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Effect of low dose mineralocorticoid receptor antagonist eplerenone on glucose and lipid metabolism in healthy adult males

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ABSTRACT

Mineralocorticoid Receptor (MR) activation is involved in blood pressure regulation and the pathogenesis of cardiovascular diseases, such as cardiac fibrosis, vascular inflammation and arterial aging. Recent investigations suggest a role for MR activation in metabolic dysregulation.

Objective. To test the effect of MR blockade on basal and postprandial glucose and lipid levels after a meal high in fat and glucose in healthy males.

Subjects and methods. A prospective, self-controlled study was performed in 13 healthy adult males aged 18–45 years. Blood was drawn before, 2 h, and 4 h after a high fat/high glucose meal (50 g fat, 75 g glucose), followed by low-dose eplerenone treatment (50 mg daily) for 14 days. Subjects returned for a second high fat/high glucose meal after the medication period. Basal and postprandial blood glucose and lipid levels were compared before and after eplerenone treatment.

Results. Eplerenone treatment affected neither basal nor postprandial glucose and lipid levels in our study population.

Conclusion. Our results suggest that low-dose, non-blood pressure-affecting, MR blockade does not alter postprandial lipid and glucose homeostasis in healthy adult subjects.

1. Introduction

The mineralocorticoid receptor (MR) is expressed in kidney epithelium mediating water and electrolyte balance, and, hence, blood pressure homeostasis [1]. Functional MR also has been demonstrated in a variety of non-epithelial tissues, including endothelial cells, vascular smooth muscle cells and peripheral blood mononuclear cells (PBMCs). MR activation is involved in cardiovascular diseases, such as arterial hypertension, cardiovascular inflammation and remodelling, and

Abbreviations: MR, mineralocorticoid receptor; PBMCs, peripheral blood mononuclear cells; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; TG, triglycerides; PA, primary aldosteronism; BMI, body mass index; EKG, electrocardiogram; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; BUN, blood urea nitrogen; HOMA-IR, homeostasis model assessment of insulin resistance.

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endothelial dysfunction. MR blockade has been shown to prevent adverse cardiovascular events in humans and animal studies [2,3].

Recent studies in humans and animals have demonstrated direct associations of the metabolic syndrome with elevated plasma levels of aldosterone, which is the natural ligand for the MR [4]. For example, a study by Goodfriend et al. showed a negative correlation between aldosterone and cardioprotective high density lipoprotein (HDL) levels [5], suggesting that these effects are, at least in part, mediated through increased MR activation. Evidence from human trials also suggests that MR activation may exacerbate alterations in glucose homeostasis, such as insulin resistance, in patients with diabetes mellitus or the metabolic syndrome [6]. However, in summary, the available data remain controversial and there is still no conclusive evidence that establishes aldosterone and MR activation as critical factors in lipid or glucose homeostasis [4].

The adverse cardiovascular effects of elevated plasma glucose levels in diabetes patients are well known [7,8]. Similarly, hyperlipidemia is a known risk factor for the onset and progression of arteriosclerosis, even in subjects without diabetes [9]. In addition, fatty acids are known to induce insulin resistance, compromise cardiac function, and promote vascular dysfunction [10]. The goal of this study was to further clarify the role of MR activation in metabolic regulation. Specifically, we tested the effect of low-dose MR blockade on basal and postprandial glucose and lipid levels in healthy males.

2. Subjects and methods

2.1. Participants

A total of 13 healthy adult males (BMI≥17 and≤27 kg/m^2), aged 18–45 years, were included in the final analysis of our study. None of the study participants had any clinical evidence of hypertension, cardiovascular, hepatic, renal or any other organ system disease, as determined by a complete physical exam, a personal medical history, family medical history, routine blood work (complete blood count, serum glucose, sodium, creatinine, potassium, liver tests), EKG and urine analysis. The upper cut-off limit of 45 years was used to reduce possible confounding due to age-related metabolic changes. Subjects with arterial blood pressure 90/60 mmHg or less were excluded from the study. Subjects taking any prescription or herbal medications were excluded, and tobacco users were excluded. Subjects with alcohol consumption of more than 2 drinks per day were excluded, as ethanol is known to affect triglyceride levels. Subjects taking dietary supplements (e.g. high dose fish oil supplements>1 g of EPA and DHA per diem) were excluded, as these substances are known to influence lipid levels. Degree of physical activity was similar in all participants prior to enrolment (maximum weekly physical activity between 2–10 h/week). All study participants were on a liberal salt diet throughout the whole study period.

The institutional review board approved the protocol (2010-P-002191/1), and each subject provided written consent prior to enrolment.

A self-controlled intervention study was conducted. After a 9–12 h fasting period subjects were admitted to the Outpatient Center for Clinical Investigation at the Brigham and Women's Hospital. After remaining supine for 30 min, blood was drawn for basal glucose, insulin and lipid measurement, including total, low density lipoprotein (LDL), high density lipoprotein (HDL), and very low density lipoprotein (VLDL) cholesterol using an indwelling intravenous catheter. Subsequently, subjects consumed a meal challenge consisting of oral fat (50 g fat as heavy cream) and oral glucose (75 g glucose as Glucola^{TM}), followed by blood draws 2 h and 4 h after the meal. Study day 1 was followed by a two-week treatment with 50 mg eplerenone daily. After two weeks, subjects returned to the study center to receive the second high fat/high glucose meal (day 15) similar to day 1.

Baseline blood pressure was measured on study days 1 and 15 prior to the meal while supine, using the average of two readings from a Dinamap automated device (Critikon, Tampa, FL, USA).

2.2. Laboratory procedures

Serum glucose and lipids were analysed using standard lab techniques in a commercial laboratory, Laboratory Corporation of America (Raritan, NJ). Insulin was analysed in the Harvard Catalyst Central Laboratory (HCCL) by AccessHigh Sensitive Insulin Immunoassay (Beckman Coulter, Chaska, MN) with a detection limit of 0.03 μIU/ml.

2.3. Assessment of Insulin Resistance (IR)

IR was evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR) using the following equation: fasting insulin (mU/l)×glucose (mmol/l)/22.5 [11].

2.4. Statistical analysis

Data are presented as means±SD. Normality of the data was assessed using normal probability plots and Shapiro–Wilk test. Assuming normal distribution and equal variance of the data, significance of differences at baseline (prior to the high fat/high glucose meal) before and after eplerenone treatment, as well as differences between different time points (basal, 2 h, 4 h) before and after eplerenone treatment was tested by 2-way Analysis of Variance (ANOVA) with repeated measures, followed by post-hoc analysis. $P<0.05$ was considered significant, analyses were performed using Sigma Plot software, version 11.0.

3. Results

3.1. Effect of MR blockade on basal glucose and lipid levels

All subjects were healthy, normotensive, and free of any metabolic, kidney or cardiovascular disease, as described in the Subjects and Methods section. Please refer to Table 1 for characteristics of the study population. Table 1 also shows glucose, insulin, insulin resistance, (as assessed by homeostasis model assessment of insulin resistance [HOMA-IR]), and lipid levels after a 9–12 h fasting period at the beginning of the study period (day 1). Two week low-dose (50 mg/day)