Multicellular organisms regulate the activity of their individual cells and organs in a coordinated way. As a potential mechanism, they use either the nervous system, allowing the exchange of information in a rapid way, or hormones, controlling activity status over a longer time period. Furthermore, there is need for coordinated defense mechanisms against bacteria and virus, mediated by the immune system. These 3 levels of communication, nervous system, hormonal system, and immune system, have many interactions. These interactions are rather complex, and we learn more about the individual players from day to day. This is important as deregulation in any of these pathways significantly contributes to disease conditions, including systemic hypertension and the subsequent end-organ damages.

Ghrelin is a 28-aa peptide released into the circulation mainly, but not exclusively, by cells in the stomach. It circulates in a highly active acylated form, although large amounts of nonacylated ghrelin are found. The latter does not bind to classical ghrelin receptors, called growth hormone secretagogue receptors, and may have nonclassical functions. However, active ghrelin binds to these receptors, which have a widespread distribution in the cardiovascular system.1

Ghrelin is a good example of a peptide that links the hormonal system, the nervous system, and the immune system. This is exemplified by the fact that plasma ghrelin levels increase during fasting and decrease with feeding. Ghrelin modulates the autonomic nervous system by reducing sympathetic activity and increasing parasympathetic activity. Ghrelin is also implicated in inflammation, possibly via its effect on vagal stimulation. Moreover, as ghrelin restores vasoresponsiveness to acetylcholine by increasing nitric oxide availability, it may influence blood pressure regulation, especially in obese patients.2 But how are these possible protective effects of ghrelin mediated?

In this issue of Hypertension, Mao et al3 studied the effects of ghrelin deficiency on cardiac hypertrophy in a model of acute pressure overload. Although there are limitations in this study, for example, the model of pressure overload induced by transverse aortic constriction does not really resemble chronic overload in humans and ghrelin deficiency does not necessarily reflect lower ghrelin plasma levels, the study under discussion can be used to learn how ghrelin affects the autonomic nervous system and the immune system, which may affect left ventricular hypertrophy in response to pressure overload. The interaction between ghrelin and vagal stimulation has previously been demonstrated. Although ghrelin can shift the ratio between sympathetic and parasympathetic nervous system into the direction of the parasympathetic nervous system, vagal stimulation can increase the release of ghrelin vice versa.4,5 Relationships between vagal stimulation and anti-inflammatory effects have been suggested, but mechanisms are unclear. Immune cells express α7-nicotinic acetylcholine receptors and growth hormone secretagogue receptors. Therefore, ghrelin may either attenuate the inflammatory activity of immune cells directly or via vagal stimulation. Mao et al4 administered nicotine to ghrelin knockout mice under transverse aortic constriction stress and showed that nicotine rescued the effect of ghrelin deficiency on transverse aortic constriction–induced heart failure. This may also be explained if ghrelin activates vagal tone and acetylcholine acts as an anti-inflammatory mediator (Figure). If, alternatively, nicotine would increase ghrelin release, nicotine would not be able to rescue ghrelin deficiency. The concept that ghrelin via inhibition of inflammation attenuates cardiac hypertrophy also requires that inflammation contributes to hypertrophy and its transition to heart failure. As a read-out for inflammation, the authors used interleukin-6 concentration in their study,3 but interleukin-6 itself can improve cardiac function, leading us to questions that still remain.6 The presented study does not really rule out the possibility that acetylcholine and ghrelin attenuate hypertrophy by acting directly on cardiomyocytes. In this case, the effect on inflammation is a bystander rather than causally responsible for the improved function in the presence of ghrelin. As the authors nicely summarize “Endogenous ghrelin plays a crucial role in … cardiac hypertrophy, and this likely occurs through the activation of the cholinergic anti-inflammatory pathway.”7 Furthermore, the finding cannot explain the positive relationship between excessive ghrelin and cardiac hypertrophy index in patients.7 In general, there are problems to translate these findings into clinical practice. On one hand, a reciprocal relationship between plasma ghrelin level and arterials stiffness in hypertensive subjects supports a direct role for ghrelin in vascular protection.8 Furthermore, improving physical activity increases plasma ghrelin concentration but reduces the amount of circulating monocytes.9 On the other hand, antihypertensive treatment disrupted the regulation of ghrelin production, indicating a potential limitation in the ability to affect the ghrelin

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From the Institute of Physiology, Justus-Liebig-University, Giessen, Germany.

Correspondence to Klaus-Dieter Schlüter, Institute of Physiology, Justus-Liebig-University, Aulweg 129, 35392 Giessen, Germany. E-mail Klaus-Dieter.Schlueter@physiologie.med.uni-giessen.de

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system under hypertensive conditions. However, the supposed link between vagus stimulation and anti-inflammatory response gives an idea how improved vagus stimulation can attenuate ventricular hypertrophy although ventricular tissue is barely innervated by the parasympathetic nervous system. In addition, clinical findings that ghrelin improves cardiovascular responses even in patients with endothelial dysfunction makes this regulatory pathway an interesting point of intervention. Moreover, the study may explain how increased physical activity can positively affect cardiac remodeling. It will be interesting to see whether the future brings progress that the published mouse study may suggest.

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Disclosures
None.

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Figure. Potential pathways by which ghrelin can reduce cardiac hypertrophy and the transition to heart failure. In pathway A, ghrelin activates the parasympathetic nervous systems (PNS) that release acetylcholine and activates nicotinergic receptors on macrophages (MØ), thereby reducing their release of interleukin (IL)-6. The proinflammatory cytokine can induce heart failure. In pathway B, the PNS activates ghrelin release that then activates growth hormone secretagogue receptors (GHSRs) on MØ, thereby reducing their IL-6 release. nicotine substitution to ghrelin knockout mice favors pathway A as it allows nicotine to rescue ghrelin knockout mice. Note that such experiments do not rule out direct effects of either ghrelin or acetylcholine on cardiac cells (dashed lines). α7-nAChR indicates α7-nicotinic acetylcholine receptors.
Pressure Overload, Sympathetic Drive, and Inflammation: Is Ghrelin the Link?
Klaus-Dieter Schlüter

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