Understanding induced conformational plasticity in G-protein coupled receptors selective pathway activation

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1. Abstract

G-protein coupled receptors (GPCRs) constitute the most important drug target family and account for 30% of the FDA approved drugs[1]. This large family of receptors detect a remarkably diverse array of molecules outside the cell and initiate a variety of intracellular signalling pathways in response. The transmembrane nature and intrinsic flexibility of GPCRs makes their crystallization difficult. But a number of technical advances, aiming to rigidify the receptor have allowed their crystallization increasing the number of available structures. Despite this breakthrough in crystallography, which lead to the Nobel prize in chemistry to Lefkowitz and Kobilka in 2012[2,3], these structures are unlikely to cover the conformational diversity of this family of receptors and must be complemented with other techniques to reveal the intrinsic dynamics of the process. We are only starting to understand the role of ligand-induced conformational changes (allostery) in GPCRs and there remains a great deal to be discovered in order to facilitate fundamental understanding of the role of allostery and the potential of new allosteric drugs[4,5]. Here we present a combination of state-of-the-art molecular dynamics enhanced sampling techniques and force fields to understand at an atomistic level how ligands and intracellular partners affect the energy and interconversion rates of GPCRs conformational repertoire. Our study is focused on a prototypical class A GPCR, the adenosine receptor A2a, which is relevant to the occurrence, development and treatment of brain ischemic damage and degenerative disorders, due to its role as neuronal and synaptic function modulator. Understanding selective pathway activation in this prototypical class A GPCR will have a significant impact on rational drug discovery allowing to decrease possible side effects of GPCR drugs and helping to design safer drugs for central nervous system diseases. G-protein coupled receptors (GPCRs) constitute the most important drug target family and account for 30% of the FDA approved drugs. This large family of receptors detect a remarkably diverse array of molecules outside the cell and initiate a variety of intracellular signalling pathways in response. The transmembrane nature and intrinsic flexibility of GPCRs makes their crystallization difficult. But a number of technical advances, aiming to rigidify the receptor have allowed their crystallization increasing the number of available structures. Despite this breakthrough in crystallography, which lead to the Nobel prize in chemistry to Lefkowitz and Kobilka in 2012, these structures are unlikely to cover the conformational diversity of this family of receptors and must be complemented with other techniques to reveal the intrinsic dynamics of the process. We are only starting to understand the role of ligand-induced conformational changes (allostery) in GPCRs and there remains a great deal to be discovered in order to

facilitate fundamental understanding of the role of allostery and the potential of new allosteric drugs.

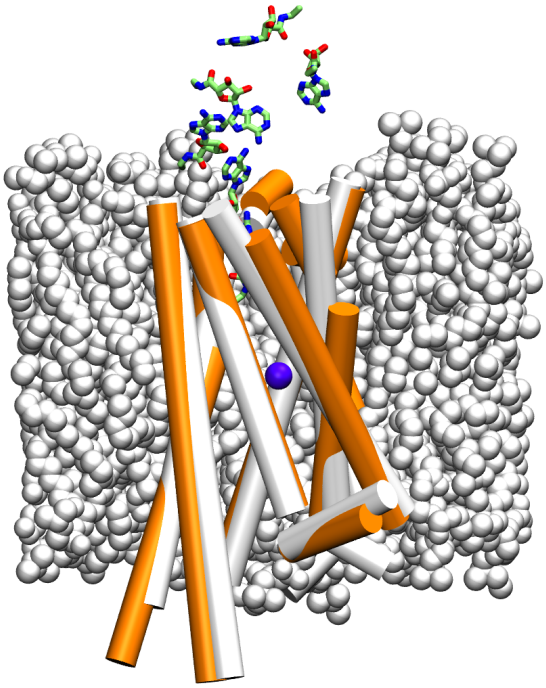

Figure 1 *Adenosine receptor inactivation process*

Here we present a combination of state-of-the-art molecular dynamics enhanced sampling techniques and force fields to understand at an atomistic level how ligands and intracellular partners affect the energy and interconversion rates of GPCRs conformational repertoire. Our study is focused on a prototypical class A GPCR, the adenosine receptor A2a, which is relevant to the occurrence, development and treatment of brain ischemic damage and degenerative disorders, due to its role as neuronal and synaptic function modulator. Understanding selective pathway activation in this prototypical class A GPCR will have a significant impact on rational drug discovery allowing to decrease possible side effects of GPCR drugs and helping to design safer drugs for central nervous system diseases.

2. References

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