Tetrahydrobiopterin and Endothelial Nitric Oxide Synthase Uncoupling

To the Editor:

Gao et al reported that oral administration of folate, the tetrahydrobiopterin (H4B) precursor, attenuated endothelial NO synthase (eNOS) uncoupling in abdominal aortic aneurysm. The beneficial effects of H4B supplementation in endothelial dysfunction are beyond dispute, but in vivo demonstration of eNOS (un)coupling by H4B is very difficult. The versatile cofactor H4B plays a crucial role in eNOS functionality. Uncoupled eNOS is assumed to produce superoxide (O₂⁻) in addition to or instead of NO (NO). Reaction of NO produced by eNOS with O₂⁻ produced by eNOS and more abundantly by other enzymes, such as NADPH and xanthine oxidases, decreases NO bioavailability.

At the very low H4B concentration of 100 nmol/L, recombinant human eNOS activity is fully developed, and NO bioavailability is not further increased by H4B (Figure). Also, 10-fold H4B concentration increase (1–10µmol/L) did not decrease O₂⁻ levels in isolated eNOS incubation mixtures. Thus, almost equimolar H4B amounts keep eNOS coupled. The aortic O₂⁻ levels measured by Gao et al are unlikely to be exclusively produced by eNOS. The effects seen in that study are likely to be because of direct O₂⁻ scavenging by the oxidation of the highly sensitive folate-derived H4B (Figure) rather than by coupling eNOS. That angiotensin II receptor blockade reduced blood pressure and oxidative stress without changing NO biosynthesis/bioavailability argues against eNOS uncoupling in activated renin-angiotensin system.

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Disclosures

None.

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References


Figure. A, [¹⁵N]nitrite (a measure of NO bioavailability) and (B) [¹⁵N]nitrite + [¹⁵N]nitrate (a measure of NOS activity) in incubation mixtures (NADPH, 800 µmol/L; FAD [flavin adenine dinucleotide], 5 µmol/L; FMN [flavin mononucleotide], 5 µmol/L; calmodulin, 500 nmol/L; CaCl₂, 500 µmol/L) of a recombinant human eNOS (385 nmol/L) formed from L-[¹⁵N₂]-arginine (20 µmol/L) in phosphate buffer (50 mmol/L; pH 7.4). Incubations were performed at 37°C as described. C, H4B-dependent oxidation of glutathione (3 mmol/L) to glutathione disulfide (GSSG) in phosphate buffer.

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