Alison Claire Waterfield, Drug Des 2018, Volume 7
DOI: 10.4172/2169-0138-C3-028

28th International Conference on
CHEMISTRY & DRUG DESIGNING
December 05-06, 2018 | Vancouver, Canada

GPCR ligand bias revisited: Opioid receptor deorphanisation guided by *in silico* docking

Alison Claire Waterfield
F Hoffman-La Roche AG, Switzerland

Introduction: Ligand bias, or biased agonism, refers to the ability of different GPCR ligands to bind and stabilize the receptor in alternative active conformations. Consequently, different ligands can differentially activate intracellular signaling pathways, a concept referred to as functional selectivity [Kenakin and Miller, 2010]. The mu (μ) opioid receptor (MOR) represents a good example where the activation of specific pathways has been linked to physiological outcomes. This led to the design of MOR agonists biased towards G-protein versus beta-arrestin pathway activation as improved analgesics, and TRV130 (Trevena/ Oliceridine) entered Phase III Clinical Trials under FDA breakthrough designation for the treatment of moderate-to-severe acute pain. However, the nature and degree of separation of adverse events from analgesic effect afforded by this molecule are not yet clear. Further work is required in order to elucidate and clearly understand the interplay of desired versus unwanted pharmacological effect profile, and the existence of highly selective probes could greatly help in this respect. The recently deorphanized cyno-specific orphan GPCR (oGPCR), MRGPRX2, is used here as an example of this concept.

Methods: Lansu et al., (2017) conducted first a physical *in vitro* compound screen utilizing a luminescence-based BrightGlo Gq assay, and intracellular calcium mobilization assay, followed by a much larger *in silico* docking screen of a ZINC database with ~3.7 million molecules, to discover probes for the orphan cyno-specific GPCR, MRGPRX2.

Results: It was found that the oGPCR MRGPRX2 responds to opioid drugs and endogenous pro-dynorphin peptides at potentially relevant concentrations and mediates opioid-induced degranulation in a human mast cell line [Lansu et al., 2017]. MRGPRX2 is an atypical opioid receptor that responds to morphinan-based opioids and transmitters. Structure-based screening afforded the discovery of the selective, submicromolar MRGPRX2 agonist (R)-ZINC-3573 (average EC_{50} in calcium mobilization assay=760 nM, n=3), which promotes degranulation in mast cells and is highly selective for MRGPRX2 over a panel of over 315 other GPCRs. The inactive enantiomer (S)-ZINC-3573 (EC_{50}>100,000nM, n=3) and the active (R)-ZINC-3573 are an effective and internally controlled probe pair for further investigation of the biology of this primate-exclusive receptor.

Conclusion: There is a clear high unmet medical need in the treatment of pain, and the principle of biased drugs for increased analgesic versus side effect profile in opioid drugs has been proved, Trevena a case in point, however further research is required to fully understand the therapeutic versus side effect profile of such biased compounds. MRGPRX2 is a novel Gαq-coupled opioid-like receptor activated by endogenous prodynorphin-derived peptides and opioid compounds, including FDA-approved drugs and their metabolites. The discovery of selective and relatively potent MRGPRX2 agonist (R)-ZINC-3573 and its inactive S-isomer provides researchers with a chemical probe pair to specifically modulate this no longer oGPCR receptor, illuminating its role in pathological reactions such as itch and potentially revealing a path for therapeutic design. The unusual specificity of ZINC-3573 against essentially the entire GPCRome and the relevant kinome and the availability of an inactive enantiomer makes this molecule a uniquely useful MRGPRX2 probe.

aliw54@hotmail.com

Notes: