The Janus Faces of iNOS

To the Editor:

Recently, two groups have reported on the phenotype of transgenic mice with cardiac-specific overexpression of the inducible nitric oxide synthase (iNOS). Although both used the α-MHC promoter to target iNOS expression, our model used the tetracycline-regulated system (αMTA/iNOS),1 whereas the other used a nonconditional approach.² Intriguingly, the phenotypes reported varied dramatically, from lethal arrhythmias in our case, to no identifiable abnormality in the second. Additionally, a recent publication from the second group³ includes criticisms of our work that are misleading.

The statement that “iNOS activity in [the nonconditional] model is approximately 100- to 120-fold higher than... in the conditional model” (page 1357)¹ is unfounded. A direct comparison between cardiac iNOS activities in the two models is not possible. Heger et al² presented S-ethylisothiourea-sensitive conversion of arginine to citrulline (control: 1.7 ± 3.1 versus transgenic: 697 ± 238 pmol/min mg protein), whereas we measured L-NMMA–sensitive Ca²⁺–independent activity (1 mmol/L EGTA) (0.056 ± 0.05 versus 4.57 ± 1.36 pmol/min mg protein).¹ While both provide measures of iNOS activity, absolute values varied considerably. Although baseline values in the Heger mice were ostensibly 30-fold higher than ours, it is apparent from these¹,² (and other³) reports that basal cardiac iNOS activity in mice is not different from zero. Thus, it is inappropriate to compare directly the reported iNOS activities in these models. Normalizing iNOS activity using control or zero. Thus, it is inappropriate to compare directly the reported iNOS activities in these models. Normalizing iNOS activity using control

In conclusion, while the differences between the two models of enhanced cardiac iNOS remain to be fully explained, it is misleading to dismiss cardiac toxicity as an artifact of the conditional system. Rather, it is more reasonable to suggest that the conditional approach is essential to overcome a lethal phenotype or adaptations that result from high levels of cardiac iNOS overexpression, likely related to uncoupled activity and increased free radical generation. Indeed, the major strength of the tTA-dependent transgenic system is its ability to overcome a well-defined and fundamental weakness of nonconditional transgenic strategies with respect to premature mortality and/or developmental adaptation.

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