Nasrollahi-Shirazi *et al.: Intrinsic Activity*, 2016; **4**(Suppl.3):A3.2
http://www.intrinsicactivity.org/2016/4/S3/A3.2
published online: 5 September 2016

22nd Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the Hungarian Society for Experimental and Clinical Pharmacology

Vienna, 8–10 September 2016

MEETING ABSTRACT

A3.2

A comparison of the β-adrenergic receptor antagonists landiolol and esmolol: receptor selectivity, partial agonism and pharmacochaperoning actions

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Background: Blockage of β_1-adrenergic receptors is one of the most effective treatments in cardiovascular medicine. Esmolol was introduced some three decades ago as a short-acting β_1-selective antagonist. Landiolol is a more recent addition. Here, we compared the two compounds for their selectivity for β_1-adrenergic receptors over β_2-adrenergic receptors, partial agonistic activity, signaling bias and pharmacochaperoning action by using HEK 293 cell lines, which heterologously expressed each human receptor subtype.
Methods: Receptor determination on the cell surface, phosphorylation of p44/p42 mitogen-activated protein kinase / extracellular signal-regulated kinase 1 and 2 (MAP kinase; ERK1/2), ligand affinity /selectivity for the receptors, and partial agonistic activity were examined by flow cytometry, immunoblotting, radioligand binding assays and [^{3}H]cAMP accumulation assay respectively.
Results: The affinity of landiolol for β_1-adrenergic receptors and β_2-adrenergic receptors was higher and lower than that of esmolol, respectively, resulting in an improved selectivity (216-fold *vs*. 30-fold). The principal metabolite of landiolol (M1) was also β_1-selective, but its affinity was very low; hence, it is unlikely to contribute to the action of landiolol *in vivo*. Both, landiolol and esmolol caused a very modest rise in cAMP levels but a robust increase in the phosphorylation of extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2) indicating that the two drugs exerted partial agonist activity with a signaling bias. If cells were incubated for ≥24 h in the presence of ≥1 μM esmolol, the levels of β_1-adrenergic, but not of β_2-adrenergic, receptors increased. This effect was contingent on export of the β_1 receptor from the endoplasmic reticulum and was not seen in the presence of landiolol.
Discussion: Based on these observations we conclude that landiolol offers the advantage of (i) improved selectivity and (ii) the absence of pharmacochaperoning activity, which sensitizes cells to rebound effects upon drug discontinuation.

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