SPONTANEOUS MYOCARDIAL INFARCTION IN MICE LACKING ALL NITRIC OXIDE SYNTHASE ISOFORMS

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BACKGROUND

The roles of nitric oxide (NO) in the cardiovascular system have been investigated extensively in pharmacological studies with NO synthase (NOS) inhibitors and in studies with NOS isoform-deficient mice. However, because of the nonspecificity of the NOS inhibitors and the compensatory interactions among NOS isoforms (nNOS, iNOS, and eNOS), the ultimate roles of endogenous NO derived from the entire NOS system are still poorly understood. In this study, we examined this point in mice deficient in all 3 NOS isoforms (triply n/i/eNOS(-/-) mice) that we have recently developed.

METHODS AND RESULTS

The triply n/i/eNOS(-/-) mice, but not singly eNOS(-/-) mice, exhibited markedly reduced survival, possibly due to spontaneous myocardial infarction accompanied by severe coronary arteriosclerotic lesions. Furthermore, the triply n/i/eNOS(-/-) mice manifested phenotypes that resembled metabolic syndrome in humans, including visceral obesity, hypertension, hypertriglyceridemia, and impaired glucose tolerance. Importantly, activation of the renin-angiotensin system was noted in the triply n/i/eNOS(-/-) mice, and long-term oral treatment with an angiotensin II type 1 receptor blocker significantly suppressed coronary arteriosclerotic lesion formation and the occurrence of spontaneous myocardial infarction and improved the prognosis of those mice, along with ameliorating the metabolic abnormalities.

CONCLUSIONS

These results provide the first direct evidence that genetic disruption of the whole NOS system causes spontaneous myocardial infarction associated with multiple cardiovascular risk factors of metabolic origin in mice in vivo through the angiotensin II type 1 receptor pathway, demonstrating the critical role of the endogenous NOS system in maintaining cardiovascular and metabolic homeostasis.

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