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

To the Editor:

Salvi et al \(^1\) 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.\(^3\) Although we found no effects of individual polymorphisms, eNOS haplotypes may affect NO formation in white\(^1\) and black\(^2\) subjects.

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,\(^2,3\) and genotypes for rs3918226 were determined by Taqman Allele Discrimination assay. Genotypes distribution was compared in subjects with the lowest fourth 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 ± 261 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 rs1799983 (\(R^2=0.16\)) and rs2070744 (\(R^2=0.12\)) in black subjects.\(^2\) Salvi et al \(^1\) reported similar linkage disequilibrium between rs391822 and rs1799983 (\(R^2=0.16\)) and rs2070744 (\(R^2=0.17\)) in whites, suggesting that these 2 last SNPs are independent from rs391822. Conversely, a haplotype block of high linkage disequilibrium (\(R^2=1\)) 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.

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Disclosures

None.

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

Department of Pharmacology
Faculty of Medicine of Ribeirao Preto
University of Sao Paulo
Sao Paulo, Brazil


Letter to the Editor

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