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Functional Antagonism of Endothelin-1-Induced Vasospasm in Rat Mesenteric Resistance Arteries

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Tight binding of endothelin-1 (ET1) to arterial smooth muscle ET_A-receptors causes long-lasting arterial contractions that are refractory to inhibition by competitive antagonists (Br J Pharmacol 2012, 166, 1833). To evaluate whether functional antagonism might be more effective, we tested the hypothesis that different mechanisms mediate initiation and maintenance of ET1-induced contractions. In isolated rat mesenteric resistance arteries, we recorded effects of vasodilator compounds (VD) on the sensitivity, maximum and maintenance of responses to ET1. The concentrations of the VD that we used maximally prevented contractile responses to either 40 mM K^+ or 10 μM phenylephrine. The potency and maximal effect of ET1 were not modified by presence of acetylcholine (stimulus of endothelium-dependent NO production and –hyperpolarisation), Bay412272 and Bay602770 (stimuli of soluble guanylyl cyclase), pinacidil (activator of K_{ATP} channels), felodipine (calcium antagonist), isoproterenol (β-adrenoceptor agonist) or OH-fasudil (inhibitor of Rho kinase, ROCK) and were only moderately reduced by forskolin (activator of adenylyl cyclase). However, presence of each of these VD (except OH-fasudil) markedly reduced the maintenance of contractile responses to ET1 and each of these VD (except OH-fasudil) caused marked relaxation of ET1-induced contractions. In contrast, U73122 (inhibitor of phopholipase C-β, PLC-β) both prevented and relaxed arterial contractile responses to ET1. We conclude that in rat mesenteric resistance arteries, initiation and maintenance of contractile responses to ET1 involve PLC-β but not ROCK and that the vasospastic effects of the peptide can be alleviated by cyclic nucleotides and by direct and indirect inhibition of calcium-influx through L-type voltage operated calcium channels.

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