Renal Sympathetic Hyperactivity in Hypertension: True or False?

To the Editor:

Increased renal norepinephrine spillover, observed by using isotope-dilution method, is thought to indicate renal sympathetic hyperactivity and to play a crucial role in hypertension. However, SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension), the first randomized sham-controlled trial, failed to show a benefit of renal denervation for resistant hypertension.1 This raises the issue of whether the sympathetic hyperactivity hypothesis is true.

In a recent issue of Circulation Research, Grassi et al2 have emphasized the presence and importance of sympathetic hyperactivity in hypertension, primarily based on the results of isotope-dilution studies. However, the isotope-dilution method cannot exclude the involvement of intraorgan platelet release of norepinephrine. We would argue that platelet norepinephrine release, rather than sympathetic nervous system alterations, may be the cause of increased norepinephrine spillover in hypertension for the following reasons.

First, the platelets may serve as a reservoir for regional norepinephrine spillover. The platelets, the carriers of norepinephrine in the blood, link the upstream (the sympathetic nervous system) and downstream (the detoxifying and excretory organs) of the norepinephrine removal system. Namely, platelets take up and store norepinephrine released from the sympathetic nervous system and carry it to the detoxifying and excretory organs for removal through an intraorgan platelet destruction mechanism. Moreover, platelet phenol sulfotransferase and monoamine oxidase can degrade norepinephrine,3 which can explain the slower and smaller change in platelet norepinephrine level in response to stress than that of plasma norepinephrine level. The platelets contain a much higher norepinephrine concentration, with a platelet:plasma ratio of 1855:1.4 The high intraplatelet norepinephrine concentration, with a platelet:plasma ratio that of plasma norepinephrine level. The platelets contain a much higher norepinephrine concentration, with a platelet:plasma ratio of 1855:1.

Second, platelet norepinephrine release may contribute to regional differences in norepinephrine spillover. Kopin et al5 found that although the mean renal norepinephrine release rate is only 2× that of the heart, the mean norepinephrine spillover from the kidneys is 10-fold greater than from the heart.5 The high level of renal norepinephrine spillover cannot be explained by sympathetic activity but may be related to platelet norepinephrine release because intraorgan platelet destruction differs from organ to organ.

Third, hypertension is associated with platelet abnormalities. These abnormalities include increased mean platelet volume,6 increased platelet norepinephrine level6 and efflux,7 increased renal platelet consumption/destruction (ie, thrombotic microangiopathy).8 These data suggest platelet norepinephrine overload in hypertension. Given that (1) platelet phenol sulfotransferase activity is positively correlated with the level of its metabolite norepinephrine sulfate in plasma9 and (2) hypertension occurs rapidly (within several weeks) after an increase in mean platelet volume,10 increased mean platelet volume may reflect saturation of platelet norepinephrine-degrading enzymes or, in other words, functional platelet failure.

Finally, platelet abnormalities can be caused by excretory insufficiency. Hypertension is associated with excretory insufficiency (eg, renal disease, low nephron number, and low sweat excretion)11 and decreased norepinephrine clearance.12 Because excretion is situated downstream of the norepinephrine removal system, excretory insufficiency could increase the burden on platelets, explaining platelet norepinephrine overload in hypertension and the observed inverse association between glomerular filtration rate and mean platelet volume.13 Consequently, intra-renal platelet destruction would release more norepinephrine in hypertensive than in normotenive subjects, and this may underlie the increased renal norepinephrine spillover in hypertension.

Although sympathetic activity, which is necessary for survival, is the source of norepinephrine, whether norepinephrine retention occurs would depend on the efficiency of the norepinephrine removal system. Given that (1) hypertension is associated with excretory insufficiency and (2) SYMPLICITY HTN-3 trial has demonstrated that renal denervation is ineffective for hypertension, it seems that hypertension is mainly due to excretory insufficiency that cannot meet the needs of the sympathetic nervous system, rather than due to sympathetic nervous system alterations.

Disclosures

None.

Shi-Sheng Zhou
Department of Physiology
Medical College
Dalian University
Dalian, China

Yiming Zhou
Renal Division
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA

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