Neurovascular Dissociation With Paradoxical Forearm Vasodilation During Systemic Tyramine Administration

Giris Jacob, MD, DSc; Fernando Costa, MD; Simi Vincent, MD, PhD; David Robertson, MD; Italo Biaggioni, MD

Background—Despite the widespread use of tyramine as a pharmacological tool to assess the effects of norepinephrine release from sympathetic nerve terminals, its vascular effects are not adequately characterized. In particular, previous results indicate that intravenous tyramine produces little if any systemic vasoconstriction, suggesting that tyramine does not cause significant norepinephrine release from sympathetic nerves innervating peripheral vascular beds. To test this hypothesis, we determined the effects of intravenous tyramine on local forearm norepinephrine spillover and vascular resistance.

Methods and Results—Seven healthy subjects were studied with systemic and local forearm norepinephrine spillover and forearm blood flow at baseline, during systemic tyramine infusion, and after sympathetic stimulation induced by the cold pressor test. Tyramine infusion caused a significant increase in systemic and forearm norepinephrine spillover. The amount of norepinephrine released into the forearm by tyramine was similar to that caused by cold pressor stimulation, 0.15±0.05 versus 0.18±0.05 ng/dL·min. As expected, forearm vascular resistance increased during the cold pressor test, but tyramine produced forearm vasodilation (4.5±1 versus −5±1 mm Hg·dL⁻¹·min⁻¹, P<0.03) despite the increase in local norepinephrine spillover. In 6 additional subjects, plasma dopamine increased significantly during tyramine administration, from 11±3 to 662±105 pg/mL.

Conclusions—Thus, systemic tyramine infusion evokes a significant increase in peripheral norepinephrine spillover, and this, paradoxically, is associated with local vasodilatation rather than vasoconstriction. (Circulation. 2003;107:2475-2479.)

Key Words: nervous system, sympathetic □ norepinephrine □ blood flow □ catecholamines

Tyramine is a naturally occurring amine that acts as an indirect sympathomimetic. It is present in considerable amounts in certain foods. Their ingestion would normally have no significant cardiovascular effects, but hypertensive crisis can occur in patients taking monoamine oxidase inhibitors. This phenomenon inspired many researchers to investigate the effects of tyramine on the cardiovascular system.1 The hemodynamic effects of tyramine are thought to be related to the release of endogenous norepinephrine from postganglionic sympathetic neurons.2

Thus, tyramine is often used as a pharmacological tool to evoke “endogenous norepinephrine release” in the belief that its cardiovascular effects mimic those produced by natural sympathetic activation. Tyramine has been widely used to understand the physiology and the pathophysiology of the autonomic nervous system regulating the cardiovascular system.3–8 This approach seems to be valid when tyramine is infused directly into a vascular bed, eg, the forearm or the coronary circulation; intra-arterial infusion of tyramine at doses devoid of systemic effects causes a significant increase in local norepinephrine release and a corresponding vasoconstriction.9,10

Surprisingly, the vascular effects of systemically administered tyramine are less well characterized. As expected, systemic infusion of tyramine elicits increments of plasma norepinephrine and norepinephrine spillover in a dose-dependent fashion.11 It also causes a significant increase in systolic blood pressure.12 It is believed that the increase in systolic blood pressure activates baroreflex mechanisms that restrain the increase in heart rate, so that heart rate increases only moderately after intravenous tyramine. Evidence of baroreflex buffering was provided by studies showing that pretreatment with atropine unmasks a significant tyramine-induced tachycardia.13 Of relevance to this study, diastolic blood pressure increases only minimally after intravenous tyramine, and in some studies, a small decrease is observed. Furthermore, the pressor effects of tyramine are not prevented by α-adrenergic receptor antagonists but rather are decreased

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with pretreatment with bisoprolol, a highly selective β1-adrenergic receptor antagonist.14,15 This calls into question the ability of systemic tyramine either to induce vasoconstriction or to evoke significant release of norepinephrine from sympathetic nerves regulating peripheral blood vessels.

