Comparison of the Pharmacophore Features of Agonists and Antagonists in β3-Adrenergic Receptors

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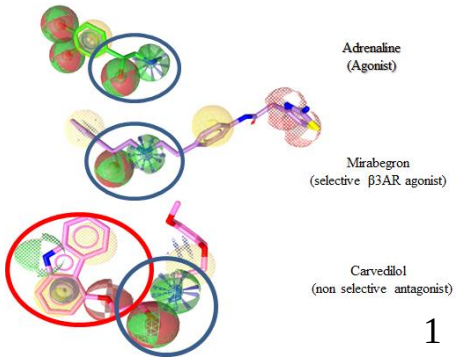
β3-Adrenergic receptors (β3-ARs), as well as β1-ARs and β2-ARs, belong to the G-protein coupled receptors (GPCRs) characterized by seven transmembranes (TM). The β3-ARs are expressed in several tissues and are considered as a drug target for the treatment of several pathologies such as obesity, type 2 diabetes, and overactive bladder [1]. Since β3-AR agonists evoked lipolysis and thermogenesis in rodents, the number of research publications related to these receptors increased dramatically [3]. However, the development of new β3-ARs antagonists is still limited, while the activation of these receptors is still the desired effect. Two compounds, L-748328 and L-748337 were reported as selective antagonists [2]. However, to support better improvement in discovery ligands of β3-ARs, the comparison of structure agonists and antagonist are still needed to be explored.

A set of β3-ARs ligands consisting of 2 endogenous agonists, 7 known β3-ARs agonists, and 7 antagonists was used for this study. The conformations of ligands were generated with LigandScout v3.12 using Omega v2.3.3. The pharmacophore features were extracted through ligand-based pharmacophore model calculations.

The endogenous agonists, the β3-ARs agonists, and the antagonists resulted in 10, 9, 11 pharmacophore features, respectively (fig. 1). The common pharmacophore features were HBD (Hydrogen Bond Donor), HBA (Hydrogen Bond Acceptor), PI (Positive Ionizable Area) located in the center of the molecules (ethanolamine moiety) indicated as the main pharmacophore of β3-AR ligands.



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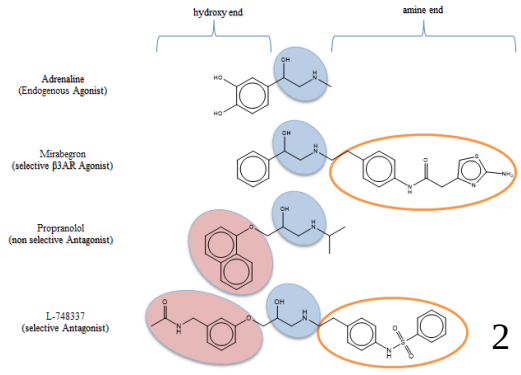

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The significant difference between agonist and antagonist were located on the hydroxy end (fig.2). In antagonist, in this part has extended hydrophobic contacts with the receptor. Interestingly, on the amine end of the selective β3-ARs antagonists contains large substituents which are typical in selective β3-ARs agonists (fig.2). The RHS gave more hydrophobic interactions indicating the possibility of the selectivity of the β3-ARs relies on this side. β3-AR should have a larger hydrophobic pocket than the other two β-ARs since its sequence possesses only 50–70% to the other two β-ARs [3], suggesting that the development of both of selective agonist and selective antagonist for β3-ARs is still achievable provided.

[1] G. P. Maria and S.Antonio, *Methods in Enzymology*, 2010, 484, 197-230
[2] M. R. Candelore, L. Deng, L. Tota, X. Guan, A. Amend, Y. Liu, R. Newbold, M.A. Cascieri and A.E. Weber, *J Pharmacol Exp Ther*,1999, 290(2):649-55.
[3] S.D. Edmondson, Comprehensive Medicinal Chemistry III, *Elsevier*, 2017, Vol.7.20, 714-737.