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

Stefano Taddei, Agostino Virdis

Exogenous ghrelin administration improves blunted endothelium-dependent vasodilation by increasing NO availability in patients with metabolic syndrome. The article by Tesauro et al 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-α and interleukin 6. Such cytokines induce endothelial dysfunction mainly by production of reactive oxygen species, which, in turn, reduces NO availability. In particular, tumor necrosis factor-α 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. Recently, ghrelin was found to inhibit proinflammatory cytokine production, nuclear factor κB activation in human endothelial cells in vitro, and endotoxin-induced cytokine production in vivo, thus providing novel evidence of anti-inflammatory action by ghrelin.

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, Iantero et al 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
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

Exogenous Ghrelin on Nitric Oxide-Endothelin 1 Imbalance in Metabolic Syndrome: Can We Kill 2 Birds With 1 Stone?
Stefano Taddei and Agostino Virdis

Hypertension. 2009;54:960-961; originally published online September 28, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.141176

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/54/5/960

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/