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Effects of aldosterone on insulin sensitivity and secretion

James M. Luther *

Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, United States
Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, United States

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ABSTRACT

Dr. Conn originally reported an increased risk of diabetes in patients with hyperaldosteronism in the 1950s, although the mechanism remains unclear. Aldosterone-induced hypokalemia was initially described to impair glucose tolerance by impairing insulin secretion. Correction of hypokalemia by potassium supplementation only partially restored insulin secretion and glucose tolerance, however. Aldosterone also impairs glucose-stimulated insulin secretion in isolated pancreatic islets *via* reactive oxygen species in a mineralocorticoid receptor-independent manner. Aldosterone-induced mineralocorticoid receptor activation also impairs insulin sensitivity in adipocytes and skeletal muscle. Aldosterone may produce insulin resistance secondarily by altering potassium, increasing inflammatory cytokines, and reducing beneficial adipokines such as adiponectin. Renin-angiotensin system antagonists reduce circulating aldosterone concentrations and also the risk of type 2 diabetes in clinical trials. These data suggest that primary and secondary hyperaldosteronism may contribute to worsening glucose tolerance by impairing insulin sensitivity or insulin secretion in humans. Future studies should define the effects of MR antagonists and aldosterone on insulin secretion and sensitivity in humans.

1. Introduction

Since Dr. Conn's initial description of hyperaldosteronism in the 1950s, aldosterone excess has been associated with diabetes, although the mechanism remains unclear [1–3]. Aldosterone-induced hypokalemia was initially described to impair glucose tolerance by impairing insulin secretion. Correction of hypokalemia by potassium supplementation only partially restored insulin secretion and glucose tolerance, however [1]. Our group and others have demonstrated that aldosterone impairs glucose-stimulated insulin secretion directly *via* reactive oxygen species [4–6]. Aldosterone-induced mineralocorticoid receptor (MR) activation also impairs insulin sensitivity in adipocytes and skeletal muscle [7]. Furthermore, aldosterone is inappropriately increased in obese subjects [8–10], and fat-derived factors stimulate aldosterone secretion *in vitro* [11–13]. Because obesity is the principal risk factor for development of type 2 diabetes (T2DM), obesity-related hyperaldosteronism may contribute to worsening glucose tolerance by impairing insulin sensitivity or insulin secretion.

Retrospective analysis of several large cardiovascular trials suggests that interrupting the renin–angiotensin–aldosterone system (RAAS) prevents the occurrence of diabetes, with recent prospective trials supporting a beneficial effect on glucose metabolism. In the DREAM trial, the angiotensin converting enzyme (ACE) inhibitor ramipril did not prevent the occurrence of diabetes, but improved fasting glycemia and 2-h plasma glucose during glucose tolerance tests [14]. In the NAVIGATOR trial, the angiotensin receptor blocker (ARB) valsartan reduced the risk of diabetes by 14% in subjects with impaired glucose tolerance [15]. The mechanism by which ACE inhibitors and ARBs reduce diabetes risk is largely unknown, although improvements in insulin sensitivity and insulin secretion have been implicated. These agents also decrease aldosterone and subsequent mineralocorticoid receptor activation, which could explain their beneficial effect on diabetes risk. We will briefly review the basic pathophysiology of diabetes and mechanisms by which aldosterone may alter glucose homeostasis.

Abbreviations: ACE, angiotensin converting enzyme; AKT, also known as protein kinase B; APA, aldosterone-producing adenoma; ARB, angiotensin II type 1 receptor blocker; *As*, aldosterone synthase; DOCA, deoxycorticosterone acetate; G6P, glucose-6-phosphate; G6Pase, glucose-6-phosphatase; GLUT4, glucose transporter type 4; HOMA-IR, homeostatic model assessment of insulin resistance; IGF1, insulin-like growth factor-I; IGF1R, insulin-like growth factor-I receptor; IHA, idiopathic hyperaldosteronism; IRS1, insulin receptor substrate 1; MR, mineralocorticoid receptor; PA, primary aldosteronism; PI3 K, phosphatidylinositol (4,5)-bisphosphate 3-kinase; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; SGK1, serum- and glucocorticoid-regulated kinase 1; T2DM, type 2 diabetes mellitus; VSMC, vascular smooth muscle cells.

* Address: 2200 Pierce Avenue, 560C RRB, Vanderbilt University Medical Center, Nashville, TN 37232-6602, United States. Tel.: +1 (615) 936 3420; fax: +1 (615) 936 2746.

E-mail address: James.Luther@Vanderbilt.edu

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2. Insulin resistance and insulin secretion in the progression of type 2 diabetes

2.1. Insulin resistance in type 2 diabetes

Development of insulin resistance is the hallmark of T2DM, although an inadequate insulin secretory response also contributes as detailed below (Fig. 1) [16]. Insulin stimulates glucose uptake in skeletal, hepatic, and adipose tissues, whereas glucose uptake in some tissues (e.g. brain) is primarily insulin-independent. Skeletal muscle accounts for the bulk of glucose disposal (~85%) during hyperinsulinemic clamps, and defective skeletal muscle glucose disposal accounts for the decrease in subjects with T2DM [17]. Excess glucose release from gluconeogenic organs (i.e. the liver and to a lesser extent the kidney) also contributes to elevated fasting glucose in subjects with diabetes. Although insulin administration normally suppresses hepatic glucose production, insulin resistance blunts this hepatic response.

