Molecular and Cellular Endocrinology 415 (2015) 143–156

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Metabolic, anabolic, and mitogenic insulin responses: A tissue-specific perspective for insulin receptor activators

Daniel H. Bedinger [a, *], Sean H. Adams [b]

[a] XOMA Corporation, Berkeley, CA, USA
[b] Arkansas Children's Nutrition Center and University of Arkansas for Medical Sciences, Department of Pediatrics, Little Rock, AR, USA

ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form
5 August 2015
Accepted 9 August 2015
Available online 12 August 2015

Keywords:
Akt
ERK
Insulin
Insulin receptor
Diabetes
Insulin-like growth factor

ABSTRACT

Insulin acts as the major regulator of the fasting-to-fed metabolic transition by altering substrate metabolism, promoting energy storage, and helping activate protein synthesis. In addition to its glucoregulatory and other metabolic properties, insulin can also act as a growth factor. The metabolic and mitogenic responses to insulin are regulated by divergent post-receptor signaling mechanisms downstream from the activated insulin receptor (IR). However, the anabolic and growth-promoting properties of insulin require tissue-specific inter-relationships between the two pathways, and the nature and scope of insulin-regulated processes vary greatly across tissues. Understanding the nuances of this interplay between metabolic and growth-regulating properties of insulin would have important implications for development of novel insulin and IR modulator therapies that stimulate insulin receptor activation in both pathway- and tissue-specific manners. This review will provide a unique perspective focusing on the roles of "metabolic" and "mitogenic" actions of insulin signaling in various tissues, and how these networks should be considered when evaluating selective pharmacologic approaches to prevent or treat metabolic disease.

Contents

Abbreviations: IR, Insulin Receptor; ERK, extracellular signal-regulated kinase; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor receptor; T2D, Type 2 diabetes mellitus; FFA, free fatty acids; MAPK, mitogen activated protein kinase; PI3K, phosphatidylinositol-4,5-bisphosphate-3-kinase; IRS, insulin receptor substrate; SOS, Son of Sevenless.

* Corresponding author. XOMA Corporation, 2910 Seventh St., Berkeley, CA, 94710, USA.
E-mail address: bedinger@xoma.com (D.H. Bedinger).

http://dx.doi.org/10.1016/j.mce.2015.08.013
0303-7207/

1. Introduction

More than 29 million people in the United States, and many more world-wide, are diabetic (cdc.gov, 2014). Approximately 90–95% of diabetics have type 2 diabetes mellitus (T2D), which is characterized by insulin resistance and for much of the disease period, hyperinsulinemia. Insulin is given to T2D patients only after they have failed several other therapies, but no pharmacological therapies have been demonstrated to halt the eventual progression to insulin dependence in the face of deteriorating blood sugar control. Yet, strong arguments can be made that hyperinsulinemia, and by extension repeated high-dose insulin therapy, could promote peripheral tissue insulin resistance (Gavin et al., 1974, Marshall and Olefsky, 1980, Garvey et al., 1985, Rizza et al., 1985) or increase risk of cancer through mitogenic actions of the hormone (Ish-Shalom et al., 1997, Sciacca et al., 2012). These observations highlight the need for development of new therapeutics that target specific cellular pathways or that have tissue-specific effects.

Insulin acts as the major regulator of the fasting-to-fed metabolic transition by altering substrate metabolism, promoting energy storage, and helping activate protein synthesis (McGarry, 1992). In addition to its glucoregulatory and other metabolic properties, insulin can also act as a growth factor (Ish-Shalom et al., 1997). The metabolic and mitogenic responses to insulin are regulated by divergent post-receptor signaling mechanisms downstream from the activated insulin receptor (IR). However, the anabolic and growth-promoting properties of insulin require tissue-specific interrelationships between the two pathways, and the nature and scope of insulin-regulated processes vary greatly across tissues (Taniguchi et al., 2006, Biddinger and Kahn, 2006). Understanding the nuances of this interplay between metabolic and growth-regulating properties of insulin would have important implications for development of novel insulin and insulin-receptor (IR) modulator therapies that stimulate insulin receptor activation in both pathway- and tissue-specific manners (Ish-Shalom et al., 1997, Shojaee-Moradie et al., 2000, Moore et al., 2014, Madsbad, 2014, Kurtzhals et al., 2000, Tompkins et al., 1981, Sciacca et al., 2010, Hansen et al., 2011, Vigneri et al., 2012, Bedinger et al., 2015a,b). This review will provide a unique perspective focusing on the roles of “metabolic” and “mitogenic” actions of insulin signaling in various tissues, and how these networks should be considered when evaluating selective pharmacologic approaches to prevent or treat metabolic disease.