To test these hypotheses, we examined the noradrenergic and vascular effects of systemically administered tyramine by measuring whole-body and forearm norepinephrine spillover and forearm blood flow. We used the cold pressor test, a procedure that induces sympathetic activation and forearm vasoconstriction, as a positive control.16 Our results indicate that the cardiovascular effects of tyramine are quite different from those of naturally occurring sympathetic activation. Paradoxically, tyramine induces a reduction of forearm vascular resistance when given systemically.

Methods

Subjects

The study group consisted of 7 healthy subjects between the ages of 21 and 43 years (31±2). The local institutional review board approved all investigational procedures, and subjects gave informed consent before the study. Subjects were studied while they were supine after a 30 to 40 minutes to allow for steady state to be reached, blood was sampled before and at peak blood pressure effect. Antecubital vein blood was sampled before and at peak blood pressure effect.

Statistical Analysis

Results are expressed as mean±SEM. Paired 2-tailed t-test was used for interindividual comparisons before and after each stimulus. One-way ANOVA for repeated measurements was used to compare the effects of the different procedures. Linear regression analysis was used to assess the baroreflex slope. Data were analyzed with Quattro Pro software (Corel Corporation Limited, 1996, version 7) and GraphPad Prism (GraphPad Software Inc, version 3.0, March 1999). A probability value of P<0.05 was considered to be statistically significant.

Results

The subjects’ mean body mass index was 23.6±0.7 kg/m², and their weight and height were 64±2.5 kg and 1.68±0.025 m, respectively. The mean dose of tyramine necessary to increase their systolic blood pressure by 25 mm Hg was 1.35±0.1 mg/min. The hemodynamic and neurohumoral characteristics at baseline, during the cold pressor test and during tyramine infusion are depicted in the Table. As expected, the cold pressor test increased systemic and diastolic blood pressure and heart rate (Table). During tyramine infusion the heart rate decreased nonsignificantly, by 6±2 bpm. The mean baroreflex slope was 18±2.5 ms/mm Hg. An increase in systolic blood pressure of ~25 mm Hg, therefore, should cause a decrease in heart rate to 49±3 bpm (calculated from individual baroreflex slopes). It could be argued, therefore, that tyramine elicited a positive chronotropic effect of ~9% that was masked by baroreflex activation. Diastolic blood pressure remained unchanged despite a significant increase in systolic blood pressure.

As expected, the cold pressor test increased arterial and venous norepinephrine and systemic norepinephrine spillover (Table and Figure 1).20 It also increased forearm norepinephrine spillover and forearm vascular resistance (Table and Figure 2). Tyramine infusion caused a significant rise in plasma norepinephrine in both vein and artery, as illustrated in Figure 1. The increment tended to be higher in the brachial artery than the antecubital vein (37±4% versus 21±5%.

Whole-body plasma clearance (systemic clearance) of norepinephrine was determined by the following equation: systemic clearance = [1H]NE infusion rate (dpm/min)/plasma [1H]NE (dpm/L), and the rate at which norepinephrine appeared in plasma (systemic spillover) was determined as follows: systemic spillover (ng/min) = systemic clearance (L/min)×arterial plasma norepinephrine concentration (ng/L). Forearm norepinephrine spillover and clearance were calculated from the following equations: forearm norepinephrine spillover = [(V−A)+EF×A]×Q(1−Hct), and forearm norepinephrine clearance = EF×Q(1−Hct), where EF=([A−V]/A)×A, A is the arterial plasma concentration, V is the local venous plasma norepinephrine concentration, A and V are the arterial and venous concentrations of tritiated norepinephrine, respectively. Q is the local forearm blood flow, EF is the fractional extraction of tritiated norepinephrine. Hct is the systemic hematocrit, and Q(1−Hct) represents the local plasma flow. Plasma catecholamines were determined as previously described.19
respectively, \(P=0.08\)). Systemic norepinephrine spillover increased by 36±4\% during tyramine infusion, and clearance remained unchanged (Figure 1). Forearm norepinephrine spillover increased by 26\% (from 0.41±0.04 to 0.59±0.06 \(\text{ng} \cdot \text{min}^{-1} \cdot \text{dL}^{-1}\)), and clearance increased by 18\% (Table and Figure 2). The forearm fractional extraction of tritiated norepinephrine decreased significantly, by 20\% (\(P<0.04\)), during tyramine infusion (compared with a 9\% decrease during the cold pressor test, \(P=0.34\)). In contrast to the effects of the cold pressor test, forearm blood flow increased by 42\% during tyramine infusion, and forearm resistance decreased by 28\%, as illustrated in Figure 2.

