World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:15, No:08, 2021

Modulation of Receptor-Activation Due to Hydrogen Bond Formation

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Abstract : A new class of drug candidates, initially derived from mathematical modeling of ligand-receptor interactions, activate the μ-opioid receptor (MOR) preferentially at acidic extracellular pH-levels, as present in injured tissues. This is of commercial interest because it may preclude the adverse effects of conventional MOR agonists like fentanyl, which include but are not limited to addiction, constipation, sedation, and apnea. Animal studies indicate the importance of taking the pH value of the chemical environment of MOR into account when designing new drugs. Hydrogen bonds (HBs) play a crucial role in stabilizing protein secondary structure and molecular interaction, such as ligand-protein interaction. These bonds may depend on the pH value of the chemical environment. For the MOR, antagonist naloxone and agonist [D-Ala2,N-Me-Phe4,Gly5-ol]-enkephalin (DAMGO) form HBs with ionizable residue HIS 297 at physiological pH to modulate signaling. However, such interactions were markedly reduced at acidic pH. Although fentanyl-induced signaling is also diminished at acidic pH, HBs with HIS 297 residue are not observed at either acidic or physiological pH for this strong agonist of the MOR. Molecular dynamics (MD) simulations can provide greater insight into the interaction between the ligand of interest and the HIS 297 residue. Amino acid protonation states are adjusted to the model difference in system acidity. Unbiased and unrestrained MD simulations were performed, with the ligand in the proximity of the HIS 297 residue. Ligand-receptor complexes were embedded in 1-palmitoyl-2-oleoyl-sn glycero-3-phosphatidylcholine (POPC) bilayer to mimic the membrane environment. The occurrence of HBs between the different ligands and the HIS 297 residue of MOR at acidic and physiological pH values were tracked across the various simulation trajectories. No HB formation was observed between fentanyl and HIS 297 residue at either acidic or physiological pH. Naloxone formed some HBs with HIS 297 at pH 5, but no such HBs were noted at pH 7. Interestingly, DAMGO displayed an opposite yet more pronounced HB formation trend compared to naloxone. Whereas a marginal number of HBs could be observed at even pH 5, HBs with HIS 297 were more stable and widely present at pH 7. The HB formation plays no and marginal role in the interaction of fentanyl and naloxone, respectively, with the HIS 297 residue of MOR. However, HBs play a significant role in the DAMGO and HIS 297 interaction. Post DAMGO administration, these HBs might be crucial for the remediation of opioid tolerance and restoration of opioid sensitivity. Although experimental studies concur with our observations regarding the influence of HB formation on the fentanyl and DAMGO interaction with HIS 297, the same could not be conclusively stated for naloxone. Therefore, some other supplementary interactions might be responsible for the modulation of the MOR activity by naloxone binding at pH 7 but not at pH 5. Further elucidation of the mechanism of naloxone action on the MOR could assist in the formulation of cost-effective naloxone-based treatment of opioid overdose or opioid-induced side effects.

Keywords : effect of system acidity, hydrogen bond formation, opioid action, receptor activation
Conference Title : ICIAM 2021 : International Conference on Industrial and Applied Mathematics
Conference Location : Istanbul, Türkiye
Conference Dates : August 16-17, 2021