Leptin, Endothelin, NADPH Oxidase, and Heart Failure

To the Editor:

We read with great interest the article by Dong et al1 in the February 2006 issue of Hypertension. They showed that leptin suppresses cardiac contractile function in ventricular myocytes by an endothelin-1 and NADPH oxidase–dependent pathway.

Interestingly, both endothelin receptor A and B antagonists were able to attenuate the cardiac functional abnormalities in response to leptin. In human myocardium, mainly the endothelin receptor A is functionally important and upregulated by heart failure.2 Furthermore, we found that patients with New York Heart Association stage III have, even independent of body mass index, higher leptin levels than New York Heart Association II patients and normal subjects.3 The impaired contractility in response to leptin observed by Dong et al4 in vitro could also play a role in the decreased ventricular function of obese patients with heart failure.

We found an induction of NADPH oxidase subunit expression and superoxide anion formation by endothelin-1 in human endothelial cells.5 Furthermore, transgenic endothelium-restricted overexpression of human endothelin-1 caused increased oxidative stress, augmented activity and expression of vascular NADPH oxidase, vascular remodeling, and endothelial dysfunction.6 Therefore, augmented endothelin levels observed in obese patients could increase superoxide anion formation in the vascularized myocardial tissue in vivo by an additional mechanism and could further potentiate the suppressive effect on cardiac contractile function.

Dong et al7 analyzed the subunit expression of the classical NADPH oxidase complex. Recently, several additional NADPH oxidase complexes have been discovered. Some of these novel NADPH oxidase complexes are involved in development and progression of cardiovascular diseases.8 Unpublished data from our laboratory suggest, in addition to the classical gp91phox/Nox2 complex, the expression of Nox1- and Nox4-containing NADPH oxidase complexes in isolated cardiomyocytes. Therefore, the leptin-mediated effects on contractile function might involve additional novel NADPH oxidase complexes as well.

In conclusion, growing evidence supports a role of the obese gene product leptin in the activation of an endothelin-1 and NADPH oxidase-dependent pathway leading to impaired endothelial and cardiac function. These data suggest a link between obesity, hypertension, oxidative stress, and heart failure.

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We thank Morawietz and Bornstein for their thoughtful comments of our study. They raised an important point regarding the role of endothelin (ET)-1 and NADPH oxidase in cardiac dysfunction under hyperleptinemia. Given the fact that leptin suppresses cardiac contractile function and contributes to cardiac hypertrophy, the previously identified leptin signaling molecules including NO, Janus kinase/signal transducers and activators of transcription, and p38 mitogen-activated protein kinase cannot satisfactorily explain the pathophysiological consequence of hyperleptinemia.1 Involvement of ET-1 in leptin-induced cardiomyocyte dysfunction adds a new sniper assignment to this “classical” cardiovascular culprit factor under hyperleptinemia. Our observation of ET-1 receptor-mediated NADPH oxidase activation and reactive oxygen species accumulation after leptin exposure is consistent with the finding of Duerrschmidt et al2 of ET-1–induced NADPH oxidase expression and superoxide formation in human endothelial cells (HUVECs). Morawietz and Bornstein also raised an issue that additional NADPH oxidase complexes may be involved in the onset and progression of cardiovascular diseases, because only p22phox, p47phox, p67phox, and gp91phox were evaluated in our study. We fully agree with this point that leptin-induced cardiomyocyte contractile response may involve novel NADPH oxidase.

Leptin is closely associated with ET-1. ET-1 stimulates leptin production in adipocytes. Vice versa, leptin may facilitate ET-1 production in endothelial cells and cardiomyocytes. Such a link between leptin and ET-1 may explain a myocardial defect under hyperleptinemia. ET-1 plays an important role in cardiac contractile function mainly mediated by ETa receptors with the ETA receptor playing a minor role. Myocardial expressions of ETA and ETa receptors are both elevated in heart failure and myocardial infarction. However, in a transgenic mouse model with elevated myocardial ET-1 levels, prolongation of survival was only achieved when both ETa/ETa receptors, rather than just ETA receptor, are blocked, indicating an important role for ETa.3 Duerrschmidt et al2 found that ET-1 induces superoxide formation and gp91phox mRNA expression via an ETa-mediated pathway in HUVECs, supporting the significance of the ETa receptor. Consistently, our earlier observation indicated that ET-1 enhanced reactive oxygen species generation, which was prevented by the ETa receptor antagonist BQ788 or the NADPH oxidase inhibitor apocynin in HUVECs.4 Nonetheless, little information is available regarding the involvement of any novel NADPH oxidase after ETa receptor activation.

Although elevated plasma leptin levels are deemed as an independent risk factor for the development of cardiovascular
disease, such as myocardial infarction, cardiac contractile dys-
function exists in both hyperleptinemic (db/db) and hypoleptine-
mic (ob/ob) mice. The cardiac defect (contractile dysfunction and 
poor β-adrenergic responsiveness) in ob/ob mice can be reversed 
with leptin replenishment, indicating a double-edged sword for 
leptin on heart function. Based on these findings, we believe that 
physiological levels of leptin may be beneficial for cardiac 
function, whereas pathological leptin levels (too much or too little) 
may be detrimental to cardiac function. A better understanding of 
the role of ET-1 and its downstream signaling mechanisms in leptin-
or hyperleptinemia-induced regulation of cardiac contractile func-
tion should provide insights for the therapeutic remedy of obesity-
associated cardiovascular complications.

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