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Effects of aldosterone on insulin sensitivity and secretion

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Abstract

Dr. Conn originally reported an increased risk of diabetes in patients with hyperaldosteronism in the 1950's, 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.

Keywords

Aldosterone; Mineralocorticoid receptor; Hypertension; Diabetes; Insulin Sensitivity; Insulin Secretion

1. INTRODUCTION

Since Dr. Conn's initial description of hyperaldosteronism in the 1950's, 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

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Disclosure Statement

The authors of this manuscript have no conflicts of interest to declare

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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-hour 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.

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 (Figure 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. 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 (Figure 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 intracellular signaling cascade resulting in generation of phosphatidylinositol (3,4,5)-triphosphate (PIP₃), activation of AKT, and translocation of glucose transporter GLUT4 to the cell membrane. Activation of AKT is a focal point for downstream insulin signaling because it is required for maximal GLUT4 recruitment. Insulin also signals *via* AS160 and Rho/Rab family GTPases (e.g. Rac1) to alter cytoskeletal reorganization and direct GLUT4 trafficking to the cell membrane (52–54). Although additional downstream insulin receptor signaling pathways have also been identified, aldosterone has been implicated in the pathways as presented in Figure 2 and as discussed below. Aldosterone may also impair insulin sensitivity secondarily by affecting the production of other circulating factors such as adipokines and inflammatory cytokines.

3.3 Role of aldosterone in vascular dysfunction, glucose, and insulin delivery (Figure 2a)

In healthy individuals, insulin and glucose administration produce vasodilation and increased capillary recruitment via increased nitric oxide production, which increases insulin and glucose delivery to target organs (51; 55; 56). This vasodilatory effect is impaired in obese or diabetic subjects (57). Excess aldosterone and MR activation adversely affects vascular function by reducing nitric oxide production and increasing reactive oxygen species, which produces endothelial dysfunction, vascular smooth muscle hypertrophy, and perivascular fibrosis and inflammation (58–60). Treatment with the mineralocorticoid deoxycorticosterone (DOCA) and salt reduces skeletal muscle capillary/fiber ratio and decreases terminal arteriole capillary vasodilation (61; 62). Aldosterone induces insulin resistance in isolated vascular smooth muscle cells (VSMC) by reducing IRS1 expression and downstream Akt signaling (63; 64). Aldosterone acts via the MR and Src-kinase activation to increase the expression of VSMC insulin-like growth factor-1 receptor (IGF1R), which can form a hybrid IR/IGF1R receptor which preferentially activates MAP-kinase pathways to promote vascular hypertrophy (65; 66). The vascular smooth muscle MR contributes to vasoconstrictor response and hypertension with ageing, demonstrating that aldosterone-MR activation has direct vascular effects independent of its renal effects (58; 67; 68). The extracellular matrix also affects angiogenesis and glucose diffusion which may

also contribute to insulin resistance more than previously appreciated (69; 70). Aldosterone-salt excess consistently induces perivascular fibrosis and inflammation (71), which may indirectly contribute to insulin resistance *in vivo* by impairing glucose diffusion. Therefore, beneficial effects of MR antagonism on insulin sensitivity could be explained by improved vascular density or function, independent of renal MR and electrolyte changes (64).

3.4 Effect of aldosterone on insulin receptor activation and immediate downstream pathways in skeletal muscle and adipocytes (Figure 2b)

Skeletal muscle is the primary insulin-sensitive target, accounting for nearly 85% of insulin-stimulated glucose uptake under experimental conditions, with adipose tissue contributing a much smaller amount (17). Systemic aldosterone-salt administration to Wistar rats reduces skeletal muscle glucose uptake, associated with decreased IR, insulin receptor substrate-1 (IRS1), and AKT expression and phosphorylation (72; 73). Aldosterone administration in fructose-fed rats also increases skeletal muscle expression of serum/glucocorticoid regulated kinase 1 (SGK1), a kinase typically affected by MR activation, suggesting that aldosterone may act via the MR directly in skeletal muscle (74). In a rat model with secondary hyperaldosteronism and insulin resistance (the Ren2 rat), MR antagonism improves insulin sensitivity and insulin receptor signaling, as assessed by *ex vivo* skeletal muscle glucose uptake, AKT and IRS1 phosphorylation, which is associated with decreased NADPH oxidase activity and reactive oxygen species (75). Although the aldosterone-sensitive pathways within VSMC have been clearly defined, further studies in skeletal muscle are needed. Aldosterone-induced skeletal muscle effects could alternatively be dependent on renal or adipocyte MR activation, which could alter electrolyte balance or adipokine production, respectively.

