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Insulin resistance in type 1 diabetes mellitus

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ABSTRACT

For long the presence of insulin resistance in type 1 diabetes has been questioned. Detailed metabolic analyses revealed 12%–61% and up to 20% lower whole-body (skeletal muscle) and hepatic insulin sensitivity in type 1 diabetes, depending on the population studied. Type 1 diabetes patients feature impaired muscle adenosine triphosphate (ATP) synthesis and enhanced oxidative stress, predominantly relating to hyperglycemia. They may also exhibit abnormal fasting and postprandial glycogen metabolism in liver, while the role of hepatic energy metabolism for insulin resistance remains uncertain. Recent rodent studies point to tissue-specific differences in the mechanisms underlying insulin resistance. In non-obese diabetic mice, increased lipid availability contributes to muscle insulin resistance via diacylglycerol/protein kinase C isoforms. Furthermore, humans with type 1 diabetes respond to lifestyle modifications or metformin by 20%–60% increased whole-body insulin sensitivity, likely through improvement in both glycemic control and oxidative phosphorylation. Intensive insulin treatment and islet transplantation also increase but fail to completely restore whole-body and hepatic insulin sensitivity. In conclusion, insulin resistance is a feature of type 1 diabetes, but more controlled trials are needed to address its contribution to disease progression, which might help to optimize treatment and reduce comorbidities.

1. Background

Type 1 diabetes mellitus (T1D) results from primary loss of β-cell mass due to complex autoimmune processes with consecutive insulin deficiency, while type 2 diabetes (T2D) arises from impaired insulin action, also termed insulin resistance, along with inadequate β-cell function and insulin secretion [1]. According to this paradigm, it is counterintuitive that T1D patients should be insulin resistant. Nevertheless, clinical and experimental evidence suggests that insulin

Abbreviations: MRS, magnetic resonance spectroscopy; AMPK, 5´AMP activated protein kinase; AGE, advanced glycation end product; ATP, adenosine triphosphate; bEGP, basal endogenous glucose production; DAG, diacylglycerol; FDR, first degree relative; FFA, free fatty acids; GIR, glucose infusion rate; HEC, hyperinsulinemic–euglycemic clamp; iEGP, insulin mediated suppression of EGP; IMCL, intramyocellular lipids; IRS, insulin receptor substrate; MCR, metabolic clearance rate; JNK, c-Jun-N terminal kinase pathway; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; PI3K-AKT, phosphatidylinositol-4,5-bisphosphate 3-kinase-protein kinase B; PKC, protein kinase C; Ra, glucose appearance rate; RAGE, receptor for advanced glycation end product; Rd, glucose disposal rate; ROS, reactive oxygen species; SREBP, sterol regulatory element binding protein; STZ, streptozocin; T1D, type 1 diabetes; T2D, type 2 diabetes.

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resistance can indeed be present in T1D. Previously, chronic hyperglycemia was considered the exclusive contributor to insulin resistance in patients with long-standing, poorly-controlled T1D [2]. More recent studies highlight a more complex nature of insulin resistance in T1D. The evidence of insulin resistance in T1D has been particularly reviewed in the context of vascular comorbidities [2,3,4,5]. Here, we aim to summarize the current literature addressing tissue-specific insulin resistance in T1D and to analyze possible contributors to insulin resistance.

The relevant literature was retrieved by searching for the terms "hepatic and whole-body insulin resistance", "hepatic glucose flux", "insulin resistance in animal models", "energy metabolism", "mechanisms of insulin resistance", "insulin treatment", "metformin", "insulin sensitizers", "glucotoxicity", "lipotoxicity", "diet", "exercise", "islet transplant" and "mitochondria" related to T1D from 1982 to February 2015 in PubMed. Further references were identified by analyzing the retrieved publications and by the authors´ personal knowledge.

