Resveratrol Dimers Synthesized by Enzymatic Oxidation Antagonize Aβ42 Aggregation

by

Jason Ching-Yao Lin

An Abstract of a Thesis Submitted to the Graduate

Faculty of Rensselaer Polytechnic Institute

in Partial Fulfillment of the

Requirements for the degree of

MASTER OF SCIENCE

Major Subject: CHEMICAL ENGINEERING

The original of the complete thesis is on file
In the Rensselaer Polytechnic Institute Library

Approved:

Dr. Peter M. Tessier, Thesis Adviser

Rensselaer Polytechnic Institute
Troy, New York

December 2009

ABSTRACT

Protein folding is not a trivial event in biological systems, and while a great amount of effort in biology and chemistry over the past few decades have been spent on determining the structure and function of different protein folds, still very little is known about structural implications and interactions of natively unfolded proteins. Protein aggregation is a phenomenon intimately relative to various neurodegenerative disorders, including prion, Alzheimer's, Huntington's and Parkinson's diseases.

Scientists and engineers have developed various methods to elucidate the molecular mechanisms of protein aggregation and tools to synthesize and screen, in high-throughput manners, compounds that can potentially act as antagonists to protein aggregation. Natural products, including polyphenols, have recently attracted significant amount of interest among the scientific community due to a wide range of medicinal benefits they provide, such as anti-inflammatory and anti-carcinogenic effects. Nevertheless, the exact mechanism in which they interact with different biological systems is still unknown, and subsequently it is very difficult to modify those compounds to improve their efficacy for use as therapeutics.

Recent work, however, has demonstrated that polyphenols can be polymerized by enzymatic oxidation to make higher molecular weight species commonly referred to as "oligophenols", and it has been shown that those oligophenols may offer improved activity over their monomeric building blocks in protein-protein interaction. This work seeks to extend previous studies into protein aggregation through β-amyloid as the model system and dimers of resveratrol as potential therapeutic targets. It is hypothesized that polyphenols such as resveratrol should be able to antagonize toxic Aβ

aggregation and that the effect may be amplified when resveratrol monomers are oxidized to form resveratrol oligomers. By polymerizing resveratrol in a similar enzymatic manner and testing their ability to inhibit Aβ fibril formation via Thioflavin T, it has been discovered that one of the resveratrol dimers is highly effective and offers improved activity over resveratrol with an IC50 value falling between 20 to 200 μM *in vitro*. This resveratrol dimer is also biocompatible in terms of cytotoxicity.

While the disaggregation activity of resveratrol dimers arrives merely as a small surprise and the exact molecular mechanism has not been determined, this work nevertheless offers a great deal of insight to an exciting area of chemical biology. With the pace of current biotechnology, the hopes of arriving at the complete understanding of the mechanisms of interactions of polyphenols with macromolecules as well as their role in antagonizing protein aggregation are well within reach.