In this issue of Circulation, Fung and coworkers report associations between hand venous responses to the indirectly acting sympathomimetic amine tyramine and single nucleotide polymorphisms (SNPs) of genes encoding particular proteins related to the synthesis, release, reuptake, and metabolism of catecholamines. The importance of these associations lies in their illustrating how genotypic differences may contribute to phenotypic differences in circulatory functions in healthy adults via sympathetic neuroeffector mechanisms. More generally, identification of SNPs related to catecholamine systems may provide insights into the pathophysiology, diagnosis, and treatment of a variety of cardiovascular disorders.

To provide perspective about these findings, this editorial compares and contrasts tyramine-induced changes and sympathetic neuroeffector functions; discusses strengths and weaknesses of the dorsal hand vein model; emphasizes the potential of clinical catecholamine neurochemistry to link genotype with cardiovascular phenotype; and conveys a viewpoint on observational versus hypothesis-driven genotyping.

Comparison and Contrast Between Tyramine-Induced Changes and Sympathetic Neuroeffector Functions

Tyramine produces vasoconstriction via release of endogenous norepinephrine, the main neurotransmitter of the sympathetic nervous system mediating cardiovascular responses to stressors. The authors relied on the local vascular actions of tyramine as an indirectly acting sympathomimetic amine to draw inferences about sympathetic neuroeffector functions.

Mechanisms of tyramine-induced norepinephrine release differ in several respects from those of sympathetically mediated norepinephrine release. The Figure depicts some of these differences.

First, tyramine releases norepinephrine in a calcium-independent manner in contrast to calcium-dependent exocytosis in response to sympathetic nerve stimulation. Tyramine displaces norepinephrine from storage vesicles, possibly by alkalinizing them. Because most of the vesicles would not be expected to be in communication with the extracellular fluid under resting conditions, most of the displaced norepinephrine would be expected to enter the cytoplasm rather than the extracellular fluid. Buildup of cytoplasmic norepinephrine would then lead to exit of norepinephrine into the extracellular fluid, such as via reverse transport through the cell membrane norepinephrine transporter (NET).

Second, because of the buildup of cytoplasmic norepinephrine, tyramine substantially augments oxidative deamination of norepinephrine, a process catalyzed by monoamine oxidase A in the outer mitochondrial membrane, converting norepinephrine to dihydroxyphenylglycol (DHPG), the main neuronal metabolite of norepinephrine. As a glycol, DHPG readily traverses the cell membrane to enter the extracellular fluid and plasma. In humans, plasma DHPG responses to intravenous tyramine therefore exceed plasma norepinephrine responses. In contrast, sympathetic stimulation results in similar absolute increments in plasma DHPG and norepinephrine levels, the increment in plasma DHPG in this setting reflecting reuptake of released norepinephrine into the cytoplasm via the NET.

Third, the NET operates as a high-affinity, low-capacity system. It is saturated at relatively low substrate concentrations. Thus, high plasma norepinephrine levels due to a pheochromocytoma interfere with cardiac uptake of the sympathoneural imaging agent 6-\[^{18}F\]fluorodopamine. Tyramine might compete with endogenously released norepinephrine for reuptake into the cytoplasm via the NET, so that for a given amount of norepinephrine released from sympathetic nerves, a greater proportion would be delivered to adrenoceptors than during sympathetic stimulation.

Fourth, tyramine in sympathetic vesicles is converted to octopamine via hydroxylation catalyzed by dopamine-β-hydroxylase. The octopamine so produced may act as a false neurotransmitter.

Fifth, obtained statistical associations between SNPs and tyramine-induced vascular responses could reflect individual differences in vesicular storage or cytoplasmic metabolism of tyramine itself. This could apply to chromogranin B (CHGB), cytochrome b-561 (CYB561), and flavin-containing monooxygenase 3 (FMO3). The question therefore remains open about whether these SNPs are associated with the fate of endogenous catecholamines.

