The hypothesis that human obesity is associated with a state of adrenergic overdrive dates back to ≈50 years ago, when a group of American investigators noted that sympathetic function was indeed altered in the obese subject. 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, 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. 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. 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 outflow or whether it rather reflects an impairment of the 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.

To the above-mentioned information, all collected in hypertensive patients, the article by Lambert et al 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, myocyte cross-sectional area, and nucleic acid synthesis from the myocardial tissue. 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. Similarly, sympathetic stimulation may activate the renin-angiotensin-aldosterone system, resulting in an increase in the circulating levels of angiotensin II, which also exerts,
throughout direct and indirect (ie, dependent on the angiotensin II–related blood pressure elevation) mechanisms, prohypertrophic and profibrotic effects on the myocardial tissue, the vessel wall, and the renal organ. Finally, short- and long-term blood pressure oscillations and blood pressure variability have been shown to be involved in the occurrence of left ventricular hypertrophy. Taken together these findings suggest that, throughout both direct and indirect pathways, sympathetic neural factors may favor the development of obesity-related end-organ damage.

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 activation may have on the outcome of congestive heart failure, myocardial infarction, stroke, and renal failure.

The article by Lambert et al obviously cannot provide an answer to all of the questions related to the role of sympathetic neural factors in the development of obesity-related end-organ damage. For example, from the study data, the participation of obstructive sleep apnea in the development of the cardiovascular and renal abnormalities cannot be ruled out. This is because sleep apnea may be one of the leading mechanisms responsible for the adrenergic overdrive in the obese state. The data do not also allow exclusion of the possibility that alterations in the dipping status may be responsible, at least in part, for the occurrence of the sympathoexcitation and, thus, for the related end-organ damage. Finally, the study by Lambert et al does not assess microalbuminuria, that is, an early marker of renal dysfunction, of which the relationship with sympathetic activity is totally unknown.

The close link between sympathetic activation and cardiovascular events makes somewhat obvious the therapeutic implication of the study, that is, the need that, in the overweight and in the obese states, the therapeutic intervention aimed at reducing visceral fat depot should be adopted as early as possible in the clinical course of the disease. The rationale for the losing weight procedure is that dietary restriction “per se” on one hand and body fat reduction on the other are accompanied by a pronounced sympathoinhibition, a renin-angiotensin deactivation, and an improvement in insulin sensitivity, with favorable consequences on cardiovascular and renal structural and functional alterations.

Disclosures

None.

References


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