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Improved Relaxations to Acetylcholine in Murine Carotid Arteries with Heterozygous Overexpression of Preproendothelin-1 in the Endothelium

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The endothelium can release both NO and contracting factors (EDCFs). Exogenous endothelin-1 (ET-1) causes ET_B receptor mediated release of NO, but also enhances endothelium-dependent contractions. Besides its propensity to exhibit EDCF-mediated contractions, the murine carotid artery is characterized by high basal and stimulated NO generation. The role of the endothelial endothelin system on endothelium-dependent relaxations in this preparation is unknown. Therefore, a model of endothelium-restricted heterozygous overexpression of ppET-1 was used (TET+/- mice). Relaxations were studied and compared in carotid arteries of 34-36 weeks old TET+/- mice and WT littermates. Experiments were performed, in the presence of meclofenamate to exclude endothelium-dependent contractions, in rings suspended in Halpern-Mulvany myographs. Responses to phenylephrine (1 nM to 30 μM) were similar between genotypes, and the final levels of contraction were not significantly different (57±6% KCl in WT vs. 49±5% KCl in TET+/-). Acetylcholine-induced relaxations were potentiated in TET+/- mice compared to littermate controls (PD_2 8.37±0.05 vs. 8.61±0.06 in TET+/-, n=7-10, P<0.01). By contrast, endothelium-independent relaxations to sodium nitroprusside were not different (n=6-8). In the presence of meclofenamate, TET+/- had no effect on contractions to the calcium ionophore A23187 (n=6-7), but maximal responses to the TP receptor agonist U46619 (0.1 nM to 3 μM) were decreased compared to WT control mice (E_{max} 123.4±3.5% vs. 108.1±2.5% KCl in TET+/-, n=6-9, P<0.01). These results suggest that moderate increases in endothelial ET-1 expression in murine carotid arteries enhance endothelium-dependent, NO-mediated relaxations and reduce smooth muscle responsiveness to TP receptor activation.

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Vascular Pharmacology of Quercetin in Rat

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Quercetin, a kind of flavonoids, exerts the cardiovascular actions. In rat aorta, quercetin (0.1 to 100μM) relaxed the contraction induced by pretreatment with 5μM NE in a concentration-dependent manner. NG-monomethyl-L-arginine acetate (L-NMMA)(100μM), a NO synthesis inhibitor, reduced the quercetin (100μM)-induced vasorelaxation from 97.0 ± 3.7% (n=10, P<0.05) to 78.0 ± 11.6% (n=5, P<0.05). Endothelium removal as well attenuated the vasodilatation. In the presence of both 100μM L-NMMA and 10μM indomethacin, the quercetin-induced vasorelaxation was further attenuated by high K (30mM) or 10μM tetraethylammonium (TEA, KCa channel inhibitor). Nicardipine caused less or no effect on the relaxation. The quercetin-induced vasodilatation was attenuated by 0.3μM apamin (SK channel inhibitor), but not by 30nM charybdotoxin (BK and IK channel blockers). Under KCl-induced vasoconstriction, the quercetin-induced vasorelaxation was attenuated by PK-C inhibitors. Gö6983 (α-, β-, γ-, δ- and ζ-sensitive) produced a stronger relaxing effect than Ro-31-8425 (α-, β-, γ- and ε-sensitive). These results indicate that the vasorelaxation is dependent on the endothelium, and is also exerted by the modulation of SK channel and PK-Cδ. In rat mesenteric artery, the quercetin-induced vasodilatation was in part resistant to both 100μM L-NG-nitro arginine methyl ester (L-NAME) and 100μM indomethacin. The L-NAME- and indomethacin-resistant quercetin-induced vasodilatation was attenuated by TEA (1 mM) and also by 100μM 18α- and 50μM 18β-glychrrhetinic acids (gap junction inhibitors). These results indicate that the vasorelaxation is also dependent on the endothelium and KCa channel, and is further produced by the modulation of the gap junction. Therefore, quercetin vasodilates the vascular smooth muscle mediated by endothelium-dependent and -independent mechanisms.