Metabolic Actions Could Confound Advantageous Effects of Combined Angiotensin II Receptor and Neprilysin Inhibition

To the Editor:

Dual angiotensin II receptor and neprilysin inhibition with LCZ696 provides additive blood pressure lowering in hypertensive patients, likely because of the well-characterized cardiovascular and renal natriuretic peptide actions. However, increased natriuretic peptide availability through neprilysin inhibition could also affect human lipid metabolism. The response could be exploited therapeutically. Yet, adverse effects on metabolic and cardiovascular risk cannot be excluded. Natriuretic peptides stimulate lipolysis in human adipocytes through natriuretic peptide receptor-A activation. The response is not attenuated by β-adrenergic receptor blockade in vitro and in vivo. Atrial and brain natriuretic peptides are more potent lipolytic agents than the prototypical β-adrenoceptor agonist isoproterenol. Systemic atrial natriuretic peptide infusion dose-dependently increases circulating free fatty acid and glycerol concentrations and improves postprandial lipid oxidation in human subjects. Therefore, medications raising systemic natriuretic peptide levels, such as LCZ696, could augment lipid mobilization and lipid oxidation. Improved lipid mobilization may be beneficial in overweight and obese patients in terms of weight loss. On the other hand, excessive lipid mobilization could promote muscular and hepatic ectopic fat storage and, thus, insulin resistance. Indeed, patients with heart failure show an increased prevalence of type 2 diabetes. Further, in heart failure, increased lipid mobilization through natriuretic peptides could sustain substrate supply to the failing heart. Yet, augmented atrial natriuretic peptide–mediated lipid mobilization and oxidation could predispose to cardiac cachexia, which carries a poor prognosis, unless adipose tissue desensitizes to natriuretic peptide–mediated lipolysis. We tested the hypothesis that the ex vivo lipolytic response to atrial natriuretic peptide is attenuated in isolated adipocytes from patients with severely impaired left ventricular function in part through changes in the expression of natriuretic peptide receptors.

We studied patients with left ventricular ejection fraction of 27±4% (6 men, 1 postmenopausal woman; 60±2 years of age); waist-to-hip ratio 0.97±0.02; body mass index 29.4±0.5 kg/m²) and control subjects with left ventricular ejection fraction of 64±4% (7 men, 1 postmenopausal woman; 60±4 years of age; waist-to-hip ratio 1.04±0.02; body mass index 30.5±1.0 kg/m²). Groups were also matched for presence of arterial hypertension and ischemic heart disease. All patients were treated with β-adrenergic receptor blockers. Seven patients in the heart failure group and 6 patients in the control group were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Homeostasis model of insulin resistance, triglyceride, cholesterol, and creatinine concentrations were similar in both groups. After an overnight fast, we obtained periumbilical subcutaneous adipose tissue needle biopsies. We isolated adipocytes by collagenase digestion. Then, we incubated adipocytes in vitro with incremental concentrations of isoproterenol or atrial natriuretic peptide for 60 minutes. Lipolytic activity was assessed by calculation of the relative increase of glycerol concentration in medium of treated adipocytes compared with untreated controls. From the remaining adipose tissue sample, we isolated mRNA and synthesized cDNA for real-time PCR. We applied the ΔΔCt method for target genes and internal control genes (18S rRNA). Natriuretic peptide receptor-A and -C mRNA expression were determined. The local ethics committee approved the study, and written informed consent was obtained. All data are expressed as mean±SEM.

The Figure shows results from ex vivo lipolysis experiments. Isoproterenol and atrial natriuretic peptide induced similar lipolytic responses in adipocytes from patients with impaired and with normal left ventricular ejection fraction. Natriuretic peptide receptor-A mRNA expression was 1.3±0.13 U in patients with and 1.0±0.10 U in patients without left ventricular dysfunction.
Natriuretic peptide receptor-C mRNA expression was 1.0±0.12 U in patients with and 1.0±0.28 U in patients without left ventricular dysfunction (P=NS).

The surprising finding of our study is that the adipose tissue natriuretic peptide system does not desensitize in heart failure patients, as evidenced by a preserved lipolytic response to atrial natriuretic peptide. In contrast, previous studies have shown that cardiovascular and renal responses to atrial natriuretic peptide are attenuated in experimental and clinical heart failure, perhaps through upregulation of the natriuretic peptide receptor-C "scavenger" receptor. Whether preserved lipolytic responses predispose to cardiac cachexia or sustain metabolism in the failing heart remains to be shown. However, the preserved lipolytic response in patients with impaired left ventricular function is likely relevant because atrial and brain natriuretic peptide concentrations are chronically elevated. Natriuretic peptides increase further during physical exertion. Therefore, we strongly suggest that medications raising systemic natriuretic peptides including LCZ696 should undergo careful testing for their metabolic actions before they are widely applied in heart failure patients. The fact that natriuretic peptide–mediated lipolysis occurs in primates only limits the applicability of preclinical data. 

**Sources of Funding**

Our work was supported in part by a grant from the Deutsche Forschungsgemeinschaft (JO 284/5-2) and a collaborative research grant of the European Commission (SICA-HF, FP7 241558).

**Disclosures**

None.

Metabolic Actions Could Confound Advantageous Effects of Combined Angiotensin II Receptor and Neprilysin Inhibition
Andreas L. Birkenfeld, Frauke Adams, Christoph Schroeder, Stefan Engeli and Jens Jordan

Hypertension. 2011;57:e4-e5; originally published online December 13, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.165159
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/57/2/e4

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/