Given the differences between mechanisms of vascular responses to infused tyramine and to sympathetic stimulation, the observed statistical associations between tyramine-
induced vascular responses and frequencies of particular
SNPs might not apply to sympathetic neuroeffector
mechanisms in as straightforward a manner as the authors wished.
In particular, the cell membrane and vesicular monoamine
transporters are major determinants of sympathetic neuroef-
fector function. Hypofunctional polymorphisms of either
transporter would be expected to be associated with de-
creased ability of tyramine to displace norepinephrine and
therefore with decreased vasoconstrictor responses to tyra-
mine. Because of the dependence of the study on the
physiological consequences of displaced norepinephrine, the
study was not designed in a manner that could distinguish
altered uptake of tyramine from altered reuptake of norepi-
nephrine. Decreased neuronal uptake might actually help to
explain the seemingly paradoxical finding of less hand vein
constriction in people with a positive family history of
hypertension: Perhaps the individuals with a family history of
hypertension had decreased cell membrane uptake of tyra-
mine. There is support in the literature for the view that
individuals with a family history of hypertension may have
decreased NET activity.12,13

If the overall purpose of the study were to understand better
the potential roles of genetic polymorphisms for catechol-
amine-related genes in hypertension, it might have made
more sense to use a test drug that increases sympathetic nerve
traffic and augments exocytosis. α2-Adrenoceptor antagonists
such as yohimbine increase norepinephrine release by these
means,14 and among healthy humans, hypofunctional poly-
morphism of the α2c-adrenoceptor is associated with aug-
mented catecholamine and pressor responses to yohimbine.15
Because genetic polymorphisms for adrenoceptors or intra-
cellular enzymes determining vascular effects of adrenoceptor
occupation may influence responses to endogenously released
norepinephrine, to take postganglionic or extrasynaptic processes
into account, it would seem important to assess local vasocon-
strictor responses to directly administered norepinephrine.

Strengths and Weaknesses of the Dorsal Hand
Vein Model to Assess Sympathetic
Neuroeffector Functions

The investigators1 wished to assess effects of tyramine in a
manner that would not be complicated or obscured by
reflexive responses to the drug given systemically. Years ago,
Miller and Streeter,16 recognizing this advantage, measured
dorsal hand vein responses to directly administered norepi-
nephrine. Numerous other studies have used essentially the
same approach, including at least 1 study involving vasocon-
strictor responses to tyramine.17

The dorsal hand vein model, however, entails potential
limitations. It is generally accepted that sympathetic norad-
renergic innervation of arterioles is more intense than that in
the walls of large veins, and changes in arteriolar vascular
resistance play a more important role in regulation of total
peripheral resistance and therefore of blood pressure than do
changes in diameter of cutaneous veins. It may therefore be
difficult to extrapolate from findings in the dorsal hand vein
to disorders involving increased total peripheral resistance,
which characterizes the majority of cases of essential hyper-
tension. This is one reason why studies of sympathetic
neuroeffector function in humans have used the alternative
model of brachial intra-arterial infusion of norepinephrine
and other test drugs, including tyramine.18–21 The brachial
arterial infusion model also enables assessment of effects of
locally administered tyramine on levels of norepinephrine in
the venous drainage of the arm.

Clinical Catecholamine Neurochemistry to
Link Genotype With Phenotype

Fung et al1 relied on an indirect physiological measure (local
vascular resistance) to indicate sympathoneural effects of
infused tyramine. Local hemodynamic changes, however,
may be related only indirectly and complexly to release of
norepinephrine from sympathetic nerves. Applications of
clinical catecholamine neurochemistry22 could have provided
valuable insights about links between the SNPs of interest
and the vascular phenotype.

Increments in plasma norepinephrine levels constitute a
key dependent measure in the assessment of sympathetic
neuroeffector function23 and have been used in studies of
blood pressure responses to intravenous tyramine and fore-
arm vascular responses to brachial arterial infusion of tyra-
mine.21,24 Given access to a sensitive, specific radioenzymatic
assay for catecholamines, the authors could have measured
increments in plasma norepinephrine in ipsilateral versus contralateral antecubital venous plasma.

