Is obstructive sleep apnea the cause of sympathetic nervous activation in human obesity?

BASED ON FINDINGS IN EXPERIMENTAL MODELS of obesity, the sympathetic nervous system has commonly been assumed to have a determining role in obesity development through its influence on the regulation of energy expenditure. An earlier hypothesis was that sympathetic nervous activity was low in obesity, which by reducing thermogenesis had led to the weight gain (2). More recent studies in human obesity, however, firmly establish that human obesity is accompanied by activation of the sympathetic nervous system rather than its suppression (3, 7, 17) and suggest that this sympathetic stimulation is important in the pathogenesis of the blood pressure elevation of obesity-related hypertension (4, 7).

What might be the basis for the sympathetic nervous system activation of human obesity? The elevated plasma concentrations of insulin (12) and the adipocyte hormone leptin (9), which accompany obesity, are candidates through acting within the brain to stimulate central sympathetic outflow, but as yet the evidence for both is inconclusive. Also possibly of importance is obstructive sleep apnea (OSA), which is common in obesity (14). Nocturnal apneic episodes in OSA are characterized by extreme levels of sympathetic nervous stimulation (15). It has been suggested that, over time, this might be “generalized” into ongoing, daytime sympathetic activation and, further, that OSA is the principal (even exclusive) cause of sympathetic activation in obese subjects (14). In support of this idea, an intriguing recent paper describes some elevation of sympathetic tone even in lean men with OSA (8), perhaps allowing a disentangling of the independent but usually combined influences of obesity and OSA, although sympathetic activity was materially lower in them than in men with both OSA and obesity.

The accompanying paper by Paul Mills and colleagues (13), in which the influence of continuous positive airway pressure (CPAP) on sympathetic nervous activity in obese patients with OSA was investigated, may help with this conundrum, although this may not have been the authors’ primary purpose. In an interesting study of sound design, the effect of CPAP on norepinephrine plasma kinetics and urinary norepinephrine excretion was studied in obese men and women. Perhaps surprisingly, the appearance rate of norepinephrine in plasma (“norepinephrine spillover”), which provides a validated estimate of whole body sympathetic nervous system activity (6), was not lowered by CPAP, suggesting that, after all, OSA perhaps might not be responsible for generating the sympatho-neural activation of obesity.

Are the methods used by the authors adequate for measuring human sympathetic nervous system activity? Clinical measurements of rates of sympathetic nerve firing using microneurography (7) and of norepinephrine release to plasma (6) provide the most secure basis for studying the human sympathetic nervous system. Measurement of the plasma concentration of norepinephrine as a test of sympathetic nervous activity has major limitations. One is the dependence of plasma norepinephrine concentrations on rates of removal of the neurotransmitter from plasma, not just sympathetic tone and norepinephrine release. Whole body norepinephrine spillover is derived as the mathematical product of norepinephrine plasma concentration and norepinephrine plasma clearance (6). In the accompanying paper (13), the authors avoided confusion potentially arising from an increase in norepinephrine plasma clearance with CPAP, which they document, by measurement of the plasma norepinephrine appearance rate using isotope dilution methodology (13). Norepinephrine plasma clearance is ultimately determined by cardiac output and regional blood flows and by the capacity for neuronal and extraneuronal norepinephrine uptake (6), but precisely how CPAP elevated norepinephrine plasma clearance remains uncertain.

When norepinephrine spillover rates are to be quantified, choice of the blood sampling site is of critical relevance. A common practice, one adopted here by Mills and colleagues (13), has been to sample blood from an antecubital vein. The underlying assumption is that, during infusion of the radiolabeled norepinephrine used in this method, the tracer is mixed evenly in plasma. This notion of a well-mixed central plasma pool, which includes the plasma in superficial veins, however, is an idealization; there are regional differences in the plasma concentration of unlabeled and tracer norepinephrine that are dependent on local processes of norepinephrine release and removal (6).

Measurement of whole body norepinephrine spillover is best done with arterial sampling (6). The commonly made choice of an antecubital venous sampling site is based only on convenience. Sampling the venous drainage of the forearm is no better, on theoretical grounds, than sampling from the venous drainage of any other organ. These criticisms might suggest that the demonstration of an absence of sympathetic inhibition with CPAP in the accompanying paper is untrustworthy. I think not; the conclusion of the paper looks well sustained. Although absolute norepinephrine clearance values may be overestimated with venous sampling, the method has in general reliably detected changes in sympathetic activity with interventions, a noteworthy example being in the Shuttle Neurolab investigation of the effects of microgravity on sympathetic activity (5).

But there is a paradox in the report of Mills and colleagues (13). Although whole body norepinephrine spillover to plasma was unchanged by CPAP, both urinary norepinephrine excretion and the previously elevated blood pressure fell. Activation of the renal sympathetic outflow, detectable by selective measurement of renal norepinephrine spillover into the renal veins (3, 17), is present in human obesity and apparently contributes importantly to the development of obesity-related hypertension. Might the observed fall in urinary norepinephrine excretion reflect a blood pressure-lowering inhibition of the renal sympathetic nerves by CPAP?

Norepinephrine excretion in urine derives from several sources, but primarily from plasma norepinephrine filtered at the glomerulus (11). Although some additional contribution is made by tubular secretion of norepinephrine released into the interstitium of the kidney by renal sympathetic nerves (1), the component of urinary norepinephrine excretion derived from renal sympathetic nerves is rather small, at most 30% (1) and

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probably less (11). Accordingly, the fall in urinary norepinephrine excretion with CPAP detected by Mills and colleagues (13) cannot be taken to be indicative of renal sympathetic inhibition.

In some clinical contexts, most notably in cardiac failure patients, CPAP does reduce sympathetic nervous system activity (10, 16). The accompanying paper, which suggests that this is not the case in obesity, argues against the sympathetic activation of obesity being primarily driven by OSA.

REFERENCES


