CALIFORNIA STATE SCIENCE FAIR
2005 PROJECT SUMMARY

Name(s)
Charles C. Wong

Project Number
S1420

Project Title
Potential Celecoxib-induced Cerebrovascular Signaling Alterations in HIV Patients

Abstract

Objectives/Goals
The blood-brain barrier (BBB) is the first line of defense against potentially harmful drugs or toxins passing from the blood stream into the brain. Human immunodeficiency virus (HIV) patients frequently take antiretroviral protease inhibitors as well as cyclooxygenase-2 (COX-2) inhibitors to treat disease-associated complications. The primary objective is to investigate potentially deleterious medication interactions, signaling induced by COX-2 inhibitor celecoxib, HIV glycoprotein 120IIIB (gp120), and HIV protease inhibitor, indinavir.

Methods/Materials
Experiments were performed using human brain microvascular endothelial cells (HBMECs) exposed to 0.4 ug/ml celecoxib, 25 ng/ml gp120, 5 uM Indinavir or combinations thereof. Doses of celecoxib and indinavir treatments were selected based on cited peak plasma concentrations after first pass metabolism. A non-toxic dose of gp120 was utilized, and a dose of 5 mM hydrogen peroxide (H(2)O(2)) sufficient to induce oxidative stress was used as a positive control for cell death. After 24-hour incubation, HBMECs were harvested and analyzed for viability along with signaling changes. Viability assays were conducted by Trypan Blue exclusion assays. Western blot analyses were subsequently performed to examine cascading protein signaling pathways. HBMEC expression of COX-2, glycogen synthase kinase 3-beta (GSK3B), and extracellular regulated kinase (ERK) phosphorylation levels were quantified via densitometry.

Results
No significant cell death was observed after single or combined treatments with celecoxib, gp120, or indinavir. However, western blot analyses of cellular fitness proteins (COX-2, GSK3B, and ERK) revealed statistically different expression and phosphorylation after singular and combined treatments.

Conclusions/Discussion
Although the combinatory drug treatments did not prove to be significantly toxic to HBMECs, Western blot analyses reveal a disruption in cellular signaling. These alterations in cell fitness associated signaling cascades, may contribute in part to neuropathogenesis of HIV in the central nervous system of patients taking both indinavir and celecoxib. The understanding of drug interactions between indinavir and celecoxib will greatly benefit clinicians in prescribing these medications and assist in educating the public about the consequences from taking these particular drugs.

Summary Statement
The experiments examined the potential of celecoxib to disrupt the BBB protein signaling cascade in patients battling HIV.

Help Received
Laboratory equipment was used at the Department of Pathology at the University of California, San Diego under the supervision of Dr. Dianne Langford and Rosemary Hurford.