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Title: Unique receptor dissociation kinetics of the novel endothelin receptor antagonist macitentan

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Body: Association and dissociation rates of G protein-coupled receptor antagonists can influence their in vivo pharmacological activity, such as duration of action, activity in situations of increased agonist concentrations and ultimately clinical efficacy. Using signaling assays in human pulmonary arterial smooth muscle cells (PASMC), we investigated the endothelin (ET) receptor inhibition kinetics of macitentan, a novel ET receptor antagonist currently in phase 3 clinical trials in pulmonary arterial hypertension, and compared them with the kinetics of bosentan and ambrisentan. Calcium flux assays showed that macitentan, but not ambrisentan or bosentan, increased in potency (10-fold) upon prolongation of antagonist pre-incubation time from 10 min to 120 min, indicating slow apparent association of macitentan with ET receptors. Macitentan furthermore displayed a slow receptor dissociation rate, as inhibition of ET-1-induced calcium flux persisted for more than 60 min after macitentan wash-out. Conversely, bosentan and ambrisentan did not maintain receptor blockade after washout and displayed a ~15-fold shorter receptor occupancy half life than macitentan. The slow dissociation kinetics rendered macitentan an efficient antagonist of ET-1-induced IP3 synthesis and ET-1-induced sustained calcium flux across the whole range of ET-1 concentrations tested. In contrast, bosentan and ambrisentan did not display antagonism against high ET-1 concentrations in these assays. In pulmonary arterial smooth muscle cells, macitentan is a slow-offset competitive antagonist and, unlike ambrisentan and bosentan, capable of efficient receptor blockade in functional assays irrespective of the ET-1 concentration.