Investigation of allosteric modulators of opioid receptors derived from carbonyl derivatives of 2-aminoimidazoline-2

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Doctoral Thesis

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Lublin 2016

At present, the complexity of protein function is in the spotlight of life science. Functional selectivity, allosteric modulation and its unique feature - probe dependence are among the most interesting, mysterious and most investigated aspects of biological macromolecules. A deeper insight into underlying effects could both improve our understanding of function of the molecular machines constituting the fundamental building blocks of life, as well as facilitate further research in the field and, possibly, rational design of novel allosteric modulators. This, in turn, could lead to design of unprecedentedly safe and selective drugs. The allosteric drugs can potentially be spatially, temporally and functionally selective, and examples of such already registered drugs (Cinacalcet, Maraviroc) prove their usefulness.

Investigation of complex and subtle allosteric events is problematic, in particular at the atomic scale. Fortunately, modern, diverse techniques of molecular dynamics (MD) constitute important computational tools to study such phenomena.

The presented study demonstrates, that meticulously prepared in silico study, that takes into account a native-like membrane environment, activation state and native complexing protein partners can successfully reproduce even very subtle probe dependence effects, which allows for the insight into underlying mechanisms at the level of particular atoms. It uses MD of active-state GPCR homology model in complex with G-protein immersed in a raft-like membrane, providing a high level of system complexity and native-likeness. These methods are used in order to investigate allosteric binding site and mechanism of action of novel antinociceptive compounds, D1 and F8. Earlier in vivo tests suggested their binding to mu opioid receptor, but exact mechanismof action remained unclear.

Here I demonstrate that D1 and F8 compounds bind in an allosteric site at the opioid receptor, and act as allosteric modulators or allosteric agonists. The receptor's 7th transmembrane helix turns out to be main component of allosteric signal transmission, ant the tyrosine 7.53 seems to be the main switch involved in the effect of modulation. The results reveal a pytative allosteric pathway in G-protein coupled receptors, and mey facilitate design of novel, allosteric drugs.