Hyperinsulinemia occurs in response to insulin-resistance in an attempt to maintain normal glucose homeostasis. Compared to insulin sensitive individuals, however, the degree of hyperinsulinemia may not adequately compensate for the severity of insulin resistance. In individuals with normal glucose tolerance, insulin sensitivity and insulin secretion are related in an inverse, non-linear manner resembling a hyperbola [18,19]. The product of the two measures, therefore remains constant in individuals with comparable glucose tolerance, but declines directly with impaired glucose tolerance [20,21]. Insulin secretion is impaired early in the pathogenesis of T2DM, and this inadequate insulin response is essential for the development of glucose intolerance and hyperglycemia [22,23]. This beta cell failure is reversible early in the course of disease, but is followed by progressive beta cell death mediated by glucotoxicity, lipotoxicity, and increased apoptosis [22]. Better understanding of the environmental factors which affect insulin sensitivity and beta cell function is needed so that additional diabetes prevention strategies can be developed. Aldosterone or MR activation may contribute to these processes, and therefore serve as a potential drug target which already has proven cardiovascular benefits.

3. Links between aldosterone, glucose tolerance, and insulin resistance

Obesity and hypertension are associated with peripheral insulin resistance, particularly in liver, skeletal muscle, and adipocytes.

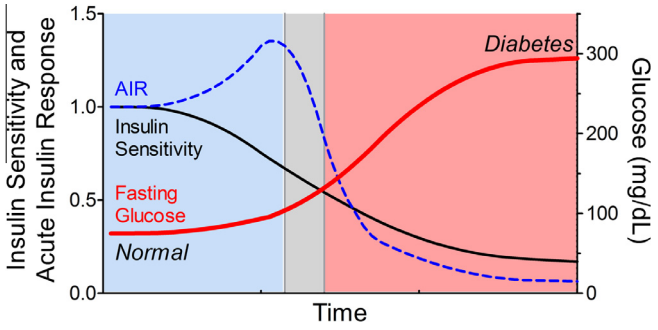

Fig. 1. Conceptualized time course of type 2 diabetes progression, relating insulin sensitivity (black line), acute insulin response (AIR, dashed blue line), and blood glucose (bold red line). Impaired insulin sensitivity occurs before detectable changes in glucose occur, which is compensated by an increase in insulin secretion (AIR) during normoglycemia (blue shading). However, an inappropriate decline in AIR coincides with development of impaired fasting glucose (gray shading) and eventual diabetes (red shading).

Insulin resistance is also associated with hypertension and has been independently linked to increased risk of cardiovascular complications, highlighting its importance [24–26]. Elevated plasma aldosterone is associated with future development of hypertension, and primary hyperaldosteronism (PA) is the most frequently identifiable cause of secondary hypertension [27,28]. Furthermore, obesity is associated with increased circulating aldosterone levels [8–10], suggesting that aldosterone could be an important link between obesity and hypertension. In addition to Conn's classic studies of diabetes in hyperaldosteronism, an aldosterone synthase (CYP11B2) −344C/C polymorphism, which has been associated with increased aldosterone, is also associated with development of metabolic syndrome and T2DM [29–32].

3.1. Clinical studies of aldosterone on glucose tolerance and insulin sensitivity

Studies suggest that aldosterone impairs insulin sensitivity in humans and in rodents *via* the mineralocorticoid receptor. Most clinical studies of aldosterone on insulin sensitivity reported estimates based on fasting glucose and insulin, or the homeostatic model assessment of insulin resistance (HOMA-IR), which generally correlates with measures obtained during the more labor-intensive hyperinsulinemic-euglycemic clamp studies [33,34]. In cross-sectional observational studies, plasma aldosterone is inversely associated with insulin sensitivity in normotensive and heart failure subjects using HOMA-IR [9,35–39] and in essential hypertension subjects using hyperinsulinemic-euglycemic clamps [40]. Insulin sensitivity is also reduced in patients with primary aldosteronism compared to hypertensive controls in some [41–44], but not all studies [45–47]. Elevated plasma aldosterone precedes and predicts the development of insulin resistance in humans after 10 years of follow-up, suggesting that the relative hyperaldosteronism could be causative [48]. Further supporting this assertion, adrenalectomy [41,46,49] or medical therapy with an MR antagonist [44] improves insulin resistance in subjects with PA. Although adrenalectomy improved fasting glucose in patients with aldosterone producing adenomas (APAs), there was no improvement in oral glucose tolerance [49]. Spironolactone administration also did not improve insulin sensitivity or glucose metabolism in a small group of subjects with idiopathic hyperaldosteronism (IHA), although these findings could be confounded by long follow-up times and weight gain [41,42,49]. In a cohort of 9 APA subjects, adrenalectomy did not affect insulin sensitivity during hyperinsulinemic clamps but did increase serum potassium values and improve insulin secretory ability [47].

3.2. Cellular insulin signaling pathways which may be affected by mineralocorticoids

Skeletal muscle insulin resistance is caused by impairment at multiple steps in glucose/insulin delivery or in the insulin signaling pathways (Fig. 2) [50]. Adequate glucose and insulin delivery is determined by tissue perfusion and rapid nutrient diffusion from the vascular compartment through the interstitium to the cell membrane. In part, this process is dependent upon regulated transport of insulin across the vascular endothelium [51]. Once glucose reaches the skeletal muscle cell, uptake is dependent on the cell membrane glucose transporter (primarily GLUT4) to facilitate diffusion into the cell. Once in skeletal muscle or adipose cells, glucose is phosphorylated by hexokinase to glucose-6-phosphate (G6P), which simultaneously increases the concentration gradient for glucose and directs glucose to either glycogenesis or oxidative metabolism. In gluconeogenic tissues such as the liver and kidney, however, G6P can be converted back to glucose and released into the circulation. Insulin receptor binding rapidly activates an