Plasma dopamine increased from 11±3 to 662±105 pg/mL (\(P<0.01\)) after tyramine given intravenously at doses (4.7±1.3 mg) that increased systolic blood pressure by 30±5 mm Hg. In ancillary studies, we determined that tyramine did not interfere with the determinations of dopamine levels in our high-performance liquid chromatography assay, at concentrations up to 400 ng/mL (data not shown).

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<th>Hemodynamic and Neurohumoral Responses to Tyramine Infusion and the Cold Pressor Test</th>
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<td><strong>Baseline</strong></td>
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<td>Diastolic BP, mm Hg</td>
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<td>Heart rate, bpm</td>
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CPT indicates cold pressor test; BP, blood pressure; NE, norepinephrine; and NSO, norepinephrine spillover.

\*\(P<0.05\), significant difference from baseline.

†Significant difference between tyramine and the cold pressor test.

Figure 1. Systemic effects of intravenous tyramine vs cold pressor test. Top, Increase in arterial and venous (antecubital) norepinephrine (NE) induced by an intravenous infusion of tyramine (TYR) or by cold pressor test (CPT). Bottom, Increase in norepinephrine spillover (NSO) and clearance.

Figure 2. Local neurohumoral effects of tyramine vs cold pressor test. Change in norepinephrine spillover (top), forearm blood flow (middle), and vascular resistance (bottom) induced by an intravenous infusion of tyramine (TYR) or by the cold pressor test (CPT).
Discussion

Our results indicate that, despite an increase in forearm norepinephrine spillover, systemically infused tyramine produced a paradoxical decrease in forearm vascular resistance. Even though this is a novel and challenging finding, a careful review of previously published data suggests that tyramine, when given systemically, has little if any vasoconstrictive properties. Previous studies consistently found an increase in systolic blood pressure to be the main hemodynamic effect of intravenous tyramine. In contrast, diastolic blood pressure increases slightly or even decreases. The increase in systolic blood pressure was abolished by pretreatment with bisoprolol, a highly selective β₁-adrenergic receptor antagonist, whereas α-adrenergic receptor antagonists were not able to influence the effect of tyramine on systolic or diastolic blood pressures. This pharmacological profile contrasts with that of exogenous norepinephrine infusion, which causes a substantial increase in systolic and diastolic blood pressure that is prevented by α-adrenergic receptor antagonists. Also, intravenous tyramine has been shown to increase indices of myocardial contractility. Available data, therefore, suggest that the pressor effects of tyramine are mediated primarily by its cardiac effects rather than by peripheral vasoconstriction.

The predominance of the cardiac effects of tyramine is consistent with the greater density of noradrenergic nerves innervating the heart compared with the peripheral circulation. This is also consistent with the substantial increase in coronary vein norepinephrine evoked by intravenous tyramine in humans and the relatively high contribution of the heart to whole-body norepinephrine spillover. It is surprising, therefore, that heart rate does not increase more during tyramine infusion. It has been proposed that the increase in heart rate produced by tyramine is masked by activation of cardiovagal baroreflexes secondary to the increase in systolic blood pressure. In support of this postulate, pretreatment with atropine potentiated the increase in heart rate and blood pressure induced by tyramine.

