Endothelial Nitric Oxide Synthase Polymorphism rs3918226 Associated With Hypertension Does Not Affect Plasma Nitrite Levels in Healthy Subjects

To the Editor:

Salvi et al reported that the single nucleotide polymorphism (SNP) rs3918226 in the promoter of the endothelial NO synthase (eNOS) gene was associated with hypertension. Although no functional studies show how this SNP affects eNOS, the authors identified a potential binding site for ETS transcription factors directly next to rs3918226, thus suggesting a potential modulation of eNOS expression.1

NO is mainly produced by eNOS in endothelial cells and is oxidized to nitrite, a useful index of endogenous NO formation that may show how genetic variations affect eNOS activity.2 We showed that eNOS polymorphisms modify endogenous NO production in healthy subjects.2,3 Although we found no effects of individual polymorphisms, eNOS haplotypes may affect NO formation in white1 and black subjects.2

To assess clinical implications for the rs3918226, we examined whether this SNP affects NO formation in 181 healthy subjects self-reported as blacks. We measured whole blood nitrite concentrations,1,2,3 and genotypes for rs3918226 were determined by Taqman Allele Discrimination assay. Genotypes distribution was compared in subjects in the lowest quartile of nitrite concentrations (L group, n=45) with those found in subjects in the highest quartile (H group, n=45) using the Fisher exact tests.

The distribution of rs3918226 genotypes showed no deviation from Hardy-Weinberg equilibrium (P=0.05), and the genotypes frequencies were 92.2% CC (n=167), 7.2% CT (n=13), and 0.6% TT (n=1). We found no significant differences between the L and H groups with respect to allele frequencies (P=0.6822) or genotype frequencies (P=0.3607). Moreover, we found no significant differences when we compared nitrite concentrations in the genotype groups (347±61 nmol/L in the CC genotype group versus 440±332 nmol/L in the CT+TT genotype group; P=0.1779). We found low linkage disequilibrium between rs391822 and rs1799893 (R2=0.16) and rs2070744 (R2=0.12) in black subjects.2 Salvi et al reported similar linkage disequilibrium between rs391822 and rs1799893 (R2=0.16) and rs2070744 (R2=0.17) in whites, suggesting that these 2 last SNPs are independent from rs3918226. Conversely, a haplotype block of high linkage disequilibrium (R2=1) formed by rs2070744 to rs3918226 was significantly associated with ankle brachial index in non-Hispanic white hypertensives.4 Although there are major populational differences in the distribution of eNOS polymorphisms and haplotypes,5 pairwise linkage disequilibrium values among eNOS polymorphisms should be further explored to interpret association signals, including rs3918226. The lack of effect for the rs3918226 polymorphism on nitrite concentrations suggests that this SNP promotes hypertension by many mechanisms to be determined.

Sources of Funding

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo.

Disclosures

None.

Marcelo R. Luizon
Ingrid F. Metzger
Riccardo Lacchini
Jose E. Tanus-Santos

Department of Pharmacology
Faculty of Medicine of Ribeirão Preto
University of São Paulo
São Paulo, Brazil

Endothelial Nitric Oxide Synthase Polymorphism rs3918226 Associated With Hypertension Does Not Affect Plasma Nitrite Levels in Healthy Subjects
Marcelo R. Luizon, Ingrid F. Metzger, Riccardo Lacchini and Jose E. Tanus-Santos

Hypertension. 2012;59:e52; originally published online April 30, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.194654
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/59/6/e52

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/