Because of the different sources and meanings of plasma levels of norepinephrine and DHPG, simultaneous measurements of these compounds provide a refined means to link genotype with phenotype. It is hoped that future studies will move beyond indirect physiological to more direct neurochemical correlates. For example, an observed association of a SNP for a monooxygenase with vascular responsiveness to tyramine could be followed up by measurement of DHPG-to-norepinephrine ratios in selected individuals.

The vascular responses to tyramine were highly variable across subjects. In a minority of subjects, tyramine actually produced local vasodilation, a phenomenon that local release of norepinephrine, a universal vasoconstrictor, could not easily explain. More detailed attention to intervening mechanisms might have helped to identify bases for this variability. For instance, conversion of tyramine in sympathetic vesicles to octopamine, a false neurotransmitter, might have limited vasoconstrictor responses to locally administered tyramine. Neurochemical data would also have helped in dealing with the thorny problem of contamination of dissolved tyramine by dopamine, infusion of which produces vasodilation. Vascular responses might also be influenced by local generation of the vasodilator nitric oxide.

Local resistance responses to tyramine would be expected to be affected importantly by adrenoceptors both on the target smooth muscle cells and on sympathetic nerves. It is unfortunate that the present study did not include SNPs for adrenoceptors. For instance, SNPs of β2-adrenoceptors, associated with high plasma norepinephrine levels, have been reported to predict future renal damage and to be associated with indices of obesity or metabolic syndrome. Vasoconstrictor responses to intra-arterial tyramine have been found to be related inversely to directly recorded sympathetic nerve activity, suggesting a balance between norepinephrine delivery to and accessibility of vascular α-adrenoceptors in healthy humans.

**Observational Versus Hypothesis-Driven Genotyping**

Over the past decade or so, numerous reports have noted statistical associations between various cardiovascular abnormalities and SNPs. Peer-reviewed journals have recently become more demanding, asking not only for statistical associations but also for studies of functional consequences of SNPs. Thus, there is a movement from mainly descriptive to more physiologically meaningful information. A power of the approach used by Fung et al is that it is deductive (ie, hypothesis driven), in that the SNPs chosen for evaluation reflect processes known to contribute to sympathetic neuroeffector functions.

A weakness of such a deductive approach is that the SNPs chosen are based on hypotheses derived from a limited fund of knowledge. One cannot prove a negative, and therefore when statistical associations fail to be established, the possibility of a real relationship remains. The study might have been powered inadequately, the population might not have been stratified correctly, the dependent measures might have been too complexly or indirectly determined, the wrong SNPs might have been chosen, and so forth. The justification for the choice of SNPs evaluated in the study of Fung et al was high prevalence in the population; however, the most prevalent SNPs might contribute relatively weakly to sympathetic neuroeffector functions, whereas less common SNPs might contribute more to disease processes.

There are many proteins, perhaps hundreds, that participate in catecholamine synthesis, storage, release, reuptake, and metabolism, and there are perhaps thousands of SNPs that could influence sympathetic neuroeffector function. The San Diego group has reported in Circulation that there are 49 SNPs of the tyrosine hydroxylase gene alone; that a SNP for the catecholamine release–inhibiting protein catestatin is related to both altered autonomic activity and risk of hypertension; and that a common SNP of C-reactive protein may be related to blood pressure and metabolic syndrome via polymorphisms at 3 loci in catecholamine biosynthetic and adrenoceptor pathways. “SNP chip” arrays have been developed involving >1000 polymorphisms for >100 genes related to catecholamine system functions. The same investigative group has published results based on ≈9800 genotypes (43 genetic variants at 17 loci) within catecholaminergic pathways. In the study of Fung et al, with only 17 polymorphisms under consideration, if the SNP search were a fishing trip, the net seemed small.

A key challenge for medical science lies in understanding how genetic changes already present at birth interact with individual life experiences and time to lead to chronic, multisystem disorders decades later, at the other side of life. Given the minute-to-minute role of the sympathetic nervous system in blood pressure responses to acute stress, it is reasonable to explore whether genetically determined alterations in catecholamine system functions contribute to chronic cardiovascular disorders such as hypertension. It is hoped that the study of Fung et al will spur further research on genotype-phenotype linkages based on catecholamine systems.

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None.

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