Adrenergic Overdrive as the Link Among Hypertension, Obesity, and Impaired Thermogenesis

Lights and Shadows

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The sympathetic nervous system plays a pivotal role in both blood pressure and metabolic homeostatic control by regulating cardiac output, peripheral vascular resistance, heat production, and resting metabolic rate, which accounts for a large fraction of adult energy expenditure. Throughout the years, the attractive hypothesis based on this evidence has been advanced that an alteration in blood pressure regulation, as well as in thermogenesis control exerted by the sympathetic nervous system, represents the pathogenetic background for 2 diseases of common detection in current clinical practice, that is, hypertension and obesity, respectively. As far as high blood pressure is concerned, a number of studies based on indirect or direct methodologic approaches to assess neuroadrenergic function have unequivocally demonstrated that a hyperactivity of the sympathetic nervous system contributes to the development, maintenance, and progression of the hypertensive state. Traditionally, obesity-related hypertension has been regarded, at least in part, as the result of a hyperactivity of the sympathetic nervous system, related to some extent to the weight-associated increase in sympathetic cardiovascular function and energy balance control, the latter being associated with larger sympathoinhibitory effects (see above). Second, the presence of cardiac and/or vascular hypertrophy, arterial and arteriolar hypertrophy, and vascular remodelling even when blood pressure is normal, an adrenergic overdrive has also been reported in the obese state and independent but additive increases in sympathetic activity have been described when obesity is coupled with hypertension. Traditionally, obesity-related hypertension has been regarded, at least in part, as the result of a hyperactivity of the sympathetic nervous system, related to some extent to the weight-associated increase in sympathetic cardiovascular drive.

In the present issue of the journal, Shibao et al publish the results of an intriguing study aimed at defining the role of the sympathetic nervous system in the development of the hemodynamic (hypertension), as well as metabolic (dysregulation of energy expenditure and caloric balance), abnormalities of frequent detection in obese individuals. Through complex and sophisticated methodologic approaches to assess sympathetic cardiovascular function and energy balance control, the authors provide 3 pieces of new information. First, they show that an enhancement of the adrenergic neural influences to the heart and the peripheral circulation is involved in the development of the hypertensive state associated with obesity. Second, they suggest that the sympathetic activation does not explain “per se” the blood pressure elevation frequently detected in the clinical history of the overweight individual but that other metabolic, hemodynamic, and neurohumoral mechanisms participate in the phenomenon. Finally, they provide evidence that the abnormal neuroadrenergic function seen in obese hypertensive subjects has no effect on resting energy expenditure and, thus, does not oppose the excessive caloric intake. In the study by Shibao et al, they assess the role of the sympathetic nervous system in blood pressure and thermogenesis control by measuring the changes of obese and lean subjects in blood pressure and in resting energy expenditure rate acutely induced by acute pharmacological ganglionic blockade (stepwise intravenous infusion of trimetaphan). By showing blood pressure decreases of greater magnitude in obese rather than in lean subjects, but superimposable trimetaphan-induced energy expenditure reductions in the 2 groups of individuals, the results clearly indicate that in obesity-related hypertension, the sympathetic nervous system is mechanistically involved in determining the blood pressure elevation but not in enhancing resting body energy expenditure. This refines the hypothesis advanced years ago by Landsberg on the mechanisms through which the hyperactivity of the sympathetic nervous system participates at the hemodynamic and metabolic alterations of obesity-related hypertension (Figure).

Two sets of considerations deserve to be made in interpreting the study’s results. The observed differences between groups in the hemodynamic, as well as in the metabolic, responses to the pharmacological challenge, are, at least in part, dependent on baseline values, which are greater for magnitude in the obese normotensive and more so in the obese hypertensive subjects as compared with the lean normotensive ones. Indeed, expression of the results in a fashion, which takes into account baseline values (percent data), hampers the difference between groups, although it does not eliminate the trend observed for absolute values. Furthermore, and more importantly, as correctly pointed out by the authors, the trimetaphan infusion technique as a tool for studying adrenergic function faces a number of limitations. Three are of relevance for the findings of the current study. First, the responses are directly proportional to the baseline level of the neuroadrenergic drive, a greater degree of sympathetic activity being associated with larger sympathoinhibitory effects (see above). Second, the presence of cardiac and/or vascular hyper-
trophy, which is of frequent detection in the obese state complicated by high blood pressure, may affect the results through a cardiovascular “amplifier” effect. Finally, the intraindividual and interindividual variability of the responses to trimetaphan administration are not negligible, thus limiting the applicability of the results obtained via this approach to the wide range of patients. It should be mentioned, however, that almost no technique used to investigate human sympathetic function is free from limitations. This is the case, for example, for the approach based on the assay of plasma norepinephrine, given the evidence that its circulating levels result not only from the secretion but also from the tissue clearance and reuptake process of the adrenergic neurotransmitter from sympathetic nerve terminals. This weakens the ability of this humoral marker to “sense” changes in sympathetic dive, as confirmed also in the study by Shibao et al by the finding that circulating plasma norepinephrine values are not different in lean and obese subjects despite the greater sympathetic nerve traffic and heart rate values detected in the latter group. Some limitations should also apply to the microneurographic approach, which represents the only available technique allowing a direct quantification of the sympathetic neural discharge in human beings. It provides, however, information on the behavior of the sympathetic nervous system limited to a specific cardiovascular district (the muscle circulation), which is not necessarily representative of the adrenergic drive detectable in other circulations (coronary, renal, and hepatic) of key relevance for blood pressure and metabolic homeostasis control.

A final result of the study deserves to be discussed briefly. Because the investigation has been carried out in obese subjects with a waist circumference >102 cm, its results should apply only to the visceral type of the obese state, which is characterized by a marked insulin resistance and a remarkable degree of sympathetic activation. Thus, whether the role of the sympathetic nervous system is similar in peripheral obesity, in which both insulin resistance and sympathetic activation are much less pronounced, remains to be seen.

Disclosures
None.

References
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