Sympathetic Activation in Obesity
A Noninnocent Bystander

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The hypothesis that human obesity is associated with a state of adrenergic overdrive dates back to \( \approx 50 \) years ago, when a group of American investigators noted that sympathetic function was indeed altered in the obese subject.\(^1\) Since then, many studies have attempted to investigate whether and to what extent sympathetic activation is a hallmark of the autonomic profile of the obese state. The results, which have also been included in a meta-analysis,\(^2\) although suggestive for a hyperadrenergic state, did not permit any definite conclusion on this issue to be drawn. Several factors may account for these inconclusive results. First, the data collected were mainly based on the biochemical assay of plasma norepinephrine or its urinary metabolites, that is, an approach known to have a limited reproducibility and sensitivity in detecting the adrenergic abnormalities characterizing a physiological or a pathophysiological state.\(^3\) Furthermore, plasma norepinephrine concentration relies on a variety of biological processes taking place both at a synaptic and at a postsynaptic level, such as the reuptake of the neurotransmitter by the adrenergic nerve terminals and the tissue clearance process of norepinephrine, as well as its functional role as a cotransmitter with epinephrine.\(^3\) These complex steps make hard to establish whether and to what extent an elevation in circulating levels of norepinephrine (or its urinary metabolites) mirrors a true increase in central adrenergic outflow or whether it rather reflects an impairment of the physiological processes mentioned above taking place at a peripheral neural level. More stringent evidence on the adrenergic overdrive characterizing the obese state came from the microneurographic nerve traffic recording, as well as the norepinephrine spillover technique.\(^3,4\) From the data obtained by these 2 approaches, the conclusion has been drawn that central sympathetic outflow is clearly potentiated in human obesity, thereby exposing different tissues and organ functions to the potential deleterious effects of an adrenergic overdrive.

The article by Lambert et al, published in the present issue of *Hypertension*,\(^5\) sheds light on this latter issue, that is, on the role of the sympathetic nervous system in the development and progression of target organ damage in the overweight and in the obese state (Figure). This role is supported by the evidence that, in a group of young obese normotensive subjects, sympathetic nerve traffic is the major determinant of the alterations in endothelial function, renal function, and left ventricular mass detected in the study population. Interestingly, this occurs in the absence of a clinical diagnosis of hypertension, thereby emphasizing the possibility that the early structural and functional cardiovascular abnormalities described in human obesity may be independent of the presence of hypertension.

### Sympathetic Activation and Organ Damage

The finding that a close association does exist between the adrenergic nervous system and the structural and functional alterations of the heart and the arterial tree is not new. Indeed, during the past few years evidence has been provided that sympathetic activation reduces arterial distensibility, augments arterial stiffness, triggers endothelial dysfunction, favors cardiac hypertrophy, and promotes left ventricular diastolic dysfunction.\(^6\)

To the above-mentioned information, all collected in hypertensive patients, the article by Lambert et al\(^5\) adds 3 pieces of new evidence. First, it shows for the first time that the association between adrenergic overdrive and vascular, cardiac, and renal organ damage is not limited to the hypertensive state, but it rather also occurs in the obese normotensive state as well. Second, it documents that, even when clinic and ambulatory blood pressure values are still in the normal range, early organ damage may take place and that this may be associated with a hyperadrenergic state. Finally, it provides evidence that, along with vascular and cardiac structural alterations, renal dysfunction may also be associated with sympathetic overactivity.

There are several potential mechanisms by which an increase in sympathetic activity may be associated with target organ damage. Data collected in experimental animal models have shown that at subpressor doses norepinephrine directly increases left ventricular weight, myocardocyte cross-sectional area, and nucleic acid synthesis from the myocardial tissue.\(^6\) A stimulation of the sympathetic nervous system, however, may favor the development of an insulin resistance state with an accompanying hyperinsulinemic state. Evidence from in vitro studies indeed suggest that insulin may trigger the development of cardiac and vascular structural alterations because of the prohypertrophic effects that this substance has on the myocardial tissue and the arterial wall, respectively.\(^6\) Similarly, sympathetic stimulation may activate the renin-angiotensin-aldosterone system, resulting in an increase in the circulating levels of angiotensin II, which also exerts,
Open Questions and Clinical Implications

The Figure, already mentioned in the initial part of this editorial, schematically depicts the chain of events leading, in the clinical course of an overweight/obese state, from the sympathetic dysfunction to end-organ damage, blood pressure elevation, and cardiovascular, metabolic, and renal disease. Although intriguing, the scheme still remains a working hypothesis that requires additional experimental support. There are, however, some data already available in favor of this hypothesis. This is the case for the promoting role that the sympathetic nervous system plays on the transition from the earlier cardiac and renal alterations to the overt disease, such as congestive heart failure and renal failure. This is also the case for the predictive value that sympathetic neural factors may favor the development of obesity-related end-organ damage.

Figure. Scheme illustrating the working hypothesis on the role of the sympathetic nervous system (SNS) in the development and progression of end-organ damage and related cardiovascular, metabolic, and renal diseases in the overweight and in the obese states. LVMI indicates left ventricular mass index; M/L, media:lumen ratio; LVH, left ventricular hypertrophy; CHD, coronary heart disease; HT, hypertension; CHF, congestive heart failure.

Disclosures

None.

References


