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Structural studies of opioid receptor activation

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Opioid receptors (OR), members of the G protein-coupled receptor (GPCR) superfamily, constitute the major and the most effective target for the treatment of pain. Both beneficial and adverse effects of illicit opioid drugs (opium, heroin) as well as approved therapeutics (morphine and codeine) are mediated by the activation of the mu-opioid receptor (μOR).

We recently described the structure of an inactive conformation of the μOR. It provided important information regarding the binding site of small morphinan antagonists, revealed a largely exposed binding pocket, and demonstrated key molecular determinants for antagonist binding preferences for OR. However, much remains to be learned about the mechanisms by which different agonists can induce distinct levels of Gi protein activation and/or arrestin recruitment upon activation of μOR.

In this study, we propose to analyse the activation mechanism of the μOR using liquid-state NMR spectroscopy and X-ray crystallography. Our goal is to provide insights into opioid receptor activation upon binding of ligands presenting distinct efficacy and/or biased signaling properties. A better knowledge of the structural basis for opioid drug efficacy may lead to new therapeutic approaches with limited side effects.