Pharmacological Characteristics of BDTI, a new isoquinoline-derived b2-adrenoceptor agonist, in caine trachea and rat heart.

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Abstract

The tracheal relaxing effects and beta 2-selectivity of BDTI (1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline HBr) were investigated in canine trachea and rat heart by radioligand binding assay and pharmacological experiments in comparison with those of other beta-adrenoceptor agonists, salbutamol and isoprenaline. The potency of relaxing effect on carbachol-induced contraction in isolated canine trachea was in the order of isoprenaline (pD2 = 6.70 +/- 0.08) > BDTI (6.11 +/- 0.06) approximately salbutamol (6.14 +/- 0.08). ICI-118,551 (a selective beta 2-antagonist) and atenolol (a selective beta 1-antagonist) inhibited the relaxant action of BDTI with pKB values of 8.4 and 5.3, respectively, corresponding to high affinity for ICI-118,551 and low affinity for atenolol in antagonizing this response. The Kd values of radioligand ([3H]-CGP12177) were 453.3 +/- 30.8 and 563.4 +/- 96.7 pmol/l in cultured canine tracheal smooth muscle cells (TSMCs) and rat cardiomyocytes, respectively, and the Bmax values were 64.6 +/- 10.7 and 245.7 +/- 44.5 fmol/mg protein, respectively. BDTI, salbutamol and isoprenaline inhibited the binding of [3H]-CGP12177 in a concentration-dependent manner in cultured canine TSMCs (Ki 0.73 +/- 0.15, 0.75 +/- 0.21 and 0.24 +/- 0.05 mumol/l, respectively) and rat cardiomyocytes (Ki 2.76 +/- 0.36, 2.31 +/- 0.26 and 0.22 +/- 0.03 mumol/l, respectively). These results demonstrated that BDTI possessed moderate selectivity (3.8-fold) to beta 2-adrenoceptors as judged from the Ki (heart)/Ki (trachea) value (salbutamol 3.1-fold, isoprenaline 0.92-fold). BDTI and salbutamol also stimulated cAMP formation in a concentration-dependent manner in cultured canine TSMCs (EC50 0.5 +/- 0.2 and 0.4 +/- 0.1 mumol/l, respectively) and rat cardiomyocytes (EC50 6.2 +/- 0.5 and 5.7 +/- 0.6 mumol/l, respectively). The selectivity of BDTI and salbutamol for beta 2-adrenoceptors on the cAMP response were 12.4 and 14.3 times, respectively. It is concluded that BDTI is a beta 2-selective adrenoceptor agonist.