β-adrenergic receptors differentially modulate local and spreading vasodilatation evoked by endothelial cell muscarinic receptors in rat pressurized mesenteric arteries

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Endothelium-dependent regulation of vascular tone reflects complex crosstalk between multiple receptor pathways. How β-adrenergic receptors might contribute to crosstalk and thus the regulation of tone is not understood. This study investigated whether luminal perfusion of β-adrenergic agonists modulated endothelium-dependent local and spreading vasodilatation to acetylcholine (ACh).

Small mesenteric arteries were dissected from male Wistar rats (225-250g), cannulated with glass pipettes and pressurized to 70 mmHg at 37ºC. Changes in arterial diameter were measured using video microscopy and edge tracking software. Phenylephrine was used to generate contraction or to standartize it to 80% when α-adrenergic agonists were applied in lumen and only caused a low level (<80%) of contraction. Cumulative responses to ACh (1 nM – 10 μM added to the bath) were assessed before and during luminal perfusion of other agonists.

Applied for ~10 minutes against comparable arterial tone, luminal adrenaline (0.5-1 μM; n=6, $P<0.001$), noradrenaline (1 μM; n=6, $P<0.001$) or isoprenaline (1 μM; n=7, $P<0.001$), but not phenylephrine (0.5 μM; n=5, $P>0.05$) or clonidine (1 μM; n=6, $P>0.05$), significantly inhibited subsequent vasodilatation to ACh. The inhibitory effect was not modified by nitric oxide synthase (NOS) block with L-NAME (100 μM), but reduced by either the β-adrenoceptor antagonist propranolol (1 μM; n=4, $P>0.05$) or the protein kinase C inhibitor BIS-I (1 μM; n=7, $P>0.05$), and mimicked by adenylyl cyclase activation with forskolin (0.5μM; n=5, $P<0.001$). The effectiveness of L-NAME against NO synthesis was demonstrated by abolition of ACh responses in the additional presence of TRAM-34 (1μM) and apamin (50 nM; n=5-10, $P<0.001$) to block the EDHF pathway. In arteries with a side branch cannulated (triple-cannulation), focal, luminal application of ACh evoked a spread of the dilatation over significant distance (up to 2mm). The local dilatation to focal perfusion of ACh was inhibited, as in the dual cannulation experiments described above, by adrenaline (0.5 μM; n=8, $P<0.05$). However, in marked contrast the spreading dilatation against the luminal and abluminal flow and away from the site of ACh application was dramatically enhanced by the presence of adrenaline (n=8, $P<0.001$).

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