Some studies have utilized potassium supplementation to prevent significant hypokalemia, although a contribution of potassium depletion in the absence of altered serum potassium cannot be excluded. In particular, renal potassium loss may confound interpretation of *in vivo* studies by worsening insulin sensitivity and insulin secretion. The development of tissue-specific MR knockout mice promises to yield further insights into extra-renal MR effects. Evidence supports the hypothesis that aldosterone and the MR directly affect skeletal muscle metabolism, in particular by increasing intracellular potassium transport in chronic adaptation to high potassium diet (76–78). This effect can be reproduced by other mineralocorticoids such as deoxycorticosterone (DOCA) but not by glucocorticoids, and can be reversed by spironolactone, suggesting that it is MR-dependent (78). The effects of insulin on glucose and potassium are not necessarily directly linked. For example, the intracellular potassium shift produced by insulin is more sensitive and longer lasting than the glucose uptake response, and occurs even in the absence of glucose (79; 80). Further studies investigating aldosterone's effect on skeletal muscle potassium and glucose insulin resistance are warranted.

Aldosterone also impairs insulin sensitivity directly in adipocytes. Aldosterone impairs glucose uptake *in vitro* in 3T3 adipocytes and is associated with reduced GLUT4 cell surface localization, and IRS1, P13K, and AKT phosphorylation (81; 82). Aldosterone may also impair insulin sensitivity by impairing normal adipocyte differentiation and function.

Aldosterone induces pre-adipocyte differentiation *in vitro* via the MR (83). Adiponectin is the best-characterized adipose-derived circulating hormone, or adipokine, which improves insulin sensitivity (84). In genetically obese and diabetic mice, MR antagonism increases adipocyte peroxisome proliferator-activated receptor (PPAR)-gamma and adiponectin expression, reduces tumor necrosis factor (TNF)-alpha and monocyte chemotactic protein (MCP)-1 expression, and improves insulin sensitivity *in vivo* (85–87). Aldosterone excess is also associated with reduced circulating adiponectin (88) and visceral adipose adiponectin expression in subjects with APA (87). Some studies argue against a direct adipose tissue effect, however, because aldosterone only impaired insulin signaling at concentrations which activate the glucocorticoid receptor (89). In the setting of diet-induced obesity, genetic aldosterone deficiency reduced adipocyte inflammation and increased circulating adiponectin, although this did not prevent development of obesity or insulin resistance, suggesting that mineralocorticoids other than aldosterone may contribute to insulin resistance *in vivo* (90).

3.5 Effect of aldosterone on cytoskeletal rearrangement and GLUT4 translocation (Figure 2c)

Aldosterone primarily stimulates translocation of sodium channels and transporters to the cell surface in the distal nephron segments via MR-dependent mechanisms, which shares similar regulatory proteins with Rho/Rab GTPase-regulated transport of GLUT4. In renal epithelial cells, aldosterone-induced AS160 phosphorylation by SGK1 regulates epithelial sodium (ENaC) cell-surface localization (91). In skeletal muscle, aldosterone administration also increases SGK1, which can phosphorylate multiple AS160 sites, but not the Ser341 site essential for 14-3-3 binding and maximal GLUT4 translocation (74; 92; 93). In skeletal muscle, aldosterone administration impairs AS160(Thr642) phosphorylation, GLUT4 expression, and glucose oxidation *in vivo* in a dose-dependent manner (72; 73). A definitive role of aldosterone-induced SGK1 phosphorylation of AS160 in skeletal muscle has not been definitely established, however.

Once glucose enters skeletal muscle, it enters either the glycolytic or glycogenic pathway, both of which are impaired in early T2DM and insulin resistance. The effect of aldosterone on oxidative versus glycogenic pathways has not been clearly defined, although aldosterone administration reduces skeletal muscle and hepatic glycogen content in Wistar rats (72; 73). This effect could be a consequence of reduced glucose entry into the cell, rather than a primary effect on these metabolic pathways.

