Insights into molecular recognition and residence times of opioids in the μ-opioid receptor from molecular dynamics simulation

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Abstract

Introduction: Synthetic opioids are powerful painkillers but are also the lead contributors to recent drug overdose deaths in the United States, prompting a need for better understanding of their structural and functional relationships. These highly abused drugs primarily target the μ-opioid receptor (mOR), as does naloxone, an mOR antagonist. Molecular dynamics is a powerful computational modeling technique that can directly connect opioid—mOR interactions to opioid—mOR residence times at atomic resolution, which may help to evaluate dosing strategies of naloxone in reversing an overdose.

Methods: A highly robust molecular dynamics technique named Metadynamics was applied to probe the dissociation of opioids from the mOR. A set of fentanyl analogs and morphinans were examined, among which were carfentanil, sufentanil, buprenorphine and naloxone. Multiple simulations were performed, and the residence times were approximated by fitting the cumulative Poisson distribution.

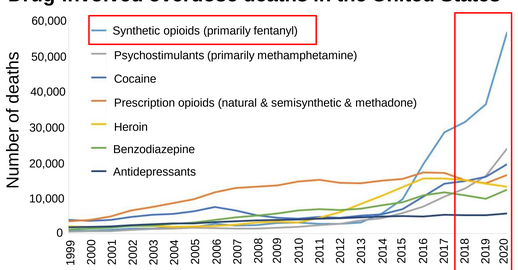
Results: The comparisons between the calculated residence times and experimentally determined binding constants demonstrated correlation and rank order agreements with Pearson and Spearman coefficients of 0.6 to 0.8. Besides the prominent salt-bridge with a conserved asparate, analyses of the simulated trajectories characterized hydrogen bonding and stacking contacts, as well as chemical elements, underlying differences in binding affinity and kinetics.

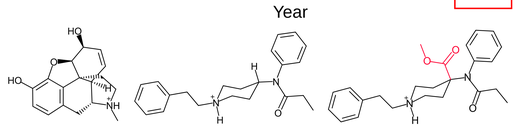
Conclusions and perspectives: This Metadynamics dynamics methodology can be used to examined newly emerging opioids and applied to quantitively assess other drug—molecular target interactions.

Background and Problems

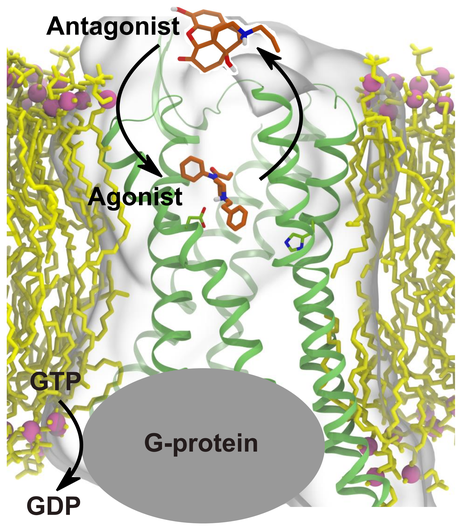
- Fentanyl is a much more powerful opioid than morphine (100x), and small modifications can produce more potent agonists, such as carfentanil.
- Opioid-induced respiratory depression is a direct cause of death from opioid overdose.

Drug-involved overdose deaths in the United States





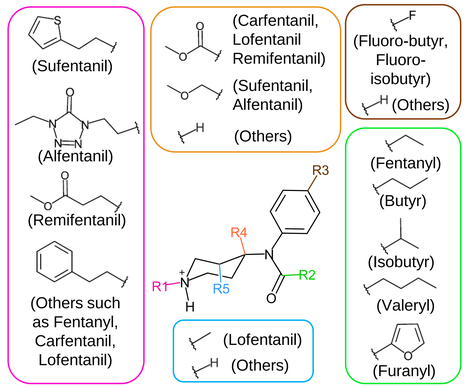
Data adopted from https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates



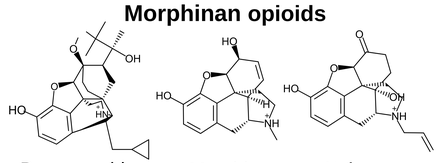
- Binding duration of opioids in the mOR may influence not only their biological activities but also the ability of antagonists, such as naloxone, to rescue an overdose.

