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G Protein βγ Subunits Mediate Upregulated ET_B- but not ET_A-Receptor Stimulated Arterial Contractile Responses

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Endothelins (ET) cause arterial contractions and vasospasm through ET_A-receptors but in stroke, ischemia and in arterial organ culture, arterial smooth muscle stimulation by ET_B-receptors is upregulated. We tested the hypotheses that ET-receptor subtypes act through different G proteins and that upregulation of ET_B-responses potentiates vasoconstrictor responses to the endogenous mixed ET_A-/ET_B-agonist ET1. Isolated rat mesenteric resistance arteries were incubated ex vivo during 18 hours and their vasomotor responses were analyzed. Incubated arteries displayed potent contractile responses to the ET_B selective agonist sarafotoxin 6c (S6c) and to the ET_B-preferring agonist ET3 which were not sustained. Next, ET1 still caused potent contraction and vasospasm. Presence of pertussis toxin (PTX) during the incubation did not alter relaxing responses to isoproterenol but abolished their reversal by neuropeptide Y (NPY) indicating inhibition of Gi proteins. PTX (100 ng/ml during 18 hours or 500 ng/ml during the last 2 hours of incubation) reduced the potency and efficacy of S6c but did not affect subsequent responses to ET1. Presence of gallein during the analysis abolished relaxing responses to calcitonin gene-related peptide and abolished reversal of β-adrenergic relaxations by NPY indicating inhibition of G protein βγ subunits. Gallein abolished upregulated responses to S6c but did not affect subsequent responses to ET1. Incubation with PTX and presence of gallein or BQ788 (ET_B-antagonist) during analysis did not significantly alter contractile responses to ET1. Also, transient exposure of incubated arteries to S6c or ET3 did not significantly alter contractile responses to ET1. We conclude that upregulated arterial ET_B-mediated contractions are brought about by G protein βγ subunits that are partly derived from Gi proteins and that are not involved in ET_A-mediated contractions. Despite ET_B upregulation, ET1-induced responses were not modified by ET_B-antagonism, ET_B-desensitization and inhibition of ET_B-signaling. This suggests that ET_A-stimulation might inhibit ET_B-signaling in arterial smooth muscle.

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