GENDER DIFFERENCES IN NITRIC OXIDE PRODUCTION BY INDUCIBLE NITRIC OXIDE SYNTHASE IN CYTOKINE-STIMULATED RABBIT CAROTID ARTERIES

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Epidemiological studies have established the role of female gender as a protective factor in the development of various cardiovascular diseases, including hypertension and atherosclerosis. Studies in animals suggest that a greater release of Nitric Oxide (NO) by female (F) than by male (M) endothelium through endothelial Nitric Oxide Synthase (eNOS) pathway may contribute to the phenomenon, but the role of gender in NO produced by inducible isoform of NO synthase (iNOS) in the vasculature is still unknown. Therefore, we analyzed the influence of NO released by cytokine (CYT)-stimulated iNOS expression on the vasoconstriction elicited by Noradrenaline (NA) in isolated carotid arteries of M and F rabbits. Two contiguous arterial rings were incubated for 7 hours in the absence or presence of a CYT mixture (Interleukin-1β, 100 ng/ml; Tumor Necrosis Factor-α, 100 ng/ml; Interferon-γ, 50 ng/ml). Vessel rings were mounted in organ chambers for isometric recording of vascular tension; nitrite production, a stable metabolite of NO, was measured colorimetrically in the incubation medium. Cumulative administration of NA (0.01-10 μM) elicited concentration-dependent contractions in M (n=8) and F (n=8) control arteries, which were significantly higher than those of M (n=8) and F (n=8) CYT-treated vessels ($P<0.005$ for both M and F). Adding to the bath solution the iNOS inhibitor 1400W (10 μM) did not affect NA-induced vasocontrictions of controls, whereas shifted to the left the concentration-response curves of both M and F CYT-treated vessels ($P<0.005$ and $P<0.01$, respectively), confirming the iNOS involvement in the phenomenon. However, the potentiation of NA contractions by 1400W was significantly greater in F than in M vessels ($P<0.05$). Moreover, nitrite production induced by CYT through iNOS expression in F vessels (0.57 ± 0.16 and 0.16 ± 0.05 μM in CYT and control, respectively; n=7 for both) was significantly higher ($P< 0.,05$) than that induced by CYT in M carotid arteries ($0.,273 \pm 0.08$ and 0.13 ± 0.06 μM in CYT and control, respectively; n=8 for both). In conclusion, our results showed that, in rabbit carotid arteries stimulated with cytokines, NO produced after iNOS expression modulates Noradrenaline-induced vasoconstriction in both M and F gender. However, NO production and its modulatory role on adrenergic constriction is greater in F than in M. Thus, this enhanced function of NO produced through iNOs pathway in females may also contribute to a lower incidence of vascular disease.