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Short Communication Open Acces

Role of Aldosterone in Insulin Resistance: Fact of Fantasy

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Abstract

Background: Recent evidence suggests that aldosterone decreases insulin sensitivity independent of its effects on blood pressure. This article discusses the evidence linking aldosterone to insulin resistance.

Objective: The role of aldosterone in causing alterations in insulin sensitivity might be relevant in patients with inappropriately elevated circulating levels of the hormone. Aldosterone and insulin resistance might together contribute to blood pressure raise and, eventually, increased cardiovascular risk.

Discussion: Evidence obtained in studies of patients with primary aldosteronism suggests that inappropriately elevated plasma aldosterone levels contribute to insulin resistance. However, the relative contribution of circulating aldosterone levels or hypertensive state itself to insulin resistance is not entirely clear.

Summary: Aldosterone antagonists might be beneficial in conditions associated with insulin resistance, but more research is needed to test this hypothesis.

Introduction

Experimental and clinical evidence indicates that activation of the renin-angiotensin-aldosterone system (RAAS) worsens insulin sensitivity and increases incidence of type-2 diabetes. Studies conducted with RAAS blockers have clearly shown the effects of these agents on glucose metabolism leading to hypothesize a dual effect of RAAS [1]. On one hand, the RAAS increases production of reactive oxygen species activating inflammatory pathways and thereby decreasing insulin secretion and sensitivity. On the other hand, the RAAS increases adipogenesis with increased release of beneficial adipocytokines and improvement of insulin secretion and sensitivity [1]. Although most studies exploring the relationship of the RAAS with glucose metabolism were focused on the role of angiotensins, substantial evidence indicates that also aldosterone might play a role in regulation of glucose metabolism and insulin sensitivity.

Because of its original description [2], primary aldosteronism (PA) has been recognized as one of the possible causes of glucose intolerance, and the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus indicated that PA might be per se a cause of diabetes [3]. Impairment of insulin secretion and decrease of insulin sensitivity in patients with this endocrine disorder were initially ascribed to the aldosterone-induced hypokalemia, but correction of plasma potassium levels with oral supplements had only partial benefits on restoration of insulin secretion and tissue sensitivity [2]. Subsequent experimental studies conducted in animal models have broadly explored the possible interference of aldosterone into insulin-related mechanisms [4]. These studies demonstrated that aldosterone impairs insulin secretion by generation of reactive oxygen species [5] and impairs insulin sensitivity in adipose tissue and skeletal muscle [6], and that cultured adipocytes produce factors that stimulate aldosterone production from the adrenal cortex [7], thereby suggesting a further link between insulin resistant states and this hormone. Despite strong experimental evidence, investigations on insulin sensitivity and glucose metabolism in patients with PA or other conditions characterized by inappropriately elevated circulating levels of aldosterone showed substantial inconsistencies. In this commentary article we briefly overview the clinical evidence linking aldosterone with glucose metabolism and insulin sensitivity.

Insulin resistance and glucose metabolism in conditions with inappropriately elevated aldosterone: insight from studies in primary aldosteronism

Many reasons could come into play to explain inconsistencies in studies conducted to investigate insulin action in patients with PA, including the small sample size of most of these studies, differences in criteria used for selection of patients and controls and, most important, methodology used to assess insulin sensitivity [8]. Initial studies did not show changes in sensitivity to insulin in patients with PA indicating instead decreased glucose tolerance due to impaired pancreatic release of insulin [9]. In a series of studies conducted by a Czech group, decreased insulin sensitivity was reported in patients with PA in comparison to normotensive controls [10], but no difference was found in glucose and insulin response to an oral glucose load when compared to patients with primary hypertension [11]. The same research group reported also that impairment of insulin sensitivity was more severe in patients with idiopathic aldosteronism than adrenal adenoma [11] and that unilateral adrenalectomy, but not treatment with aldosterone antagonists, restored insulin sensitivity [12], a finding that was not confirmed by the same group in a subsequent study [13]. More recently, Giacchetti et al. [14] reported that surgical treatment of aldosterone-producing adrenal adenoma improved glucose tolerance, whereas medical treatment with spironolactone blocked further progression of the metabolic

complications, rather than reversing them. An increased prevalence of the metabolic syndrome was reported in a large group of patients with PA in comparison to essential hypertensive controls [15]. In this study, the difference was due to higher fasting plasma glucose in patients with PA that was related to a significantly higher prevalence of diabetes (8.2%) than in primary hypertension (3.4%), but no differences were seen in the other components of the metabolic syndrome. However, increased prevalence of non-alcoholic fatty liver disease (NAFLD), an additional component of the metabolic syndrome, has been reported in a recent study of patients with PA [16].

