Letter to the Editor

Tetrahydrobiopterin and Endothelial Nitric Oxide Synthase Uncoupling

To the Editor:

Gao et al\textsuperscript{1} reported that oral administration of folate, the tetrahydrobiopterin (H\textsubscript{4}B) precursor, attenuated endothelial NO synthase (eNOS) uncoupling in abdominal aortic aneurysm. The beneficial effects of H\textsubscript{4}B supplementation in endothelial dysfunction are beyond dispute, but in vivo demonstration of eNOS (un)coupling by H\textsubscript{4}B is very difficult. The versatile cofactor H\textsubscript{4}B plays a crucial role in eNOS functionality.\textsuperscript{2} Uncoupled eNOS is assumed to produce superoxide (O\textsubscript{2}\textsuperscript{−}) in addition to or instead of NO (NO). Reaction of NO produced by eNOS with O\textsubscript{2}\textsuperscript{−} produced by other enzymes, such as NADPH and xanthine oxidases, decreases NO bioavailability.\textsuperscript{3}

At the very low H\textsubscript{4}B concentration of 100 nmol/L, recombinant human eNOS activity is fully developed, and NO bioavailability is not further increased by H\textsubscript{4}B (Figure). Also, 10-fold H\textsubscript{4}B concentration increase (1–10 \textmu mol/L) did not decrease O\textsubscript{2}\textsuperscript{−} levels in isolated eNOS incubation mixtures.\textsuperscript{2} Thus, almost equimolar H\textsubscript{4}B amounts keep eNOS coupled. The aortic O\textsubscript{2}\textsuperscript{−} levels measured by Gao et al\textsuperscript{1} are unlikely to be exclusively produced by eNOS. The effects seen in that study are likely to be because of direct O\textsubscript{2}\textsuperscript{−} scavenging by the oxidation of the highly sensitive folate-derived H\textsubscript{4}B\textsuperscript{2} (Figure) rather than by coupling eNOS. That angiotensin II receptor blockade reduced blood pressure and oxidative stress without changing NO biosynthesis/bioavailability\textsuperscript{3} argues against eNOS uncoupling in activated renin-angiotensin system.

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Disclosures

None.

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References


Figure. A, [\textsuperscript{15}N]nitrite (a measure of NO bioavailability) and (B) [\textsuperscript{15}N]nitrite + [\textsuperscript{15}N]nitrate (a measure of NOS activity) in incubation mixtures (NADPH, 800 \textmu mol/L; FAD [flavin adenine dinucleotide], 5 \textmu mol/L; FMN [flavin mononucleotide], 5 \textmu mol/L; calmodulin, 500 nmol/L; CaCl\textsubscript{2}, 500 nmol/L) of a recombinant human eNOS (385 nmol/L) formed from L-[\textsuperscript{15}N\textsubscript{2}]arginine (20 \textmu mol/L) in phosphate buffer (50 mmol/L; pH 7.4). Incubations were performed at 37°C as described.\textsuperscript{4} C, H\textsubscript{4}B-dependent oxidation of glutathione (3 mmol/L) to glutathione disulfide (GSSG) in phosphate buffer.

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