CALIFORNIA STATE SCIENCE FAIR
2004 PROJECT SUMMARY

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S0426

Project Title
Modeling of Tyrosine Sulfation Sites in 7TM Receptors: A Novel Approach to Pharmaceutical Drug Design

Abstract

Objectives/Goals
Sulfation as a post-translational modification of tyrosine has been shown to influence the physiology of proteins and play a role in protein-protein interactions. Determination of the location of sulfation sites in three-dimensional structures of proteins may help elucidate the precise function of tyrosine sulfation in drug-cell interactions. The purpose of this study is to suggest the role of tyrosine sulfation in ligand-binding. This understanding will allow us to create pharmaceutical drug designs that more effectively target cells involved in diseases such as Alzheimers, Parkinsons, and AIDS.

Methods/Materials
21 Seven-transmembrane receptors (7TMs) were selected based on their scores in the Position-Specific-Scoring-Matrix for tyrosine sulfation. The Position-Specific-Scoring-Matrix assigned a score denoting the probability that tyrosine sulfation occurred at a specific site. The three-dimensional model of Rhodopsin was used to align various receptors. Amino acid sequence alignments, enhanced by the use of helical wheels, were used to align the equivalent amino acids of the known Rhodopsin structure with the predicted tyrosine sulfated sites.

Results
The three-dimensional locations of all predicted sulfated tyrosines existed in a ring-like formation within 10 angstroms of the ligand-binding site, suggesting that sulfation plays a role in ligand-binding affinity and specificity. The helical and extracellular alignments showed regions with predicted sulfation sites that were conserved throughout all receptors, suggesting the common function of tyrosine sulfation. The concentration of putative sites of sulfation in the extracellular regions suggests the role of sulfation in the binding process of drugs.

Conclusions/Discussion
As the predicted sulfation sites are located within 10 angstroms of the ligand-binding site, they are accessible to the ligand and may interact with it to regulate binding affinity and specificity. Sulfation has been proven to increase binding of the HIV-1 virus, and understanding its role in drug-cell interactions may lead to improved pharmaceutical therapies, including small-inhibitor drugs. As 7TM receptors are currently known to play a role in up to seventy percent of drug-cell interactions, a model for the role of tyrosine sulfation in these receptors would benefit pharmaceutical designs for compounds that more effectively target the binding sites of 7TM receptors.

Summary Statement
The purpose of this study is to suggest the role of tyrosine sulfation in drug-cell interactions and to create pharmaceutical drug designs that more effectively target these receptors.

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