3.5 Effect of aldosterone on hepatic glucose production and fatty liver

In the fasting state, the liver and kidney maintain circulating glucose within a tight range by releasing glucose from glycogen (glycogenolysis) or by converting precursor molecules to glucose (gluconeogenesis). The liver is the major source of circulating glucose in the fasted state, and therefore most studies of aldosterone have been performed in cultured hepatocytes to examine the effects on gluconeogenesis. Gluconeogenic organs express glucose-6-phosphatase (G6Pase), which converts G6P to glucose, which can then be released into the circulation. The MR is expressed in rat liver and hepatoma cell lines, although at a lower level than in heart or hippocampus (94; 95). Aldosterone increases expression of G6Pase

and the essential gluconeogenic enzymes fructose-1,6-bisphosphatase and phosphoenolpyruvate carboxykinase *in vitro* (96; 97). Some of the effects of aldosterone only occurred at micromolar concentrations, however, raising the possibility that they may be nonspecific or physiologically irrelevant. Furthermore, aldosterone blunts the inhibitory effect of insulin within this system, and a single dose of aldosterone elevates fasting blood glucose in mice, suggesting that aldosterone increases hepatic glucose production (96). This effect of aldosterone on G6Pase increases further when given in micro-molar concentrations and is blocked by glucocorticoid receptor antagonist RU486 but not MR antagonists suggesting that this effect may only occur at supraphysiologic concentrations *via* glucocorticoid receptor activation (96). In contrast, Liu et al found that MR antagonism or siRNA treatment decreases G6Pase expression (97). The effect of aldosterone on hepatic glucose production in humans has not been assessed, although this is possible with the use of tracer methodologies.

In the setting of severe hepatic insulin resistance, liver fat accumulates and contributes to hepatic insulin resistance and dyslipidemia. In high fat-, fructose-fed, and genetic models of obesity, MR antagonism ameliorates fatty liver disease with reduction in histologic injury and hepatic triglyceride content (98–100). we similarly observed that aldosterone synthase deficiency ameliorates high fat diet-induced fatty liver histology and hepatic triglyceride content (90). On the other hand, one study found no effect of adrenalectomy or MR antagonism on fatty liver severity (101). Data in humans is limited, but fatty liver disease has been associated with plasma aldosterone, low potassium, and insulin resistance in a cohort of patients with APA (102).

4. EFFECT OF ALDOSTERONE ON INSULIN SECRETION

Conn originally implicated hypokalemia and insulin secretion in the pathogenesis of hyperaldosteronism-induced T2DM, although correction of hypokalemia only partially corrected the insulin secretory defect (1). Studies in rodents also demonstrate a reduced insulin secretion after systemic aldosterone or DOCA-salt administration in Wistar rats (103). In aldosterone deficient mice, glucose-stimulated insulin secretion is markedly increased during normal, high sodium, and high fat diets without any alteration in islet density, suggesting that endogenous aldosterone impairs insulin secretion by directly altering islet function (5; 90). This effect occurs without altered insulin sensitivity and after elevated serum potassium is normalized by high sodium diet, suggesting that endogenous aldosterone directly decreases insulin secretion in pancreatic islets. Furthermore, aldosterone impairs glucose-stimulated insulin secretion within either isolated murine or rat islets or the clonal beta cell MIN6 line, systems which are independent of potassium (4–6). Pancreatic islet MR expression is localized to delta and PP cells, although their physiologic relevance is uncertain and expression in other islet cell types cannot be excluded (5; 104). The inhibitory aldosterone effect on insulin secretion was not prevented by available MR antagonists spironolactone, eplerenone, or RU-28318 (5), but was reversed by either the superoxide dismutase mimetic tempol (5) or the reactive oxygen species scavenger N-acetylcysteine (4).

A relatively recent finding in the aldosterone field has been the identification of GPR30 as a membrane receptor for aldosterone which may mediate rapid actions of aldosterone (105–

107). Interestingly, GPR30 activation mediates pregnancy- and estrogen-induced beta cell proliferation by down-regulating the micro RNA miR-338-3p (108). Estrogen induced GPR30 activation also potentiates insulin secretion in murine islets (109; 110). Therefore, the known effects of GPR30 activation within islets do not appear to explain the actions of aldosterone on insulin secretion. This field of aldosterone-GPR30 signaling remains in its infancy, and additional membrane receptors could be identified in the future to shed light on these findings (106; 111).

