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Structural insights into the activation process of the opioid mu receptor

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Opioid receptors (OR), members of the G protein-coupled receptor (GPCR) superfamily, constitute the major target for the treatment of pain. The use of opioid drugs acting at these receptors is however a leading cause of death by overdose in Europe and North America. Our collaborators recently described the structure of an antagonist-bound inactive and agonist bound conformation of the μOR. It demonstrated the key molecular determinants for ligand binding and activation process common to other GPCRs. However, much remains to be learned about the mechanisms by which different agonists can induce distinct levels of Gi protein activation and/or arrestins recruitment upon activation of μOR. Pharmacological and biophysical studies suggest that this versatility can be achieved through the structural plasticity of GPCRs. In this work, we analyse the conformational landscape of the μOR in distinct pharmacological conditions (full and partial agonists, antagonist) using liquid-state NMR spectroscopy in light of the X-ray structures. We also investigate the structure and dynamics changes upon binding the effector Gs protein and a mimetic nanobody thereof. Our results show that there is very weak allosteric coupling between the agonist binding pocket and G protein coupling interface. Furthermore, the analysis provides clues on the successive structural events leading to the full active conformation of μOR. We can extend this approach to biased ligands that are able to elicit G-protein activation without arresting activation. A better knowledge of the structural basis of all activation pathways for opioid drug efficacy may lead to new therapeutic approaches with limited side effects.

Biography

Hélène Déméné has completed her PhD from University of Paris and Post-doctoral studies at the Mount Sinai Hospital (New York, US) and at the Institut de Biologie Structurale (Grenoble, France). She is now Research Associate at the Centre of Biochimie Structrale (Montpellier, France) where she specialized in the Structural Biology of GPCRs. She has published more than 25 papers in reputed journals.

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