Vitamins Reverse Endothelial Dysfunction Through Regulation of eNOS and NAD(P)H Oxidase Activities

Sibel Ülker, Pascal P. McKeown, Ulvi Bayraktutan

Abstract—Antioxidant vitamins C and E have protective properties in genetic hypertension associated with enhanced oxidative stress. This study investigated whether vitamins C and/or E modulate vascular function by regulating enzymatic activities of endothelial nitric oxide synthase (eNOS) and NAD(P)H oxidase using thoracic aortas of 20- to 22-week-old male spontaneously hypertensive rats (SHR) and their matched normotensive counterparts, Wistar-Kyoto rats (WKY). SHR aortas had impaired relaxant responses to acetylcholine but not to sodium nitroprusside, despite an ~2-fold increase in eNOS activity and NO release. The levels of superoxide anion (O_2^-), a potent NO scavenger, and NAD(P)H oxidase activity were also 2-fold higher in SHR aortas. Mechanical but not pharmacological inactivation of endothelium (by rubbing and 100 μmol/L L-NAME, respectively) significantly abrogated O_2^- in both strains. Treatments of SHR aortas with NAD(P)H oxidase inhibitors, namely diphenyleneiodinium and apocynin, significantly diminished O_2^- production. The incubation of SHR aortas with different concentrations of vitamin C (10 to 100 μmol/L) and specifically with high concentrations of vitamin E (100 μmol/L) improved endothelial function, reduced superoxide production as well as NAD(P)H oxidase activity, and increased eNOS activity and NO generation in SHR aortas to the levels observed in vitamin C- and E-treated WKY aortas. Our results reveal endothelial NAD(P)H oxidase as the major source of vascular O_2^- in SHR and also show that vitamins C and E are critical in normalizing genetic endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities. (*Hypertension*. 2003;41:534-539.)

Key Words: nitric oxide ■ endothelium ■ enzymes ■ antioxidants ■ hypertension, experimental ■ vitamins