Creating a Less Addictive Opioid using Computational Chemistry

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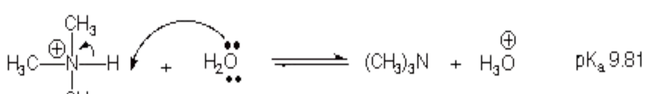
INTRODUCTION

Opioids are highly effective in providing pain relief but are highly addictive; an opioid capable of providing pain relief without dangerous side effects is currently not available. Using computational chemistry, a pH specific binding morphine derivative is aimed to induce selective binding in acidic tissues rather than tissues at the physiological pH of 7.4. Since injured tissue has a pH of about 6.5, in comparison to normal tissue, the binding of the morphine derivative becomes more specific to the peripheral acidic tissue. The morphine derivative will not induce the addictive high as it will not bind to opioid receptors located in the brain.



The tertiary amine of the opioid is protonated prior to binding to mu-opioid receptors. Although opioids vary in structure, most have the same base groups. Due to this, similar studies on fentanyl can apply to morphine. Evidence in research done on fentanyl shows that a fluorinated fentanyl derivative is successful in binding in acidic conditions above physiological pH (Spahn, et. al, 2017).

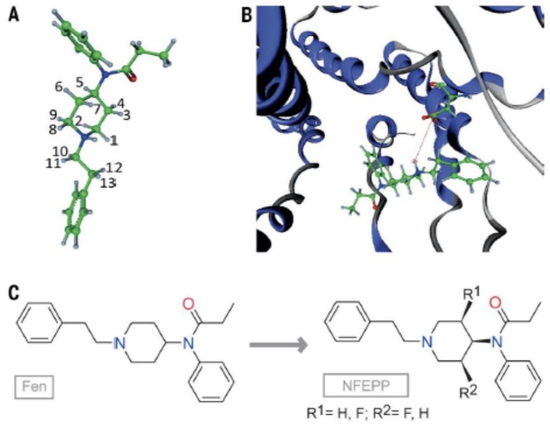


Fig. 1. The fluorinated fentanyl derivative from the studies on the fluorination of fentanyl that binds in peripheral, acidic tissue (Spahn, et. al, 2017).

METHODS

In order to effectively lower the pH of morphine, our approach was to experiment with different locations on the molecule to add a fluorine atom to employ inductive effects and consequently lower the pKa.

- The acid dissociation constant, pKa, is an equilibrium constant defined as the ratio of the protonated and the deprotonated form of a compound.
- Gaussian software calculated the free energy of protonated and deprotonated morphine wherever fluorinated to determine pKa using the following equation:

$$pK = \frac{\Delta G(aq)}{RT*\ln(10)}$$

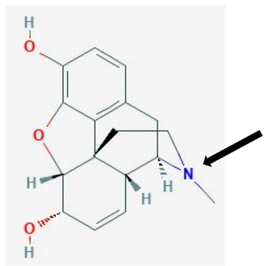


Fig. 2. The chemical structure of morphine. The arrow denotes the tertiary amine to be protonated.

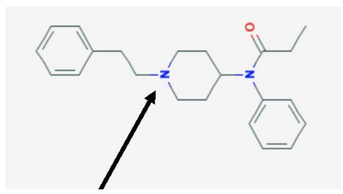
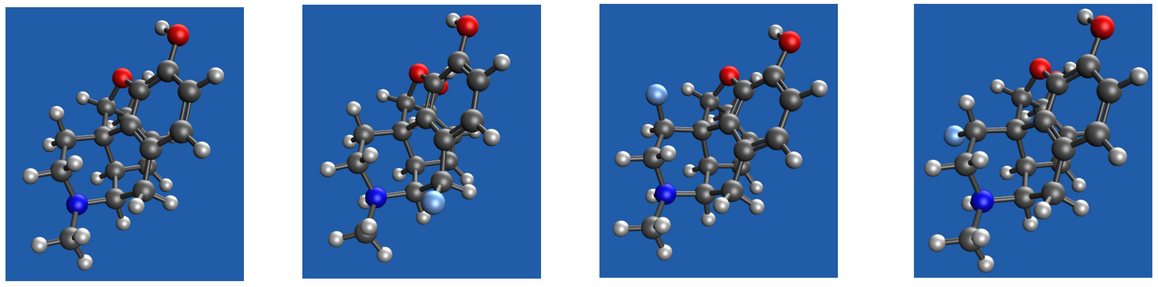


Fig. 3. The chemical structure of fentanyl. The arrow denotes the tertiary amine to be protonated.

RESULTS



Morphine | Morphine Beta Fluorine Equatorial (right of amine) | Morphine Beta Fluorine Equatorial (left of the amine) | Morphine Beta Fluorine Axial (right of amine)

Tbl. 1. The experimental pKa values calculated for each other the β-fluorinated morphine molecules and the deprotonated morphine molecule.

Morphine Molecule Fluorine Variation	pKa value
Deprotonated Morphine	8.02
Protonated β-Fluorine Axial Position	6.07
Protonated β-Fluorine Equatorial Position (left of amine)	5.26
Protonated β-Fluorine Equatorial Position (right of amine)	6.12

DISCUSSION

The best location to fluorinate is the β-carbon to the left of the tertiary amine in the equatorial position. The experimentally calculated pKa at this position was 5.26 compared to 8.02 of morphine. The more acidic molecule most selectively binds in acidic and peripheral tissues due to inductive effects decreasing pKa of the molecule. This will discourage opiate binding in the brain, which results in addiction and euphoria.

FUTURE DIRECTION

GROMACS molecular dynamics simulation allow users to calculate the properties of rendered proteins. Molecules can be manipulated by adding water boxes, changing restrains, and several other configurations. In the future, we aim to visualize and comprehend the interaction between the opioid molecule and the mu-opioid receptor. We are currently attempting to propose a mechanism for this interaction and the protonation of the tertiary amine. Aditionally we are continuing to explore the impact of flourination sites and interaction with the MORE binding site on the pKa.

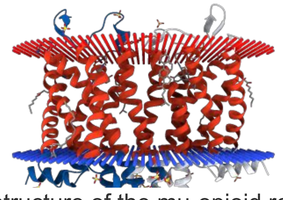


Fig. 4. Crystal structure of the mu-opioid receptor bound to a morphinan antagonist

REFERENCES

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