As outlined above, most of the controversies in the field are generated by inappropriate control groups and by weakness of the methodology commonly used to assess insulin resistance. This is why we examined by use of a standard oral glucose tolerance test and hyperinsulinemic-euglycemic clamp a substantial group of patients with PA who were compared to age, sex, and body mass matched subjects with either primary hypertension or normal blood pressure [17]. In PA, we found significantly greater insulin response to the oral glucose load than in normotensive healthy subjects, suggesting that insulin secretion is not impaired in these patients. Significantly higher HOMA-index associated with decreased metabolic clearance rate of glucose during the hyperinsulinemic clamp was observed in patients with PA in comparison to subjects with normal blood pressure, clearly indicating that patients with PA are insulin resistant. Insulin resistance of patients with PA, however, was comparable to that observed in patients with primary hypertension. Similar findings were reported by Matrozova et al. [18] who examined retrospectively the gluco-metabolic variables of a large French cohort of patients with PA who were compared to matched patients with primary hypertension. Fasting plasma glucose levels as well as the prevalence of hyperglycemia were comparable supporting the contention that abnormal carbohydrate metabolism and insulin resistance are equally frequent in PA and primary hypertension. These results, together with our previous results, would suggest that hypertensive states are associated with insulin resistance and abnormal glucose metabolism independent of their etiology [19]. This conclusion does not preclude the possibility that aldosterone contributes, among other factors, to insulin resistance in hypertensive patients. In a 6-year follow-up of our patients with PA, we observed that abnormal variables of glucose metabolism and insulin sensitivity were significantly, although not entirely, corrected by both treatment with adrenalectomy and aldosterone antagonists [17].

Aldosterone and insulin resistance in hypertension

Development of insulin resistance is a hallmark of obesity and type-2 diabetes mellitus and in these conditions hyperinsulinemia ensues in the attempt to compensate for the decreased peripheral effects of the hormone [20]. Obesity is also associated with increased circulating aldosterone levels [21], suggesting that aldosterone could be an important link between obesity and insulin resistance as suggested in some studies [22]. Insulin resistance impacts also on subjects with normal blood glucose and family history of diabetes and predicts worse cardiovascular outcome in these subjects [23]. Similar to type-2 diabetes and obesity, primary hypertension is associated with insulin resistance and hyperinsulinemia [24,25] and aldosterone or mineralocorticoid receptor activation might contribute to these abnormalities. The issue of a possible relationship between plasma aldosterone and insulin resistance is important because aldosterone has been shown to contribute, independent of blood pressure, to the development of cardiovascular damage [26] and because insulin resistance and hyperinsulinemia are predictors of cardiovascular events in hypertensive patients [27]. Two large studies that were conducted in families of African descent in the Seychelles [28] and in African Americans [29] reported that plasma aldosterone levels are associated with the metabolic syndrome and markers of insulin resistance [29] in normotensive and hypertensive subjects. In contrast, in a subanalysis of the Trial of Preventing Hypertension Study no evidence for elevated aldosterone was found in individuals with high normal blood pressure and the metabolic syndrome when compared with control subjects without the syndrome [30]. In this study, however, 82% of patients were white, raising the issue of a race-specific effect. In a study of 356 patients with primary hypertension we examined the relationship of plasma aldosterone with glucose metabolism and insulin sensitivity as defined by use of a hyperinsulinemic-euglycemic clamp [31]. A positive association with increasing plasma aldosterone concentrations was observed for fasting plasma glucose, insulin, C-peptide and HOMA-index and the clamp showed a significant decrease of the metabolic clearance rate of glucose with increasing aldosterone levels. These findings extend the evidence of an association between aldosterone, hyperinsulinemia, and insulin resistance to white subjects with hypertension. Thus, the role of aldosterone in causing alterations in glucose metabolism might be relevant not only in patients with PA, but also in patients with lesser degrees of aldosterone excess and it could be speculated that aldosterone and insulin resistance might together contribute to rising blood pressure and, eventually, increased cardiovascular risk.

Conclusion

Evidence obtained in studies of patients with PA suggests that inappropriately elevated plasma aldosterone levels contribute to insulin resistance (Figure 1). However, the relative contribution of circulating aldosterone levels or hypertensive state itself to insulin resistance is not entirely clear and the issue will deserve further research. Intervention studies with aldosterone antagonists or other types of drugs including the new aldo synthase inhibitors [32] should be performed in selected groups of patients with hypertension and insulin resistance to better clarify the impact of aldosterone on insulin sensitivity.

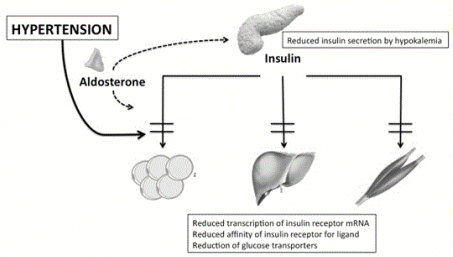

Figure 1: Mechansims of insulin resistance in hypertension and contribution of aldosterone.

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