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Endothelium-dependent vasodilation and the role of endothelium-derived hyperpolarization in a rat model of diet-induced obesity and human mesenteric artery

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Control of vascular tone is dependent on the balance of constrictor and dilator action, with altered tone being a primary factor for vascular disease etiology, such as that resulting from obesity. In rat mesenteric artery (MA), vasodilation to endothelium-derived hyperpolarization (EDH) is dependent on the activity of small and intermediate conductance calcium-activated potassium channels (S/IK_{Ca}) and gap junctions at myoendothelial (ME) microdomain sites. This study characterizes key anatomical and related functional EDH characteristics in a validated rat model of diet-induced obesity, as well as the EDH-type response in human MA. The hypothesis examined is that EDH mechanisms are consistent between rat and human MA, and are altered in disease.

Adult male Sprague Dawley rats were fed chow (control; 536 ± 12 g) or high fat (obese; 667 ± 27 g; $P<0.05$) diet. Control or obese MA (4th order) were isolated. Human MAs were obtained from colorectal patients following surgery. Myogenic responses in a pressure myograph and smooth muscle cell (SMC) membrane potential (E_m) were measured. Vessel morphology determined by electron microscopy.

Hypotrophic inward remodelling occurs in obese rat MA. IK_{Ca} expression was the same in control and obese rat MA, and whilst internal elastic lamina (IEL) hole, ME gap junction (MEGJ) and IK_{Ca} density sites correspond in control; this relationship was altered in obesity. ACh (1μM)-induced EDH-mediated SMC hyperpolarization was impaired in obese compared to control animals. Furthermore, ACh-mediated EDH is sensitive to 50 nM apamin and 1 μM TRAM-34 (S and IK blockers, respectively) in control; and to TRAM-34 alone in obese rat MA, where EDH is reduced (Table 1).

Treatment	ACh-induced hyperpolarization (E_m) and relaxation (RVD)					
	Control			Obese		
	E_m (mV)	RVD (%)	n	E_m (mV)	RVD (%)	n
Vehicle	-75.5 ± 2.2	98.1 ± 0.5	9-12	-68.4 ± 1.2	95.9 ± 1.8	9-12
Apamin	-50.3 ± 1.9	75.1 ± 7.7	5	-53.6 ± 2.4	81.4 ± 5.3	9
TRAM-34	-54.5 ±2.7	79.9 ± 8.3	4	-42.7 ± 0.8	65.9 ± 2.4	4
Apamin + TRAM-34	-41.3 ± 1.2	70.3 ± 5.9	4	-40.9 ± 1.1	61.9 ± 6.3	4

Table 1 Effect of SK and IK blockers on ACh-induced hyperpolarization and relaxation in rat MA

In human MA, MEGJs are numerous and their associated IEL hole and IK_{Ca} densities correspond. In these vessels, apamin and TRAM-34 cause a rightward shift in endothelium-dependent relaxation to bradykinin (pEC_{50}: 8.3 ± 0.2 vehicle, $n=4$ *vs.* 6.7 ± 0.3 apamin/TRAM-34, $n=3$; $P<0.01$) and a 40% reduction in E_{max}; demonstrating a significant K_{Ca}-dependent EDH component.

These data suggest that ME microdomain signalling sites are required for EDH in rat and human MA. Furthermore, EDH appears to be altered in a rat model of diet-induced obesity, in which SMC hyperpolarization and relaxation is dependent on IK_{Ca} activation alone. The manipulation of such signalling sites represents a potential selective therapeutic target to control vascular disease.