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Effect of diet-induced obesity on endothelium-dependent relaxation in rat saphenous artery

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Endothelium-dependent relaxation (EDR) is critical for control of vascular tone and is mediated by nitric oxide (NO), prostaglandin (PGI_2) and non-NO/PGI_2 endothelium-derived hyperpolarization (EDH); the latter characterized by small and intermediate conductance calcium-activated potassium channel (S/IK_{Ca}) and myoendothelial gap junction (MEGJ) activity. The present study determines the characteristics of endothelium-dependent relaxation in adult rat saphenous artery (SA), where EDR has been shown to be entirely NO dependent. The hypothesis examined is that the EDR mechanism is altered in a rat model of diet-induced obesity.

Adult male SD rats were fed chow (control) or high fat (obese) diet for 20wks. Control (536 ± 38g) or diet-induced obese (772 ± 79g; $P<0.05$) SA were isolated and cannulated in a pressure myograph (80 mmHg basal pressure). Vessels were pre-constricted with phenylephrine (PE; 1 μM) and subsequent responses to ACh (0.001-10 μM) assessed endothelium-dependent relaxation. Vessel diameter changes were monitored using computer tracking (Diamtrak). L-NAME and ODQ blocked NOS/sGC activity. EDH-type responses were characterized by inhibiting S/IK_{Ca} using apamin (Apa) and TRAM-34, respectively, or through MEGJ block using connexin (Cx)-mimetic peptides. Confocal immunohistochemistry, electron microscopy and Western blotting examined S/IK_{Ca} and MEGJ distribution and expression.

Treatment	ACh-induced relaxation (to PE constriction) in SA					
	Control			Obese		
	E_{max} (%)	pEC_{50}	n	E_{max} (%)	pEC_{50}	n
Vehicle	97.6 ± 1.0	7.0 ± 0.1	11	98.9 ± 0.9	7.1 ± 0.1	19
Apa/TRAM-34	97.6 ± 1.9	7.3 ± 0.1	6	96.7 ± 1.8	6.0 ± 0.1*	5
Apa/TRAM-34/ L-NAME/ODQ	10.1 ± 1.9#	6.4 ± 0.7#	5	13.4 ± 7.5*	7.9 ± 2.5	4
Apa	-	-	-	98.7 ± 0.5	7.2 ± 0.1	3
TRAM-34	-	-	-	94.2 ± 3.6	6.4 ± 0.1*	5

$P<0.05$: #compared to vehicle treated vessels in control group, *compared to vehicle treated vessels in obese group

In control, apamin and TRAM-34 had no effect on ACh-induced relaxation; with EDR being primarily mediated by NO; L-NAME and ODQ abolishing the response (Table). However, in obese animals, ACh-induced an EDH-type response sensitive to apamin and TRAM-34, compared to vehicle (Table). In addition, gap junction block with Cx-mimetic peptides attenuated ACh-induced relaxation. Moreover, IK_{Ca} and MEGJ expression increased in obese compared to control SA.

The present data suggest that in rat SA, endothelium-dependent vasodilation switches from an entirely NO-mediated event in normal conditions to a significant EDH contribution under condition of vascular stress, such as that associated with obesity. The manipulation of this compensatory mechanism may provide selective therapeutic targets against obesity-related vascular disease.