Targeted Increases in Endothelial Cell Superoxide Anion Production Stimulate eNOS-Dependent Nitric Oxide Production, Not Uncoupled eNOS Activity

Hao Xu, Kirkwood A. Pritchard Jr

Every once in a while a paper comes along that makes us question our understanding of cell biology. Current theory holds that oxidative stress increases oxidation of tetrahydrobiopterin (BH4), which in turn uncouples endothelial nitric oxide synthase (eNOS) activity. Numerous publications, using a variety of experimental approaches, provide strong support for the BH4 oxidation hypothesis. Indeed, nearly 10 years ago it was shown, using purified recombinant eNOS, that loss of this critical cofactor promoted eNOS activity. Numerous publications strongly support for the BH4 oxidation hypothesis. Indeed, this observation is consistent with a recent report showing that when hsp90 associates with eNOS the targeted chaperone disrupts hsp90 association to increase uncoupled eNOS activity. Interestingly, what does seem to be involved in maintaining coupled eNOS activity is an increase in hsp90 association. Although the exact mechanisms by which O2− from NOX5 stimulates eNOS-dependent NO production remain to be determined, cell biology studies indicate that differences in eNOS phosphorylation or monomer/dimer formation are likely not involved. What does seem to be involved in maintaining coupled eNOS activity is an increase in hsp90 association. This observation is consistent with a recent report showing that when hsp90 associates with eNOS the targeted chaperone activity increases NO production, which can be confirmed by disrupting hsp90 association to increase uncoupled eNOS activity in either cells or vascular endothelium.

The studies by Zhang et al2 raise important new questions about the role of O2− in vascular function (Figure). If BH4 oxidation is not involved in this model, then what are the signaling mechanism(s) activated by O2− that increase coupled eNOS activity? Does O2− activate specific kinases that direct hsp90 to bind to eNOS or influence hsp90 acetylation to modulate chaperone-dependent signaling with eNOS? Are other chaperones required for eNOS activation and optimal coupled activity? Will other radical nitrogen- or lipid-derived species induce eNOS to generate NO? Is it just a matter of the degree of oxidative stress? And, if so, how much is required to oxidize BH4 before uncoupled eNOS can be detected? Or more importantly, have we simply misinterpreted the findings implicating BH4 oxidation and overlooked other potential mechanisms for governing eNOS activation and function?
Disclosures
None.

References


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