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Research Article

Neutral endopeptidase inhibitor versus angiotensin converting enzyme inhibitor in a rat model of the metabolic syndrome

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Abstract

The antihypertensive treatment in patients with metabolic syndrome is unclear. We therefore used a rat model of the metabolic syndrome and compared the effects of enalapril, an angiotensin-converting-enzyme inhibitor, with candoxatril, a neutral endopeptidase inhibitor that inhibits degradation of atrial natriuretic peptide and, in addition to lowering blood pressure, exerts metabolically beneficial activity. Ten male Sprague Dawley rats were fed regular rat chow for 5 weeks. Fifty male Sprague Dawley rats were fed a high-fructose diet for 3 weeks, followed by addition of enalapril, 10 mg/Kg/d, or candoxatril, 25, 50, or 100 mg/Kg/d, for 2 weeks. Systolic blood pressure, plasma triglyceride level, and insulin level were measured at baseline and after 3 weeks and 5 weeks. Three weeks of a high-fructose diet led to a significant increase in all metabolic parameters. Candoxatril and enalapril lowered systolic blood pressure significantly (candoxatril -10 ± 1 to -22 ± 1 mm Hg and enalapril -27 ± 2 mm Hg). High-dose candoxatril and enalapril significantly decreased plasma triglyceride levels (by 17.8% and 32.8%, respectively), but only high-dose candoxatril decreased plasma insulin levels significantly (by 25.3%). High-dose candoxatril is a metabolically favorable option for lowering blood pressure in a rat model of metabolic syndrome. J Am Soc Hypertens 2014;8(4):227–231. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Candoxatril; enalapril; atrial natriuretic peptide.

Introduction

The metabolic syndrome (MeS) is a cluster of abnormalities commonly observed in Western populations.[1] It includes central obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol level, high blood pressure (BP), and insulin resistance (manifested by raised fasting plasma glucose and impaired glucose tolerance).[2] The syndrome is a risk factor for type 2 diabetes mellitus and cardiovascular disease,[3] both of which carry considerable morbidity and mortality. Pharmacologic treatment of the MeS as a whole is lacking, and current recommendations address each disorder separately.[4]

Regarding elevated BP, several classes of medications have been found effective, but the drug of choice in the context of the MeS remains controversial.[5] The issue is further complicated by the complex relationship among the various components of the disease. For example, the MeS-induced dysregulation of the renin-angiotensin-aldosterone system (RAAS) not only leads to high BP,[6] but also exacerbates insulin resistance.[7] Although angiotensin-converting-enzyme (ACE) inhibitors possess antihypertensive properties and have proven metabolically effective in reducing insulin resistance,[8] improving the lipid profile,[9] and lowering the incidence of type 2 diabetes,[10] some studies reported conflicting data.[5] To date, RAAS blockers have not been recognized as being better than other antihypertensive drugs in the treatment of MeS.[11]

Recently, atrial natriuretic peptide (ANP) has emerged as a potential treatment for hypertension owing to its effect on

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sodium homeostasis.[12] Furthermore, ANP is metabolically active, exerting a lipolytic action on adipose cells,[13] which makes it a plausible option for the treatment of hypertension in the MeS. ANP is degraded by the neutral endopeptidase (NEP) enzyme, and the inhibition of NEP raises plasma ANP levels.[14] The aim of the present study was to compare the effects of enalapril, an ACE inhibitor, with candoxatril, a prodrug of candoxatrilat, a metalloproteinase that inhibits mainly NEP, on hypertension and other metabolic parameters in a rat model of the metabolic syndrome.

Methods

Study Design and Setting

The study was conducted in a rat model of the MeS. The design was based on previous findings[15] that Sprague Dawley rats fed high-fructose diet develop metabolic abnormalities (hypertension, insulin resistance, dyslipidemia) resembling human MeS.

The study was approved by the Institutional Review Board of Sheba Medical Center, and all procedures using animals were performed in accordance with the hospital's guidelines.

