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Agonist- and System-Dependent Arterial Effects of Endothelin ET_A-Receptor Stimulation

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The 21 amino acid bicyclic endothelin peptides (ET) activate the 7 transmembrane domain ET_A- and ET_B-receptors and are proposed to be involved in several diseases. ET1 and ET2 differ in 2 amino acids in their N-terminal loop, bind to ET_A and ET_B with equal affinity and have been proposed to display comparable pharmacological properties. We recently observed significant differences in the apparent affinity of low molecular weight ET_A-antagonists against arterial effects of ET1 and ET2 (Br J Pharmacol 2012, 166, 1833). Here we tested the hypothesis that these agonists stimulate different signal-transduction pathways in arteries from different vascular beds. We recorded vasomotor responses to 0.25 - 16 nM ET in isolated rat mesenteric resistance (MrA) and -basilar arteries (BA) pretreated with capsaicin and studied in the continuous presence of L-NAME and indomethacin in order to concentrate on arterial smooth muscle responses. Pharmacological tools were tested at concentrations that prevent arterial contractile responses to 40 mM K^+ or 10 μM phenylephrine. In MrA and BA, ET1 and ET2 caused contractions, but Sarafotoxin 6c (ET_B-agonist) failed to elicit a vasomotor response. In both tissues the potency and maximal effects of ET1 and ET2 did not differ but their potency was somewhat larger in BA than MrA. 1 nM felodipine (calcium antagonist) did not alter sensitivity to ETs and caused full and partial relaxation of ET1-induced contractions in MrA and BA, respectively. 10 μM OH-fasudil (inhibitor of Rho kinase, ROCK) did not alter sensitivity to ETs, relaxed only ET2-induced responses in MrA but relaxed ET1- and ET2-induced responses in BA. 10 μM U73122 (inhibitor of phopholipase C-β, PLC-β) on the other hand, relaxed ET1- and ET2-induced responses in MrA but only relaxed ET1-induced responses in BA. We conclude that arterial smooth muscle ET_A-receptor activation displays agonist- and system-dependent properties. This should stimulate development of selective negative allosteric modulators for treatment of ET-related diseases.

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