Results and Discussion

Fentanyl and derivatives

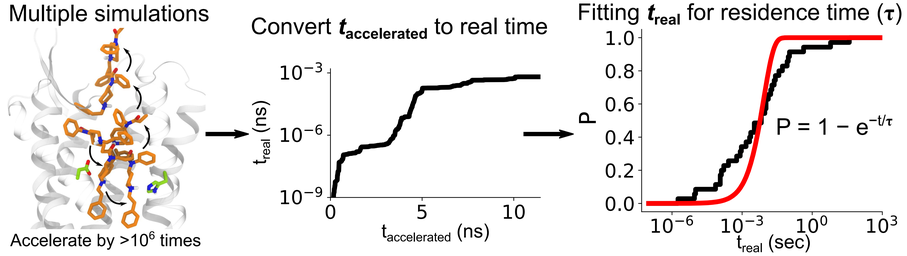


Morphinan opioids

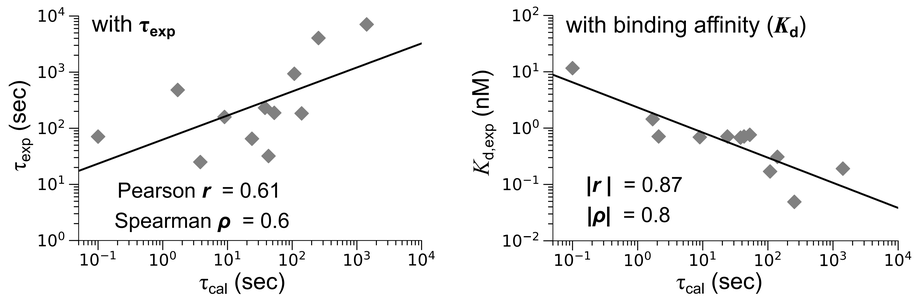


R1, **R2**, **R3**, **R4** and **R5** are chemical substituents of the fentanyls being examined.

Applications of Metadynamics to elucidate opioid--mOR dissociation

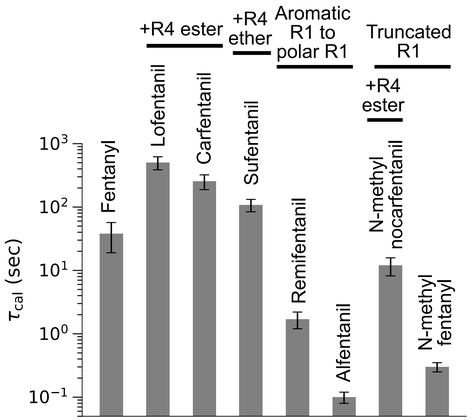


Agreements between calculated residence times of the opioids and experimentally measured values

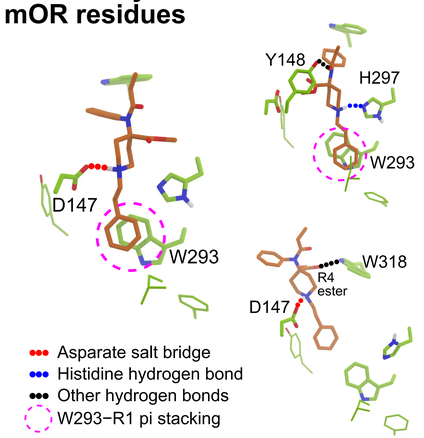


The experimentally measured values were measured at the Veterans Affairs (VA) Portland Health Care System (J. Mann,…, Z Li. Clin. Pharm. Therapeutics, 2022, in press).

R1 and R4 substituents modulate residence times of the fentanyls



Characterized contacts between the fentanyls and conserved mOR residues



Remarks

- Metadynamics effectively predicts opioids—mOR residence times and distinguishes opioids with long and short binding duration.
- The outcome of this investigation may encourage proper and rigorous applications of computational modeling techniques in drug development.
- The technique can be combined with cheminformatics and other structural—based modeling techniques to improve the ability to identify potentially harmful drugs.

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