Studies also suggest that aldosterone impairs insulin secretion in humans. In Conn's classic studies, he demonstrated that 14/27 (52%) of patients with PA exhibited impaired glucose tolerance and an impaired insulin response after oral glucose administration (1). More recently investigators estimated beta cell function using fasting glucose and insulin concentrations and noted a decrease in HOMA2- β and fasting C-peptide in patients with APA versus essential hypertension (112). Fischer *et al* demonstrated impaired acute glucose-stimulated insulin secretion in patients with APA versus essential hypertension using frequently-sampled intravenous glucose tolerance tests, which improved after adrenalectomy (47). Shimamoto also observed impaired glucose tolerance and insulin secretion in APA subjects and normalization after adrenalectomy which correlated strongly with potassium, although insulin sensitivity was increased as well (113). Taken together, these studies suggest that aldosterone may primarily affect insulin secretion. These studies were potentially confounded by significant differences in potassium or blood pressure, however. Further studies which more closely match these variables could exclude such an effect, although this is difficult to accomplish in clinical practice. The effect of MR blockade on insulin secretion has not been formally investigated and requires further study.

Additional clinical evidence supports an effect of the RAAS on insulin secretion in humans. As mentioned above several retrospective studies and two large prospective, randomized placebo controlled trials demonstrate that ACE inhibitors or ARBs improve glucose homeostasis and reduce the incidence of T2DM in subjects at high risk of cardiovascular events (14; 15; 114). AngII activation of AngII type I receptor (AT1) is a potent stimulus for aldosterone secretion, and both ACE inhibitors and ARBs reduce plasma aldosterone concentrations clinically. During thiazide treatment in hypertensive subjects, the ARB azilsartan preserved glucose tolerance compared to amlodipine treatment, which appears to have been mediated by preservation of the insulin secretory response (115). In a separate study, valsartan improved both insulin secretion and insulin sensitivity, assessed by hyperglycemic clamps and hyperinsulinemic clamps, respectively (116). Although aldosterone reduction could contribute to the beneficial effects of RAAS blockade, the relationship between aldosterone and insulin secretion was not assessed in these studies and also requires further investigation.

5. CLINICAL AND THERAPEUTIC IMPLICATIONS

Aldosterone is inappropriately elevated in 10–15% of patients with resistant hypertension, and contributes significantly to cardiovascular disease. Autonomous, AngII-independent aldosterone secretion is classified as primary hyperaldosteronism (PA). Most commonly this is due to either an aldosterone producing adenoma (APA) or idiopathic hyperaldosteronism

(IHA). Treatment with an MR antagonist improves hypertension control and prevents hypokalemia, although it commonly produces a compensatory increase in plasma aldosterone concentrations (117). Based on the above data, this would be predicted to improve insulin sensitivity due to MR antagonism in muscle, adipocytes, and liver, or via secondary effects on circulating adipokines, cytokines, and electrolytes. Treatment with MR antagonists could also worsen insulin secretion due to the compensatory increase in plasma aldosterone. Along these lines, spironolactone worsened glycemic control compared to placebo in a group of diabetic subjects with poorly controlled hypertension (118). Further studies are needed to determine the net effect of MR antagonism on insulin secretion and insulin resistance in humans at risk for diabetes before drawing firm conclusions. Aldosterone synthase inhibitors, which are currently in development for human use, may provide an alternative strategy to treat hyperaldosteronism which could have favorable metabolic effects compared to MR antagonists or diuretics.

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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
PI3K	Phosphatidylinositol (4,5)-bisphosphate 3-kinase
PIP₃	Phosphatidylinositol (3,4,5)-triphosphate
SGK1	Serum- and glucocorticoid-regulated kinase 1

T2DM	Type 2 diabetes mellitus
VSMC	Vascular smooth muscle cells

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HIGHLIGHTS

- Aldosterone excess is associated with obesity, hypertension, and diabetes.
- Renin-angiotensin system antagonists reduce aldosterone concentrations and diabetes risk.
- Aldosterone reduces insulin sensitivity in skeletal muscle and adipocytes.
- Aldosterone impairs insulin secretion in isolated islets and patients with hyperaldosteronism.
- Hypertension treatment may worsen glucose tolerance by increasing aldosterone.

Figure 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).

Figure 2. Insulin signaling and glucose delivery

Cellular insulin and glucose delivery is dependent on insulin transport and diffusion from the intravascular compartment, through the interstitium (a) to the cell membrane where insulin binds to the insulin receptor (IR) and glucose enters the cell via GLUT4. Insulin signaling is mediated by multiple pathways including IRS1, PI3K, and PDK1 which activate Akt (b). Akt and other pathways, e.g. Rac1, increase GLUT4 trafficking to the cell surface in part via actin cytoskeleton rearrangement. Glucose is taken into the cell and is converted to energy via oxidative metabolism or stored as glycogen for use in the future (d). Aldosterone and MR activation can affect multiple steps in the pathway by activating SGK1 or Src/MAPK/JNK pathways.