Drug Discovery and Development: The Senna Plant and Phosphomevalonate Kinase Inhibition

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Abstract

Heart disease is one of the most prominent causes of death in the United States. Hypercholesterolemia is an underlying factor leading to heart disease. By inhibiting the cholesterol synthesis pathway, scientists can develop ways to reduce the number of heart disease-related deaths. One way could be by inhibiting the actions of phosphomevalonate kinase (PMK), a cytoplasmic enzyme found in the liver. The Valders SMART Team (Students Modeling A Research Topic), in collaboration with MSOE, built a 3D physical model of PMK. Both mevalonate 5-phosphate (M5P) and ATP bind to the enzyme. Using ATP, PMK converts M5P to mevalonate 5-diphosphate, a precursor to cholesterol. The inhibition of this process may be possible through a drug derived from the Indian senna plant, which is predicted to bind in place of M5P.

I. Introduction

Heart disease is the leading cause of death in the United States and as such, naturally attracts the attention of persons looking to improve the lives of U.S. citizens. Developing drugs to combat heart disease is a major focus of proteomic researchers. One success was the creation of statins, but the treatment is not perfect; it may result in side effects such as kidney damage. For this reason, research continues into different treatment options with the intention of eliminating these concerns.

II. Old Idea, New Application

Researchers are exploring whether compounds extracted from the Asian senna plant, Cassia angustifolia, may be used as a substitute to statin drugs. The senna plant has long been used in folk remedies in Myanmar and Thailand, but has only recently attracted the attention of researchers who are looking for new drug options.

III. Exploring the Options

Initially, the senna plant was analyzed and nearly seven hundred compounds were identified as potential therapies (i.e. PMK inhibitors). Via computer simulation, the compounds were tested for their ability to inhibit the synthesis of cholesterol and the top five were selected for more thorough testing. According to computer predictions, the most likely candidate is a phenolic compound. (As shown in the photo to the right.)

IV. A Closer Look at Cholesterol Synthesis

It now becomes necessary to consider the specifics of the process that cholesterol-lowering drugs attempt to inhibit (figure 1). There is only one pathway by which cholesterol is synthesized in humans, the HMG-CoA reductase pathway. Statins inhibit an early step in this process. The phenolic senna compound would inhibit a later step, the synthesis of mevalonate 5-diphosphate (a precursor to cholesterol) from mevalonate 5-phosphate. Phosphomevalonate kinase is the enzyme that makes the transition possible, as it positions M5P and ATP in a way that allows for the transfer of the γ-phosphate on ATP to the M5P.

VI. Mechanism for Phosphorylation of M5P

Mevalonate-5-phosphate becomes mevalonate-5-diphosphate by means of phosphorylation. This process requires the binding of two ligands, M5P and ATP, to PMK. ATP binds first, resulting in a widening of the PMK binding site. When M5P binds later, it contracts the binding site to allow γ-phosphate transfer to occur. The “Walker A” loop counters these opposing charges with its high positive charge density (figure 2). A number of positively charged amino acids (such as Arginine 18, 19 and 110 and Lysine 17, 19 and 22), work to stabilize this negative charge to permit the phosphate transfer reaction to occur. There are also hinge residues that permit the two domains to move together so the reaction may occur.

VII. Conclusion

In 2008, the leading cause of death in the United States was heart disease. Familial hypercholesterolemia (genetically high cholesterol) is a major factor responsible for this unfortunate statistic. Inhibiting this pathway is the purpose of cholesterol lowering drugs, such as statins. Proteomic researchers are looking into new potential drugs, such as phenolic compounds found in the senna plant, to be used instead of statins. Phenolic compounds will hopefully inhibit the actions of phosphomevalonate kinase, (PMK), which phosphorylates a precursor to cholesterol called mevalonate 5-diphosphate. If proven successful, the next logical step is to develop a way to extract the necessary compound from the senna plant in an efficient manner, that would allow the drug to be readily available to those suffering from hypercholesterolemia.

VIII. References

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