

Role of Nitric Oxide Synthase System in the Cardiovascular System: Lessons from Mice Lacking All Nitric Oxide Synthase Isoforms

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Nitric oxide (NO) is produced in almost all tissues and organs, exerting multiple biological actions under both physiological and pathological conditions. NO is synthesized by three different isoforms of NO synthase (NOS), including neuronal, inducible, and endothelial NOSs. Due to the substantial compensatory interactions among the NOS isoforms, the ultimate roles of endogenous NO in our body still remain to be fully elucidated. To address this point, we have successfully developed mice in which all three NOS genes are completely disrupted. NOS expression and activities were totally absent in the triply $n/i/eNOS^{-/-}$ mice before and after treatment with lipopolysaccharide. While the triply $n/i/eNOS^{-/-}$ mice were viable, their survival and fertility rates were markedly reduced as compared with wild-type mice. The phenotypes of those mice that we first noticed were polyuria, polydipsia, and renal unresponsiveness to vasopressin, characteristics consistent with nephrogenic diabetes insipidus. We subsequently observed that in those mice, arteriosclerosis is spontaneously developed with a clustering of cardiovascular risk factors. These results provide the first evidence that the systemic deletion of all three NOSs causes a variety of cardiovascular diseases in mice, demonstrating a critical role of the endogenous NOSs system in maintaining cardiovascular homeostasis.