More difficult to explain is the lack of peripheral vasoconstriction during tyramine infusion. It could be proposed that tyramine does not elicit a significant release of norepinephrine from the sympathetic nerves regulating peripheral blood vessel tone. Our results do not support this potential explanation. We found a significant increase in forearm norepinephrine spillover during tyramine infusion. Paradoxically, this increase in local norepinephrine spillover was not associated with a corresponding increase in forearm vascular resistance. On the contrary, tyramine induced forearm vasodilation. This, at first glance, would seem to be an unexpected finding. Previous studies, however, observed substantial increases in cardiac release of norepinephrine evoked by intravenous administration of tyramine, but this was not accompanied by a corresponding increase in coronary vascular resistance. Therefore, even though this neurovascular dissociation was not reported previously, it was most likely present in previous studies.

The mechanisms underlying this phenomenon are not known. It is unlikely that they involve local effects of intravenous tyramine in the forearm, because direct application of tyramine into the forearm circulation consistently produces vasoconstriction, as shown by several laboratories. It is possible, therefore, that intravenous tyramine induces the release of biogenic amines that act as circulating vasodilators. Experimental evidence indicates that tyramine evokes the release of dopamine in addition to norepinephrine. Furthermore, tyramine can be converted enzymatically to dopamine in the liver through CYP450. Although it is not clear whether physiological levels of dopamine can be generated in vivo through this mechanism, it is possible that circulating dopamine released or produced by tyramine mediates the paradoxical vasodilation observed in this study.

Although this mechanism remains speculative, we documented that intravenous tyramine evokes a substantial increase in plasma dopamine. Tyramine also evokes the release of epinephrine, and this could arguably contribute to vasodilation through activation of β₂-adrenergic receptors. We observed only marginal increases in plasma epinephrine with intravenous tyramine. Future studies are necessary to determine the potential role of dopamine and epinephrine in tyramine-induced vasodilation.

Our results also show marked differences between the responses elicited by tyramine and the cold pressor test. Tyramine is widely used as a pharmacological tool to induce the release of endogenous norepinephrine from sympathetic nerve terminals and assess the effect this may have on human physiology. It was previously known, but perhaps not widely recognized, that the pressor response to tyramine cannot be used alone as evidence of autonomic dysfunction in autonomic disorders, because incomplete lesions that cause subnormal amounts of norepinephrine release may still elicit substantial pressor responses because of receptor supersensitivity or impairment of baroreflex buffering. Our results also indicate that the cardiovascular actions of intravenous tyramine are quite different from those obtained by naturally occurring sympathetic activation. Previous results using tyramine, therefore, should be interpreted in light of these findings.

There are potential limitations of our study. Sympathetic activation is not a homogeneous process and, depending on the stimuli, may induce preferential vasoconstriction in some vascular beds but not in others. We used the cold pressor test to compare its effects with those of tyramine. Other paradigms that induce “naturally occurring” sympathetic activation could have a different vasoconstrictive pattern. We selected this stimulus because it produces an increase in blood pressure of a magnitude similar to the one we induced with tyramine. It also causes forearm norepinephrine release and vasoconstriction, the phenomenon we wanted to investigate. It should also be noted that changes in flow may affect the accuracy of forearm norepinephrine spillover measurements. We do not believe, however, that it will impact the directional changes we report here.

On the basis of this and previous studies, we conclude that systemically administered tyramine increases systolic blood pressure primarily through its cardiac effects. In contrast to the vasoconstrictive effects tyramine has when applied directly into a vascular bed, intravenous tyramine does not induce forearm vasoconstriction despite eliciting an increase in norepinephrine spillover. We speculate that tyramine-
induced release of other bioactive amines, eg, dopamine, plays a role in this paradoxical effect. This hypothesis needs to be tested experimentally. Clinical studies using tyramine as a diagnostic and pharmacological tool should be interpreted with caution and should consider the complex actions of tyramine reported here.

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References
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