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Vasodilation During Systemic Tyramine Administration

To the Editor:

Jacob et al. recently reported that systemic administration of tyramine, which is widely used as a pharmacological tool to assess sympathetic nervous system function, resulted in unexpected and seemingly paradoxical forearm vasodilation. Tyramine infusion is well known to increase entry of the sympathetic neurotransmitter, norepinephrine, into the extracellular fluid. By this indirect sympathomimetic effect, one would expect increased peripheral resistance to blood flow in tissues possessing sympathetic noradrenergic innervation. Instead, systemic tyramine infusion produced a clear decrease in forearm vascular resistance despite concurrently increased forearm norepinephrine spillover.

In the same study, plasma levels of dopamine increased remarkably, by ~50-fold, during tyramine infusion. The authors speculated that circulating dopamine, released or produced from tyramine, might mediate the paradoxical vasodilation. Dopamine might be released with norepinephrine from sympathetic nerves, or tyramine might be converted enzymatically to dopamine in the liver. The authors concluded with the hypothesis that tyramine-induced release of other bioactive amines (eg, dopamine) plays a role in this paradoxical effect.

We also noted a large increase in plasma dopamine levels during systemic tyramine infusion and were also perplexed. By assaying the catechol contents of the infusate, we tested whether the infusate might have become contaminated with dopamine. At a tyramine concentration of 1 mg/cm³ (7.30 μmol/cm³), the concentration of dopamine averaged ~7.2 μg/cm³ (~0.048 μmol/cm³), indicating 0.7% contamination. This relatively small percent contamination, enabling the infusate to meet quality-control criteria, nevertheless would be more than sufficient to increase circulating dopamine concentrations to values similar to those reported by Jacob et al.

When we diluted tyramine powder in water and assayed the catechol contents immediately, dopamine was already detectable, albeit at a concentration much less than a thousandth that in the infusate we had used until that point. Since then, we have infused aliquots of tyramine solution kept in the dark at ~70°C. We have not yet noticed a clear effect on plasma dopamine concentrations.

Nonenzymatic oxidation of tyramine to dopamine appears to resolve the paradox of tyramine-induced vasodilation despite norepinephrine release. Future studies involving hemodynamic effects of systemic tyramine infusion should consider the possibility of contamination of the infusate by dopamine, due to a process analogous to that causing nonenzymatic oxidation of tyrosine to L-dihydroxyphenylalanine.

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Response

In their original publication, Goldstein and Holmes concluded that intravenous tyramine induces the release of dopamine in humans. They now seem to believe they were mistaken, because their tyramine solution was contaminated with dopamine. We recently reported in this journal that dopamine increased plasma dopamine. Like Goldstein and Holmes before us, we suggested that this increase could be due to endogenous dopamine produced from, or released by, tyramine. We ruled out tyramine interference with the assay of dopamine in alumina-extracted samples but had not considered the possibility of contamination. We have since confirmed the presence of ~1% dopamine even in our sodium metabisulfite-stabilized tyramine preparation. This contamination, of course, does not negate the possibility that endogenous dopamine is being released by tyramine also, for which there is substantial evidence from in vitro and animal studies.

In their letter, Goldstein and Holmes seem to imply that dopamine contamination explains the paradoxical vasodilation induced by systemic tyramine administration. This is an intriguing possibility, but it would be regrettable if it finds its way into the literature as a proven hypothesis before it is adequately tested. Assuming a 1% contamination with dopamine, we would have infused a 0.21 μg/kg · min dopamine dose in our subjects. Goldstein and Holmes provide no evidence that these doses will counteract tyramine-induced vasoconstriction. Furthermore, contamination with dopamine would not explain the observation that intra-arterial tyramine induces vasoconstriction, but intravenous tyramine does not.

In our publication, we were careful not to conclude that dopamine mediates the paradoxical vasodilation induced by systemically administered tyramine. We urge Goldstein and Holmes, and particularly the readers of this journal, to apply the same caution to these new findings. If Goldstein and Holmes are correct, then systemic infusion of “dopamine-free” tyramine should induce vasoconstriction. We eagerly await studies elucidating the mechanisms of the paradoxical vasodilation induced by systemic tyramine.

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