Correspondence

Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

Endothelial Nitric Oxide Synthase and Heart Rate
To the Editor:
We read with interest the recent study by Brunner et al., which provides compelling evidence that high concentrations of nitric oxide (NO) generated from endothelial nitric oxide synthase (eNOS) overexpression reduces cardiac contraction by decreasing myocardial calcium sensitivity. Their data also suggest that NO has very little effect on the autonomic modulation of cardiac excitability. This latter finding, however, must be viewed with caution. Although there is no convincing functional evidence supporting a role for endogenously produced NO in the postsynaptic autonomic regulation of heart rate, NO donors are capable of increasing heart rate by cyclic guanosine monophosphate (cGMP) dependent activation of the hyperpolarization-activated current (Ih) in pacemaking cells. Moreover, NO generated from neuronal nitric oxide synthase (nNOS) in intrinsic cardiac ganglia during stimulation of the vagus nerve enhances the magnitude of the bradycardia by facilitating acetylcholine release. Consistent with this, nNOS knockout mice have an impaired heart rate response to vagal activation, whereas their rate response to acetylcholine itself remains intact. Thus, although eNOS-NO has very little effect on the cholinergic regulation of heart rate to bath applied neurotransmitter, nNOS-NO activated physiologically by vagal stimulation clearly affects heart rate control. When these results are taken together with Brunner et al., they further reinforce the notion of the differential site-specific action that various NOS isoforms play in modulating cardiac function.

Neil Herring, DPhil
David J. Paterson, DPhil
University Laboratory of Physiology
Oxford University
Oxford, United Kingdom


Response
We thank Drs Herring and Paterson for their comments on our recent publication, in which we found no effect of myocyte-derived nitric oxide (NO) on heart rate in conscious mice, or on beating rate in isolated hearts perfused with acetylcholine. The authors correctly point out recent evidence for a bradycardic role of NO derived from neuronal NO synthase (nNOS). We are aware of the significantly higher mean heart rate and lower heart rate variability in conscious nNOS knockout mice, as well as the higher baseline heart rate in isolated right atrial preparations from such animals, but would like to stress that the relevance of these observations for in vivo control of heart rate in genetically unaltered mice or other species is not known. Also, in the latter report, pharmacological inhibition of nNOS was only marginally effective in attenuating heart rate response to vagus nerve stimulation (difference to control, 15 to 20 beats per min, at a basal heart rate of ~320 min⁻¹), and the tachycardia induced by atropine was only marginally less in nNOS knockout atria than normal mouse atria (5.4% versus 8.0%), casting doubt on the significance of prejunctional NO in the release of acetylcholine from parasympathetic nerve terminals in this preparation. Finally, although stimulation of the hyperpolarization-activated inward current (Ih) via NO/cGMP may explain the increased beating rate of isolated spontaneously beating guinea-pig right atria, blockade of this current with Cs⁺ had a similar effect on spontaneous beating rate in wild-type and nNOS knockout mouse atria, suggesting that Ih did not likely contribute to the elevated heart rate in the nNOS knockout atria of this species. Thus, further studies are necessary to substantiate a role for nNOS-derived NO in control of heart rate in the baseline state.

Friedrich Brunner, PhD
Penelope Andrew, PhD
Gerald Wöllkart, PhD
Bernd Mayer, PhD
Institut für Pharmakologie und Toxikologie
Karl-Franzens-Universität Graz
Graz, Austria

Rudolf Zechner, PhD
Institut für Molekularbiologie, Biochemie und Mikrobiologie
Karl-Franzens-Universität Graz
Graz, Austria

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Neil Herring and David J. Paterson

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