Ambrisentan and Tadalafil Synergistically Relax Endothelin-Induced Contraction of Rat Pulmonary Arteries

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Endothelin receptor antagonists and phosphodiesterase type 5 inhibitors are used to treat pulmonary arterial hypertension. We tested the hypothesis that a selective endothelin type A receptor antagonist (ambrisentan) and a phosphodiesterase type 5 inhibitor (tadalafil) may act synergistically to relax endothelin-constricted pulmonary arteries. Rat isolated intrapulmonary arterial rings contracted with 8 nmol/L endothelin-1 were relaxed by 10 nmol/L ambrisentan and 30 nmol/L tadalafil alone by 26±3% and 21±1%, respectively, whereas both drugs in combination acted synergistically to relax arterial rings by 83±6%. The nonselective endothelin type A and B receptor antagonists bosentan (100 nmol/L) and macitentan (30 nmol/L) alone relaxed endothelin-contracted rings by 30±5% and 24±3%, respectively. Combinations of 30 nmol/L tadalafil with 100 nmol/L bosentan or 30 nmol/L macitentan relaxed endothelin-contracted rings by 53±5% or 46±7%, respectively; these values are similar to the calculated sums of the individual effects of these compounds. Denudation of endothelium from pulmonary arterial rings abolished the vasodilator response to 30 nmol/L tadalafil and the synergistic vasorelaxant effect of tadalafil with ambrisentan. In the presence of 1 μmol/L BQ-788, a selective endothelin type B receptor antagonist, the vasorelaxant effects of 10 nmol/L ambrisentan and 30 nmol/L tadalafil were additive but not synergistic. These data can be interpreted to suggest that ambrisentan and tadalafil synergistically inhibit endothelin-1-induced constriction of rat intrapulmonary arteries and that endothelin type B receptors in endothelium are necessary to enable a synergistic vasorelaxant effect of the drug combination.