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BQ-788, A Selective Endothelin ET_B Receptor Antagonist

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ABSTRACT

We describe characteristics of a selective endothelin (ET) ET_B receptor antagonist, BQ-788 [*N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine], which is widely used to demonstrate the role of endogenous or exogenous ETs *in vitro* and *in vivo*. *In vitro*, BQ-788 potently and competitively inhibited ^{125}I-labeled ET-1 binding to ET_B receptors in human Girrardi heart cells (hGH) with an IC_{50} of 1.2 nM, but only poorly inhibited the binding to ET_A receptors in human neuroblastoma cell line SK-N-MC cells (IC_{50}, 1300 nM). In isolated rabbit pulmonary arteries, BQ-788 showed no agonistic activity up to 10 μM and competitively inhibited the vasoconstriction induced by an ET_B-selective agonist (pA_2, 8.4). BQ-788 also inhibited several bioactivities of ET-1, such as bronchoconstriction, cell proliferation, and clearance of perfused ET-1. Thus, it is confirmed that BQ-788 is a potent, selective ET_B receptor antagonist. *In vivo*, in conscious rats, BQ-788, 3 mg/kg/h, i.v., completely inhibited a pharmacological dose of ET-1- or sarafotoxin6c (S6c) (0.5 nmol/kg, i.v.)-induced ET_B receptor-mediated depressor, but not pressor responses. Furthermore, BQ-788 markedly increased the plasma concentration of ET-1, which is considered an index of potential ET_B receptor blockade *in vivo*. In Dahl salt-sensitive hypertensive (DS) rats, BQ-788, 3 mg/kg/h, i.v., increased blood pressure by about 20 mm Hg. It is reported that BQ-788 also inhibited ET-1-induced bronchoconstriction, tumor growth and lipopolysaccharide-induced organ failure. These data suggest that BQ-788 is a good tool for demonstrating the role of ET-1 and ET_B receptor subtypes in physiological and/or pathophysiological conditions.