
In response:

Drs Zhou and Zhou¹ write a challenging letter that aims to turn concepts of sympathetic nerve biology and norepinephrine plasma kinetics upside down. Their letter claims that there is a previously unsuspected primary importance for platelets in norepinephrine disposition after release of the transmitter from sympathetic nerves in individual organs and in clearance of norepinephrine from the circulation. Imagination is a fine thing in science, not least for overturning a dominant paradigm, but supporting quantitative analysis must buttress this.

Before addressing the specific issues raised by the 2 authors in their letter,¹ we would like to emphasize that, as extensively discussed in our article,² the evidence of a sympathetic hyperactivity in hypertension is based not only on the results of the isotope-dilution studies but also, and probably to a greater extent, on other techniques assessing neuroadrenergic drive, the most important of them being represented by the microneurographic nerve traffic recording. Thus, the statement by Drs Zhou and Zhou that “the importance of sympathetic hyperactivity in hypertension is primarily based on the results of isotope-dilution studies” is not supported by current knowledge.

Let us focus on the weaknesses in the correspondents’ case. The first concerns norepinephrine plasma clearance and specifically whether this is primarily dependent on uptake from plasma into platelets. Tracer kinetics analyses demonstrate total norepinephrine plasma clearance in humans to be 2 to 4 L/min. This is equivalent to the calculated sum of measured clearances by individual organs, indicating that significant removal of norepinephrine from plasma only occurs in the regional microcirculations of the body.¹ Unlike acetylcholine, where removal speedily occurs from plasma through the action of cholinesterases, norepinephrine is not removed from free plasma in the circulation in any quantity, so that in humans the concentration of norepinephrine in the arterial plasma pool is identical throughout. Norepinephrine uptake into platelets cannot begin to match the measured rate of plasma clearance of 2 to 4 L/min. The correspondents omit the key influence of neuronal uptake of norepinephrine from the plasma pool,¹⁴ while inexplicably emphasizing platelet uptake, and even suggesting sweating is a mechanism of some importance.

And the second weakness concerns the proposal, without evidential support, that the prime determinant of norepinephrine overflow to the circulation, norepinephrine spillover,¹⁴ is release of platelet norepinephrine by platelet degranulation in individual organs. Accordingly, regional norepinephrine spillover is claimed not to be indicative of efferent sympathetic nerve firing rates. This is the primary premise, despite 5 decades of research that demonstrates a general relationship, in experimental and clinical studies, between stimulated or spontaneous efferent sympathetic nerve firing rates and norepinephrine overflow into the regional draining veins.¹⁴ The mismatching of norepinephrine release and norepinephrine spillover in the heart and kidneys mentioned in the letter as indicative of a platelet effect (proportionally greater norepinephrine spillover in the kidneys) is well documented to be attributable to the greater capacity for neuronal reuptake of norepinephrine in the heart.¹ The claim that intraorgan platelet release of norepinephrine, rather than sympathetic nervous alterations, underlies the increased norepinephrine spillover in hypertension is unconvincing. Would the correspondents extend their claim for platelets also to the increased norepinephrine spillover from the heart accompanying the sympathetic activation of heart failure, exercise, and laboratory mental stress⁵? The Symplicity HTN-3 trial,⁶ which demonstrated that renal denervation is ineffective for hypertension, is invoked as additional evidence for an absence of neuroadrenergic alterations in hypertension. This really does not constitute evidence, and readers perhaps need to be reminded that the jury is still out on this issue of the efficacy of catheter-based renal denervation in resistant hypertension. In the words of Dr Bakris, Symplicity HTN-3 trial cochief investigator, “…it is highly likely that renal denervation as it was performed in HTN-3 was technically inconsistent at best, but technically inadequate at worst.”⁷

Drs Zhou and Zhou are correct that norepinephrine is taken up by platelets. This is a low-affinity process, with long time constant (ie, flux is slow). This means that the transfer of norepinephrine into, and out of platelets, is sluggish. This principle was important in the occasional use, in previous years, of platelet norepinephrine concentration measurements in the diagnosis of pheochromocytoma.¹⁷ The platelet value, because of the slow rate of exchange, damped out the rapid changes that occur in plasma norepinephrine concentration in this disorder, this smoothing out helped with diagnosis. We think it is not possible for platelets to be a determinant of norepinephrine disposition after release from sympathetic nerves or of norepinephrine plasma clearance. First, the time constant of carrier-mediated platelet norepinephrine flux is too long, that is, exchange is too slow, to materially influence transmitter disposition and spillover to plasma after release. Norepinephrine spillover to plasma is primarily determined by rates of sympathetic nerve firing.¹⁴ And second, the platelet norepinephrine pool size is so small, miniscule in relation to sympathetic neuronal stores, for platelet norepinephrine uptake to contribute materially to plasma clearance of the transmitter. Conversely, sympathetic neuronal norepinephrine uptake is an important component of plasma clearance.¹⁴ So in short, the correspondents’ ideas are novel, but perhaps fanciful, and certainly not well sustained.

Disclosures

None.

Guido Grassi
Clinica Medica
Dipartimento di Scienze della Salute
Università Milano-Bicocca
Milano, Italy

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Guido Grassi, Allyn Mark and Murray Esler

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