Molecular Dynamics Approach to Pharmacophore Modelling of Mu Opioid Receptor Ligands and DAMGO

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Everyday, 115 Americans die from opioid overdose. These opioids, such as morphine, are often used as pain-management therapeutics. However, morphine and other synthetic drugs induce adverse effects, including respiratory depression, vomiting, constipation, and severe dependence. For this reason, scientists are trying to identify ligands, small molecules, with drug-like properties that function in analgesia by activating the mu opioid receptor (MOR), but that do not cause as many adverse effects. Investigation of these molecules was done through computational modeling, as limitations on cost and resources prevent a thorough search on millions of potential therapeutics in wet labs. Machine learning specifically provides the ability to differentiate between types of ligands quickly and efficiently. To train the deep neural network to differentiate between agonists, which activate the MOR, and antagonists, which inhibit the MOR, a pharmacophore model was created for each of the ligands in the dataset. The machine learning algorithm achieved a 97% accuracy, meaning that the model was able to differentiate between the ligands classes correctly, and can be used for the screening of potential drug candidates. Additionally, 4 conformations of DAMGO, a MOR ligand and potential morphine replacement, were discovered. The fourth conformation was taken with a high frequency, indicating selectivity for the MOR because the molecule will not change its pose and trigger an adverse signaling pathway; it can thus be used as a morphine replacement. By quickly identifying effective analgesics with reduced adverse effects we can help resolve the opioid crisis running rampant in the United States.

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