2. Background on insulin: a metabolic and anabolic hormone

2.1. Metabolic actions of insulin

Insulin is secreted by pancreatic β-cells in islets of Langerhans in response to increases in blood levels of glucose and select amino acids, with a modulating role attributed to free fatty acids (FFA). Insulin secretion is modulated by both hormonal and neural regulation (Ahren and Holst, 2001, Chandra and Liddle, 2014, Molina et al., 2014). Interestingly, maximal glucose- or amino acid-stimulated insulin release requires the presence of fatty acids (Stein et al., 1996, Dobbins et al., 1998), highlighting the close connection of this hormone with whole-body fuel metabolism. The secreted insulin travels to the liver via the hepatic portal vein, resulting in the exposure of the liver to much higher insulin levels than the systemic circulation (Rojdmark et al., 1978). The liver has high IR levels and removes roughly half of the secreted insulin from portal blood via receptor-mediated endocytosis (Chap et al., 1987). Insulin in the portal blood that is not cleared by the liver is then delivered into the larger systemic circulation where it can stimulate other insulin-sensitive tissues such as muscle, adipose, and the hypothalamus (Biddinger and Kahn, 2006). In times of fasting or low nutrient abundance, insulin levels are decreased, and the levels of insulin's opposing pancreatic hormone, glucagon, are elevated (Unger and Cherrington, 2012). This low insulin/high glucagon state stimulates glucose-sparing metabolic functions such as the lipolysis of triglycerides and release of FFA in adipose tissue, the release of amino acids and lactate from muscle, and the increase in hepatic β-oxidation, ketone body production, and glucose output (McGarry and Foster, 1980).

The bulk of these metabolic actions result from the activation of the canonical PI3K/Akt IR signaling pathway (Fig. 1). The insulin receptor (IR) is a hetero-tetramer with two wholly extra-cellular α-subunits and two plasma membrane-spanning β-subunits that contain intracellular tyrosine kinase domains (reviewed in (De Meyts, 2008, Ebina et al., 1985, McKern et al., 2006, Kido et al., 2001)). The specific pathways engaged downstream of the IR have been recently and thoroughly reviewed in (Taniguchi et al., 2006, Cheng et al., 2010, Ramalingam et al., 2013, Steelman et al., 2011), and are only briefly discussed here. Insulin stimulates IR autophosphorylation, leading to insulin receptor substrate (IRS) protein binding and phosphorylation, followed by the association and activation of phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K). PI3K increases membrane abundance of phosphatidylinositol-3,4,5-triphosphate (PIP3), which leads to the activation of phosphoinositide-dependent kinase 1 (PDK1) and other factors. PDK1 then activates the enzyme Akt by phosphorylating it at Thr^{308} (Taniguchi et al., 2006, Tan et al., 2012). The Akt serine/threonine kinase is a key enzyme in regulating the majority of metabolic actions of insulin (Miinea et al., 2005, Dong et al., 2008, Shepherd et al., 1998). IR signaling is terminated by dephosphorylation of IR by protein tyrosine phosphatase 1b (PTP1b) and tyrosine-protein phosphatase non-receptor type 2 (PTPN2); PI3K signaling is inhibited by activation of both phosphatase and tensin homologue (PTEN) and SH2-containing inositol 5′-phosphatase-2 (SHIP2), which dephosphorylate PIP3 (Taniguchi et al., 2006, Galic et al., 2005).

2.2. Growth actions of insulin signaling

In addition to this role as a metabolic regulator, insulin also functions as a growth factor and has been considered to be the most anabolic hormone (Saltiel and Kahn, 2001, Duarte et al., 2012, Chakrabarti et al., 2013). Despite the well-established requirement for insulin in growth, its role as proliferative or mitogenic