Endothelial Nitric Oxide Synthase Polymorphisms and Susceptibility to Hypertension: Genotype Versus Haplotype Analysis

To the Editor:
Zintzaras et al reported interesting results of a meta-analysis of all the available studies on the possible association between endothelial NO synthase (eNOS) polymorphisms and hypertension.\(^1\) They concluded that there is evidence for significant association between the 4b/4a variable number of tandem repeats polymorphism in intron 4 of the eNOS gene and susceptibility to hypertension, without significant influence for other eNOS polymorphisms.\(^1\)

Although meta-analysis may shed some light on contradictory results derived from a number of different case-control studies, we believe that haplotype (or diplotype) analysis can provide more relevant biological information. In fact, the analysis of haplotypes (specific combinations of genetic markers within a chromosome cluster location) has been valued as a more powerful approach in association studies than the analysis of single polymorphisms. For example, we have recently reported that eNOS haplotypes involving 3 of the most studied eNOS polymorphisms are associated with the development of hypertension.\(^2,3\) Interestingly, single eNOS polymorphisms were not associated with hypertension in these studies. Therefore, our haplotype findings would have been missed if specific eNOS genotypes alone had been considered.\(^2,3\) Importantly, we found that the same specific eNOS haplotypes are associated with susceptibility to hypertension in subjects with different ethnic backgrounds,\(^4\) even though significant interethnic differences exist in the distribution of eNOS genotypes or haplotypes.\(^4,5\) Our results support the suggestion that significant interactions between individual eNOS polymorphisms play a role in the genetic susceptibility to hypertension, but not individual eNOS polymorphisms. This conclusion would hardly be drawn with a meta-analysis based on single polymorphism studies, as the one conducted by Zintzaras et al. We believe that a meta-analysis based on eNOS haplotypes can lead to more reliable conclusions than that based on eNOS genotypes.

Disclosures
None.

Jose Eduardo Tanus-Santos
Department of Pharmacology
Faculty of Medicine
University of Sao Paulo
Ribeirao Preto, Brazil

Antonio Casella-Filho
Atherosclerosis Unit, Heart Institute (Incor)
Faculty of Medicine
University of Sao Paulo
Sao Paulo, Brazil

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