2. Definition and Measurement of Insulin Resistance

Impairment of insulin action comprises reduced insulin responsiveness and insulin sensitivity. In vitro, a lower maximal effect of insulin reflects decreased insulin responsiveness, whereas lower insulin sensitivity is defined by a higher insulin concentration eliciting the maximal response to insulin, i.e. a right shift of the dose response curve [6]. In vivo, the gold-standard hyperinsulinemic–euglycemic clamp test (HEC) would theoretically allow for separation of insulin responsiveness from sensitivity. However, most clinical–experimental studies employ the HEC with one signal insulin dose rather than across a broad range of insulin doses so that insulin resistance generally reflects a reduction of both features of insulin action. Nevertheless, HEC is optimal for assessing glucose fluxes in T1D, while fasting indices of glucose tolerance tests, as frequently used in T2D patients, rely on insulin secretion and therefore are not applicable due to the insulin deficiency in T1D patients [2,6]. When combined with dilution techniques using isotopically labeled glucose tracers, the HEC provides information about glucose fluxes and tissue-specific insulin sensitivity in vivo. In the absence of exogenous insulin and in the presence of normoglycemia, the rate of glucose disappearance (Rd) equals the rate of glucose appearance (Ra), which then represents basal (fasting) endogenous glucose production (bEGP). In the presence of supraphysiological insulin concentrations, the exogenous variable input of glucose required to achieve euglycemia at steady state is given by the glucose infusion rate (GIR) and Rd. Under these hyperinsulinemic conditions, insulin-mediated endogenous glucose production (iEGP) is suppressed. Lower response to insulin results in insufficient suppression of iEGP and lower Rd [6]. In addition, adipose tissue insulin resistance can be derived from impaired insulin-mediated suppression of lipolysis, reflected by impaired lowering of circulating free fatty acids (FFA) or more precisely by using lipid tracers [7,8].

3. Key Mechanisms Underlying Insulin Resistance

Insulin resistance can be a (patho)physiological phenomenon occurring as transient adaptation to puberty, dehydration, infections, several drugs, and smoking [31,32]. On the other hand, common insulin resistance as observed in obesity and T2D results from a complex interaction of environmental and inherited factors and progresses chronically.

At the cellular level, stimulation by insulin activates tyrosine kinase of the insulin receptor, which stimulates insulin receptor substrate (IRS) phosphorylation followed by activation of phosphatidylinositol-4,5-bisphosphate 3-kinase-protein kinase B(PI3K-AKT). Several mechanisms can induce insulin resistance by interfering with the insulin signaling cascade, i.e. elevated blood glucose, lipids and amino acids, oxidative and endoplasmic reticulum stress, systemic and cellular inflammation and inherited variations in the signaling molecules (Fig. 1).

Hyperglycemia lowers insulin signaling through different mechanisms including higher glucose flux to the hexosamine pathway, activation of stress-regulated pathways such as c-Jun-N terminal kinase pathway (JNK), protein kinase C (PKCs), preferentially PKCβ activation and oxidative stress driven pathways [9]. Hyperglycemia is also known to increase the formation and accumulation of advanced glycation end products (AGE), which contribute to inflammatory pathways and may also directly interfere with insulin signaling and hepatic energy metabolism [10,11,12]. Short-term high-dose glucose infusion in rats reduced hepatic and whole-body insulin sensitivity, which associated with doubling of muscle diacylglycerol (DAG) and malonyl-CoA along with a 50% decrease in AMPK activity [13]. This highlights an overlap between the downstream effects of hyperglycemia and higher accumulation of toxic lipid metabolites, in line with the concept of glucolipotoxicity [14].

Excessive availability of lipids and amino acids is known to interfere with the insulin signaling cascade. Lipid infusion studies resulting in elevated circulating FFA, provide important insight into the acute sequence of events, by which certain muscle C18-DAG causes translocation of PKCθ with subsequent inhibitory serine phosphorylation of IRS-1 and reduction of insulin-mediated glucose transport/phosphorylation followed by impaired glycogen synthesis in skeletal muscle [15,16]. Short-term elevation of circulating amino acids also results in lower insulin-mediated muscle glucose transport/phosphorylation along with impaired hepatic glycogen synthesis [17]. This is likely due to amino acid-induced activation of the rapamycin-sensitive mTOR/serine-6-kinase-1 pathway, which causes inhibitory serine phosphorylation of IRS-1 [18].

Other mechanisms, particularly cellular inflammatory pathways resulting in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription and JNK activation can contribute to chronic insulin resistance. Circulating cytokines, but also FFA, can activate JNK, which directly inhibits phosphorylation of IRS-1 and has been associated with insulin resistance and obesity [19]. Other abnormalities of insulin signaling include the loss of activation of the PI3K pathway, mitogen activated protein kinase (MAPK) pathway,