The complexity of signal transduction as elucidated by molecular dynamics

Rachid Charbel Maroun*[1], Ld Herrera-Zuniga , Lm Moreno-Vargas , J Correa-Basurto , D Prada , P Curmi , and Jm Arrang

[1]UMR-S U1204, INSERM/Université d'Evry-Val d'Essonne/Université Paris-Saclay, 91025 Evry, FRANCE – Institut National de la Santé et de la Recherche Médicale - INSERM – France

Abstract

In this work, we study the mechanisms of activation and inactivation of signal transduction by the histamine H3 receptor (H3R), a 7TM GPCR through extended molecular dynamics (MD) simulations of the receptor embedded in a hydrated double layer of dipalmitoyl phosphatidyl choline (DPPC), a zwitterionic poly-saturated ordered lipid. Three systems were prepared: the apo H3R, representing the constitutively active receptor; and the holo-systems: the H3R coupled to an antagonist/inverse agonist (ciproxifan) and representing the inactive state of the receptor; and the H3R coupled to the endogenous agonist histamine and representing the active state of the receptor. An extensive structural and dynamical analysis of the MD simulation trajectories shows that the three states of H3R present important structural and dynamic differences in several geometric and energy properties and that the behavior of this system is complex given that the measured properties interact in multiple and inter-dependent ways. For instance, rotamer toggle switches involved in the mechanism are multiple and not just single nor double, as reported before. In addition, the MD simulations describe an unexpected escape of histamine from the binding site, in agreement with the experimental rapid off-rates of agonists.

Keywords: 7TM receptors, GPCR, signal transduction, histamine H3 receptor, molecular dynamics

*Speaker