

## **GENDER-DIFFERENCES IN NO AND EDHF MODULATION OF VASCULAR REACTIVITY IN RABBIT MESENTERIC ARTERY**

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Gender-related differences have been reported in most cardiovascular diseases including coronary heart diseases, stroke, diabetes and hypertension. Although the mechanisms underlying these gender differences are still largely unknown the involvement of gender differences in endothelium physiological function has been suggested. The endothelium controls the vascular tone through synthesis and release of relaxing factors, namely nitric oxide (NO) and endothelium hyperpolarizing factor (EDHF). Since gender differences in the endothelium-dependent regulation of vascular smooth muscle tone have been observed, we hypothesized that a different contribution of NO and EDHF may account for the phenomenon. Therefore, endothelium-dependent relaxations induced by carbachol (CC) or vasoconstrictor sympathetic responses induced by transmural adrenergic nerve stimulation (TNS) were studied in ring segments of rabbit mesenteric arteries (RbMa) of both sex. Moreover, NO production after CC stimulation of endothelium was assessed.

In presence of the NOS inhibitor, L-NNA (0.1mM), the concentration-response curves to CC (0.01-10  $\mu$ M) were significantly rightward shifted in both sex ( $P < 0.001$ ;  $n = 9$  for both) in comparison to their own controls, but relaxations of female were reduced more than those of males and the residual relaxation observed in female ( $23 \pm 6\%$ ) was significantly higher than in males ( $55.7 \pm 5\%$ ;  $P < 0.05$ ). Accordingly, L-NNA shifted to the left frequency-contraction curves induced by TNS in both sex ( $n = 9$  for both), but the vasoconstrictor responses of female vessels were higher than those of males ( $P < 0.05$ ). Experiments in which NO production was assessed through colorimetric method, indicated that both male ( $n = 7$ ) and female ( $n = 6$ ) produced the same amount of NO under basal condition, but addition of  $1 \mu$ M CC to the bath solution caused a significant increase of NO production only in female vessels ( $P < 0.05$ ). The EDHF inhibitors, apamin ( $1 \mu$ M) plus charybdotoxin ( $0.1 \mu$ M), significantly reduced the vasodilator responses to CC ( $n = 5$ ;  $P < 0.01$ ) and potentiated the sympathetic contraction ( $n = 8$ ;  $P < 0.005$ ) in male vessels, whereas they did not affect nor the vasoconstrictions induced by TNS ( $n = 8$ ) nor the CC-induced relaxations ( $n = 5$ ) in female arteries. Our data demonstrate that the relative contribution of NO and EDHF in the agonist stimulated vasodilatation and in the modulation of sympathetic vasoconstriction differs between males and females. Although NO appears to exhibit a primary role to modulate the vascular tone in both sex, it is functionally more important in females where it is produced in higher amount, whereas EDHF is a necessary contributor in males.

In summary it may be hypothesized that this gender difference in endothelium physiology could partially explain the different predisposition to cardiovascular disease observed in male and female, and could give the input to the development of gender-specific therapeutics