessels, ovary, prostate and practically in every tissue of the body, where it controls metabolism, cell proliferation and differentiation via autocrine and paracrine actions (Stewart and Rotwein, 1996). The biological activities of IGF-I are mainly modulated by the IGF-I receptor (IGF-IR) and heterodimeric insulin/IGF hybrid receptors. IGF-I can also interact with insulin receptor (IR), but with a lower affinity (Siddle, 2012).

IGF type II (IGF-II) is a 67 amino acid polypeptide which has 67% homology with IGF-I. IGF-II is mainly produced by the liver and modulates foetal development and differentiation, but in adults its function is unclear. IGF-II exerts its activity through the interactions with IGF-IR, IR and hybrids of these two receptors. IGF-II also binds the IGF-II/mannose-6-phosphate receptor. This receptor does not play a major role in IGF signal transduction, but it is involved in the clearance and degradation of IGF-II, preventing the extracellular accumulation of this hormone (Livingstone and Borai, 2014).

The action of IGFs (IGF-I and IGF-II) is regulated by IGF binding proteins (IGFBPs) and IGFBP proteases. The IGFBPs represent a family of six binding proteins (IGFBP-1-6) with high affinity and specificity for the IGFs. Approximately 75% of IGFs circulates in plasma as a ternary 150 kDa complex, composed of IGF-I or IGF-II, IGFBP-3 and the acid labile subunit (ALS) protein. This complex represents an IGF reservoir, regulates the amount of IGF available for receptor binding and influences transport through compartments. IGFBPs limit IGF-I and IGF-II action by restricting access to their receptors. In fact, IGF-I is biologically active only in its free form, which performs nearly 1% of total IGF-I. Therefore the IGF-I/IGFBP3 molar ratio is recognized as a better indicator of IGF-I bioavailability than total IGF-I. Binding of IGFBPs to IGFs also preserves these hormones from degradation by proteases and prolongs the half-life of IGF-I and IGF-II (Rosenzweig, 2004). In addition, IGFBPs appear to have also direct cellular effects independent of the IGFs. The activity of IGFBPs is also modulated by specific proteases, which cleave IGFBPs, producing fragments with lower or no binding affinity for IGFs (Ranke, 2015).

Insulin and its signaling are implicated in both central and peripheral mechanisms influencing the ingestion, distribution, metabolism, and storage of nutrients in organisms ranging from worms to humans. Insulin interacts with the IR and activates a complex of intracellular downstream pathways, which stimulates glucose uptake. Almost all insulin signals are produced or modulated through tyrosine phosphorylation of IRS1 or its homolog IRS2 or other scaffold proteins (White, 2003). IRS-proteins are adapter molecules that link the IR and IGF-IR to common downstream signaling cascades and heterologous regulatory mechanisms (White, 2003; Sun et al., 1995). Following tyrosine phosphorylation, each substrate associates with one or more intracellular molecules through interaction of the tyrosine phosphorylation sites in the substrates with SH2 domains of intracellular proteins to generate downstream signals. The two most important SH2 molecules associated with insulin action are the enzyme phosphatidylinositol 3-kinase (PI3K) and the adaptor molecule Grb2 (Skolnik et al., 1993; Cheatham et al., 1994). Grb2 links insulin action to the Ras-MAP kinase pathway, and plays a role in the ability of insulin in stimulating cell growth and differentiation (Skolnik et al., 1993). PI3K, on the other hand, is the critical link between the IR and metabolic activity (Cheatham et al., 1994). In particular, PI3K activates Akt/protein-kinase B and protein-kinase C, which consequently leads to activation of p70 S6K and glycogen-synthase kinase 3. This results in stimulation of glycogen, lipid and protein synthesis, as well as in glucose transporter translocation to the plasma membrane with an increase in glucose transport (Kohn et al., 1996). Akt/protein-kinase B also phosphorylates forkhead transcription factors of the FOXO subfamily, and this leads to their inactivation and retention in cytoplasm (Van Der Heide et al., 2004). Under insulin withdrawal condition, FOXO proteins are not phosphorylated and reside into the nucleus, where they are active and regulate gene expression (Van Der Heide et al., 2004). Depending on the nature of the activation signal, FOXO can regulate apoptosis, cell cycle, differentiation, or the expression of genes involved in DNA repair and oxidative stress resistance (van der Horst and Burgering, 2007).

In addition, insulin signaling pathway is negatively regulated by protein tyrosine-phosphatases, particularly PTP-1B, and the lipid phosphatases PTEN and SHIP2, which can dephosphorylate the products of PI3K signaling (Choi et al., 2002).

2. GH/IGF-I/insulin system and ageing: evidence from animal models

In several animal models reduced GH/IGF-I and insulin signaling pathways have been associated with a longer life span and reduced risk of several age-related diseases (Sell, 2015; Longo and Finch, 2003; Bartke et al., 2013).

In nematodes, Caenorhabditis elegans mutations in the daf-2 gene, a homolog of the insulin/IGF-I receptor, induced a downregulation of this system and an increase in the nematode's life span, that was 2.3-fold greater than wild type (Kenyon et al., 1993).

Similarly in fruit fly Drosofila melanogaster disruption of insulin/IGF-I receptor-like protein gene INR (which is homologous to daf-2 of the C. elegans) and of the insulin receptor substrate CHICO increased the life span up to an 85% and 48% extension, respectively (Tatar et al., 2001; Clancy et al., 2001).

In mammals, the insulin/IGF signaling is much more complex, since there are specific receptors for insulin and IGF-I, with distinct pathways and different functions (Nakae et al., 2001). Furthermore, while lower species have insulin/IGF-I receptors signaling through the nervous system, and their disruption translates to anabolism (fat accumulation) and longevity, in contrast, mammals have insulin/IGF-I receptors in all tissues with different function if they are located in the central nervous system (catabolic effects) or in the periphery (anabolic effects) (Boulianne, 2001).

An increased longevity was shown in many, but not all, mice models with down regulated GH/IGF-I/insulin system, with several differences in relation to the type of model and mouse strain. The most prominent increases in life span have been attained in mice defective in genes involved in pituitary development (prop-1, pit-1) (Longo and Finch, 2003). An extended longevity has been also observed in knockout mice for GH receptor/GH binding protein (Coschigano et al., 2000, 2003) and for GH releasing-hormone (Sun et al., 2013). However, this beneficial effect disappeared in mice with targeted deletion of GH receptor in the liver, muscle or adipose tissue (Bartke et al., 2016).Heterozygous *IGF-IR* knockout mice had a life span 26% longer than the wild type, and showed an increased resistance to oxidative stress (Holzenberger et al., 2003). Similarly to whole body heterozygous *IGF-IR* mice (34), brain-specific heterozygous *IGF-IR* knockout mice with genetically induced hyposensitivity for IGF-I in the central nervous system, showed a life span extension (Kappeler et al., 2008).

Interestingly, lower levels of IGF-I compared to controls have been reported in the majority of these models of long-lived rodents (Rincon et al., 2005). Wild type animals showed higher levels of GH/IGF-I early in life that gradually declined with age. In these knockout models low levels of GH/IGF-I delay puberty and reproduction, perhaps shifting a 'biological timer' that could also delay

Please cite this article in press as: Vitale, G., et al., GH/IGF-I/insulin system in centenarians. Mech. Ageing Dev. (2016), http://dx.doi.org/10.1016/j.mad.2016.12.001