Animals

Sixty male Sprague Dawley rats weighing 259 ± 21g were purchased from Harlan Laboratories (Jerusalem, Israel). Rats were housed in regular cages situated in an animal room at 22°C, with a 14-hour light/10-hour dark cycle and food and water ad libitum. Rats were acclimatized for 2 weeks before onset of the study.

Interventions and Procedure

At the beginning of the study, weight, systolic blood pressure (SBP), plasma triglyceride levels, and insulin levels were measured. Rats were then randomly divided into six groups of 10 rats each. Five groups were fed a high-fructose diet composed of 60% fructose, 21% protein, 8% cellulose, 5% fat, 5% mineral mix, and 1% vitamin mix (Harlan Teklad, Madison, WI, USA), and one group (control) was fed regular rat chow consisting of 50% starch, 21% protein, 4.5% cellulose, 4% fat, 5% mineral mix, and 1% vitamin mix (Koffolk, Tel Aviv, Israel). After 3 weeks, weight, SBP, and plasma triglyceride and insulin levels were measured again, and the following drugs were orally administered to four of the five high-fructose diet groups: the NEP inhibitor candoxatril, 25, 50, or 100 mg/Kg/day, or the ACE inhibitor enalapril, 10 mg/Kg/day. After 2 weeks of treatment, the study was terminated, and weight, SBP, and plasma triglyceride and insulin levels were measured a third time.

Measurements

Rats were warmed to 37°C for 30 minutes, and SBP was then measured three times in succession using the tail-cuff technique (BP Recorder 58500; Ugo Basile, Comerio, Italy), and the average value was calculated. Plasma triglyceride and insulin levels were measured in blood samples taken from the retro-orbital sinus under light anesthesia with isoflurane after a 5-hour fast. Plasma triglyceride levels were determined with the enzymatic colorimetric method (AU 270; Olympus, Hamburg, Germany), and insulin levels, with a radioimmunoassay kit (INSIK-5; DiaSorin, Saluggia, Italy).

Statistical Analysis

Results are presented as mean ± standard error of the mean (SE). Differences between series of data were analyzed by two-tailed paired and unpaired Student *t* tests for group comparisons. $P < .05$ was considered significant.

Results

Induction of the MeS

The values of the metabolic parameters in the experimental (five-group average) and control groups at baseline and after 3 weeks are shown in Table 1.

Three weeks of feeding with high-fructose diet resulted in a weight gain of 77 ± 6 g (from 255 ± 6 g to 332 ± 8 g); a 17 mm Hg increase in SBP (from 135 ± 1 mm Hg to 152 ± 1 mm Hg); a two-fold increase in plasma triglyceride level (from 95 ± 10 mg/dL to 200 ± 22 mg/dL); and a 25.9% increase in plasma insulin level (from 22 ± 1.3 μU/mL to 27.7 ± 1.6 μU/mL). The regular chow diet group gained 62 ± 2 g (from 285 ± 3 g to 348 ± 3 g) with no significant changes in any of the other parameters.

Table 1
Values of metabolic parameters in rats treated with a high-fructose diet or regular chow, at baseline and after 3 weeks

Group	Parameter	Baseline	3 Weeks
Regular chow	Weight (gr)	285 ± 3	348 ± 3
	SBP (mmHg)	135 ± 1	134 ± 1
	TG (mg/dL)	80 ± 7	69 ± 6
	Insulin (μU/mL)	19.3 ± 1	18.9 ± 0.9
High-fructose diet (5 groups average)	Weight (gr)	255 ± 6	332 ± 8[†]
	SBP (mmHg)	135 ± 1	152 ± 1[*,†]
	TG (mg/dL)	95 ± 10	200 ± 22[*,†]
	Insulin (μU/mL)	22 ± 1.3	27.7 ± 1.6[*,†]

SBP, systolic blood pressure; TG, trigylcerides.
[*] $P < .01$ compared with regular chow group at 3 weeks.
[†] $P < .01$ compared with baseline within high-fructose diet group.

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