Tetrahydrobiopterin and Endothelial Nitric Oxide Synthase Uncoupling

To the Editor:

Gao et al\(^1\) reported that oral administration of folate, the tetrahydrobiopterin (H\(_4\)B) precursor, attenuated endothelial NO synthase (eNOS) uncoupling in abdominal aortic aneurysm. The beneficial effects of H\(_4\)B supplementation in endothelial dysfunction are beyond dispute, but in vivo demonstration of eNOS (un)coupling by H\(_4\)B is very difficult. The versatile cofactor H\(_4\)B plays a crucial role in eNOS functionality.\(^2\) Uncoupled eNOS is assumed to produce superoxide (\(O_2^-\)) in addition to or instead of NO (\(\mathrm{NO}^-\)). Reaction of \(\mathrm{NO}^-\) produced by eNOS with \(O_2^-\) produced by eNOS and more abundantly by other enzymes, such as NADPH and xanthine oxidases, decreases \(\mathrm{NO}^-\) bioavailability.

At the very low H\(_4\)B concentration of 100 nmol/L, recombinant human eNOS activity is fully developed, and \(\mathrm{NO}^-\) bioavailability is not further increased by H\(_4\)B (Figure). Also, 10-fold H\(_4\)B concentration increase (1–10 \(\mu\)mol/L) did not decrease \(O_2^-\) levels in isolated eNOS incubation mixtures.\(^2\) Thus, almost equimolar H\(_4\)B amounts keep eNOS coupled. The aortic \(O_2^-\) levels measured by Gao et al\(^1\) are unlikely to be exclusively produced by eNOS. The effects seen in that study are likely to be because of direct \(O_2^-\) scavenging by the oxidation of the highly sensitive folate-derived H\(_4\)B\(^2\) (Figure) rather than by coupling eNOS. That angiotensin II receptor blockade reduces blood pressure and oxidative stress without changing \(\mathrm{NO}^-\) biosynthesis/bioavailability\(^3\) argues against eNOS uncoupling in activated renin-angiotensin system.

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Disclosures

None.

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References


Figure. A, \(^{15}\mathrm{N}\)nitrite (a measure of NO bioavailability) and (B) \(^{15}\mathrm{N}\)nitrite \(+^{15}\mathrm{N}\)nitrate (a measure of NOS activity) in incubation mixtures (NADPH, 800 \(\mu\)mol/L; FAD [flavin adenine dinucleotide], 5 \(\mu\)mol/L; FMN [flavin mononucleotide], 5 \(\mu\)mol/L; calmodulin, 500 nmol/L; CaCl\(_2\), 500 nmol/L) of a recombinant human eNOS (385 nmol/L) formed from L-\(^{15}\mathrm{N}_2\)-arginine (20 \(\mu\)mol/L) in phosphate buffer (50 mmol/L; pH 7.4). Incubations were performed at 37°C as described.\(^4\) C, H\(_4\)B-dependent oxidation of glutathione (3 mmol/L) to glutathione disulfide (GSSG) in phosphate buffer.
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