Exogenous Ghrelin on Nitric Oxide-Endothelin 1 Imbalance in Metabolic Syndrome
Can We Kill 2 Birds With 1 Stone?

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hrelin is a recently identified growth hormone–releasing peptide, isolated from the stomach, initially described as an endogenous ligand for growth hormone secretagogue receptors. Although essentially a gastric hormone, which is involved in regulating energy balance and exerts influence on the pituitary-gonadal axis, additional growth hormone–independent cardiovascular actions have been attributed recently to this peptide. Among others, a significant impact on endothelial function has been identified, because ghrelin receptor expression has been documented in human endothelial cells.1 Experimental reports indicated that exogenous ghrelin administration ameliorates endothelial dysfunction and reduces the vasoconstrictor effect of endothelin 1 (ET-1) and, at higher doses, also decreases arterial pressure.

Obese patients with metabolic syndrome are characterized by reduced circulating ghrelin levels.2 These findings, together with evidence of compromised NO availability and enhanced ET-1–mediated vasoconstriction,3 make obesity a useful experimental model for investigating the impact of ghrelin on NO and ET-1.

In this issue of Hypertension, Tesauro et al4 investigated whether exogenous ghrelin may exert a beneficial effect on NO and ET-1 imbalance in the forearm microcirculation of patients with obesity-related metabolic syndrome. NO availability was assessed by intra-arterial infusion of the NO synthase inhibitor N\textsuperscript{\textalpha}-monomethyl-L-arginine, whereas ET-1–mediated vasoconstriction was investigated by using the ET\textalpha receptor antagonist BQ-123. In basal conditions, patients showed a higher vasodilating response to BQ-123 and a reduced contracting effect of N\textsuperscript{\textalpha}-monomethyl-L-arginine as compared with controls, suggesting predominantly ET-1–mediated vasoconstriction and a reduced NO vasodilator effect in this clinical condition. The novel aspect of the study by Tesauro et al4 is the demonstration that the unfavorable imbalance between NO and ET-1 was reversed by exogenous ghrelin. Thus, intra-arterial infusion of this peptide reduced enhanced ET-1–dependent vasoconstriction and reversed impaired NO-dependent vasodilation in patients. No effect was observed in control subjects. These findings allowed the authors to conclude that, beyond its classic effect in regulating energy balance and food intake, ghrelin also greatly contributes to maintaining vascular homeostasis by restoration of a balance between endothelium-derived contracting and vasodilator forces.

This study extends the authors’ previous finding that exogenous ghrelin administration improves blunted endothelium-dependent vasodilation by increasing NO availability in patients with metabolic syndrome.2 The article by Tesauro et al5 is methodologically of high quality and provides novel insight into the role of ghrelin in the regulation of vascular tone in metabolic syndrome. However, some possible mechanisms whereby ghrelin exerts a positive impact on endothelial dysfunction, although briefly mentioned speculatively, were not investigated in the study and require further comments.

One possible mechanism concerns a ghrelin-induced anti-inflammatory effect. Low-grade inflammation has acquired progressive recognition over the past few years as a mechanism for cardiovascular damage. Experimental evidence indicates that visceral fat may play a direct role in provoking low-grade inflammation by secreting tumor necrosis factor-\textalpha and interleukin 6.6 Such cytokines induce endothelial dysfunction mainly by production of reactive oxygen species, which, in turn, reduces NO availability. In particular, tumor necrosis factor-\textalpha and interleukin 6 stimulate reactive oxygen species production via activation of 2 major sources of reactive oxygen species, NAD(P)H oxidase and xanthine oxidase, respectively. Interleukin 6 also stimulates C-reactive protein synthesis by the liver, which, in turn, decreases the expression of endothelial NO synthase, leading to reduced NO production. In addition, other important proteins, such as leptin and adiponectin, should be mentioned. Elevated leptin concentrations, a feature of obesity, may contribute to the proinflammatory state of obesity. Conversely, adiponectin, of which the concentrations fall in obesity, is anti-inflammatory and potentially antiatherogenic.5 Recently, ghrelin was found to inhibit proinflammatory cytokine production, nuclear factor \textkappa B activation in human endothelial cells in vitro, and endotoxin-induced cytokine production in vivo, thus providing novel evidence of anti-inflammatory action by ghrelin.6

Another possible mechanism, not necessarily alternative to that described above, is the induction of NO production by phosphatidylinositol 3-kinase (PI3K) signaling. In a recent experimental study, Iantorno et al7 convincingly demonstrated the ability of ghrelin to facilitate PI3K activity, with consequent Akt phosphorylation, which, in turn, activates phosphorylation of endothelial NO synthase. An important

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aspect emerging from the study by Iantorno et al.\textsuperscript{7} is that the PI3K-Akt pathway is the same signaling pathway as that through which insulin has been hypothesized to stimulate NO production and, consequently, induce vasorelaxation. The metabolic action of insulin is also at least in part modulated by signaling pathways requiring PI3K activity.\textsuperscript{8} Because, in a condition such as metabolic syndrome, reduced NO availability and insulin resistance occur simultaneously, it is reasonable to conclude that the increased NO production via PI3K-Akt signaling may be a mechanism shared by both ghrelin and insulin. In this suggested scenario, it is not surprising that ghrelin infusion is actively involved in acute and long-term control of glucose metabolism and insulin sensitivity, as documented recently in humans.\textsuperscript{9} Taken together, these data allow the conjecture that, concomitantly with its beneficial effect on the imbalance between NO and ET-1, ghrelin may also contribute to cellular glucose uptake. Thus, vascular actions of ghrelin could be important for coupling hemodynamic and metabolic homeostasis, thereby providing a link between obesity and other major cardiovascular morbidities, such as hypertension and diabetes mellitus, that are characterized by endothelial dysfunction and insulin resistance. However, the therapeutic impact of ghrelin aiming to simultaneously ameliorate both endothelial dysfunction and insulin resistance is at present only an attractive hypothesis that needs future clinical investigation.

The figure summarizes some potential biological effects of ghrelin, many of which are not discussed in the text. Some of the proposed actions require future confirmation.

Given this wide spectrum of biological activity, it is evident that the discovery of ghrelin is opening up many new research perspectives. The present article by Tesauro et al.,\textsuperscript{4} together with previous results from the same group, substantially enriches our understanding of the beneficial effect of ghrelin toward the vasculature and highlights the ghrelin system as a promising candidate for cardiovascular drug discovery. In the meantime, to mimic the ghrelin-related effects, lifestyle changes, such as weight loss associated with regular physical activity, which increase circulating ghrelin levels, can be recommended.\textsuperscript{10}

### Disclosures

None.

### References


