Cell-based and in-silico studies on the high intrinsic activity of two boron-containing salbutamol derivatives at the human b2-adrenoceptor

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A b s t r a c t

Salbutamol is a well-known b2 adrenoceptor (b2AR) partial agonist. We synthesized two boron-containing salbutamol derivatives (BCSDs) with greater potency and efficacy, compared to salbutamol, for inducing b2AR-mediated smooth-muscle relaxation in guinea-pig tracheal rings. However, the mechanism involved in this pharmacological effect remains unclear. In order to gain insight, we carried out binding and functional assays for BCSDs in HEK-293T cells transfected with the human b2AR (hb2AR). The transfected hb2AR showed similar affinity for BCSDs and salbutamol, but adenosine 30,50-cyclic phosphate (cAMP) accumulation induced by both BCSDs was similar to that elicited by isoproterenol and greater than that induced by salbutamol. The boron-containing precursors (boric and phenylboronic acids, 100 lM) had no significant effect on salbutamol binding or salbutamol-induced cAMP accumulation. These experimental results are in agreement with theoretical docking simulations on lipid bilayer membrane-embedded hb2AR structures. These receptors showed slightly higher affinity for BCSDs than for salbutamol. An essential change between putative active and inactive conformational states depended on the interaction of the tested ligands with the fifth, sixth and seventh transmembrane domains. Overall, these data suggest that BCSDs induce and stabilize conformational states of the hb2AR that are highly capable of stimulating cAMP production.