Hypertension as a Maladaptive “Fight-or-Flight” Response?: Confirmatory Molecular Genetic Evidence From the Human Catecholamine Biosynthetic Pathway

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THE CURRENT DANISH MONICA REPORT ON HYPERTENSION AND GENETIC VARIATION AT TYROSINE HYDROXYLASE

Nearly 100 years ago, the great American physiologist Walter Bradford Cannon (1871–1945) coined the term “fight-or-flight”¹ to refer to activation of the sympathetic branch of the autonomic nervous system in response to environmental threat. In the current issue of the American Journal of Hypertension, Nielsen and colleagues² from Copenhagen, Denmark, utilize the longitudinal MONICA (MONItoring of trends and determinants in Cardiovascular disease, of the World Health Organization) cardiovascular cohort to provide convincing confirmatory evidence that links population basal BP to genetic variation in the rate-limiting point in catecholamine biosynthesis: tyrosine hydroxylase (TH). The Danish study demonstrated effects of the TH promoter variant C-824T (rs10770141) on both office and 24-h ambulatory blood pressure (BP), as well as the prevalence of hypertension. Coordinate effects of C-824T on heart rate as well as BP were consistent with an effect on sympathetic tone.

THE SYMPATHETIC SYSTEM AND TH

The sympathoadrenal system exerts minute-to-minute control over cardiac output and vascular tone. The enzyme TH (tyrosine 3-monoxygenase; TH; EC-1.14.16.2, chromosome 11p15.5) catalyzes the rate-limiting step in catecholamine biosynthesis: conversion of the amino acid L-tyrosine to L-DOPA, and may thus function as a “master switch” for sympathochromaffin function. TH is abundantly expressed in specific neurons of the locus coeruleus, ventral tegmental area, and substantia nigra, as well as the adrenal medulla and sympathetic ganglia.³ Earlier studies suggested that genetic variation at TH might associate with human hypertension.⁴ In 2007, systematic polymorphism discovery across the TH locus, coupled with autonomic phenotyping in twin pairs, revealed that common variation in autonomic function (i.e., catecholamine secretion and stress BP increments) mapped onto the proximal promoter block of linkage disequilibrium, rather than onto the 13 coding exons.⁵ Among four common variants in the proximal promoter, two (C-824T, rs10770141; A-581G, rs10770140) were strongly associated with autonomic function, while one (C-824T) displayed a replicable effect on basal BP and hypertension in the population.

When subjected to functional tests,⁶ C-824T and A-581G altered TH promoter strength in transfected luciferase reporter plasmids, under both basal and secretory-stimulation states. Computationaly, C-824T disrupted predicted promoter binding by the trans-acting factors MEF2, SRY, and FOXD1, and such predictions were borne out by effects on co-transfection as well as CHromatin ImmuPrecipitation (ChiP).

GENETIC APPROACHES TO BP AND THE COMPLEX TRAIT OF HYPERTENSION

This is a straightforward but quite interesting study, which is the first to replicate the finding that TH common promoter variant C-824T has an effect on BP and hypertension,⁵ here shown in a well-documented, independent, and population-based cohort. The BP was measured by both office and ambulatory methods, which serves to inspire even more confidence in the findings. These results emerge from a classical, hypothesis-testing experimental approach, proceeding from candidate gene to complex trait, by taking advantage of previous knowledge of vascular and sympathetic physiology and pathology. The lack of measurements of intermediate phenotypes is a limitation and can be investigated in the future.⁷

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