Response to Letter Regarding Article, “Effect of Sulfaphenazole on Tissue Plasminogen Activator Release in Normotensive Subjects and Hypertensive Patients”

We thank Drs Brown and Pretorius for their interest in our article about the effect of sulfaphenazole on tissue plasminogen activator (t-PA) release. Drs Brown and Pretorius are correct in observing that the t-PA concentrations in Table 2 are reported as ng · min⁻¹ · 100 mL⁻¹ instead of ng/mL, which is a clear typographical error. In fact, the calculation of t-PA release (balance) was properly reported in the Methods, and t-PA release was calculated accordingly.

We agree that t-PA release by bradykinin in our study is lower than that reported by other investigators with similar doses. A possible explanation is that our study population is significantly older (42±6 years) than that of Brown et al (28.9±2.1 years). Aging significantly reduces nitric oxide (NO) availability. Given that an NO pathway promotes t-PA release, an aging effect is conceivable. Moreover, we infused a single bradykinin dose (equivalent to 225 ng/min) for 10 minutes instead of cumulative doses (100 to 400 ng/mL) for 5 minutes each. The different methodological approach could explain the discrepancy.

Conflicting results relative to the role of NO on stimulated t-PA release exist. Brown and Pretorius observed no effect of NO synthase inhibitor N′-monomethyl-L-arginine (L-NMMA) on bradykinin-stimulated t-PA release. A likely explanation is an insufficient endothelial NO synthase inhibition, as demonstrated by the concomitant lacking effect of L-NMMA on bradykinin-induced vasodilation. Available evidence clearly demonstrates that L-NMMA inhibits bradykinin-induced vasodilation in healthy subjects. DeSouza et al reported an increase of bradykinin-induced t-PA release in the presence of L-NMMA, a finding possibly related to the higher dose used (5 mg/min) compared with the one we infused (1 mg/min). Moreover, the NO-clamp technique was not used. Because t-PA balance is a function of plasma flow, it is conceivable that the greater vasoconstriction induced by the higher dose of L-NMMA could account for the observed increase of t-PA release. Use of the NO clamp, which restores basal blood flow after L-NMMA–induced vasoconstriction, overcomes this methodological limitation.

Finally, sodium nitroprusside is an exogenous NO donor, acting directly on vascular smooth muscle cells. Our finding that this compound failed to stimulate t-PA release reinforces the concept that the relationship between NO and fibrinolysis mainly exists within endothelial cells.

Disclosures
None.

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