CALIFORNIA STATE SCIENCE FAIR
2003 PROJECT SUMMARY

Name(s)
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Project Number
S0411

Project Title
Amyloid Peptide Mediates Monocyte Transmigration by Inducing Inflammatory Genes in Alzheimer's Disease

Abstract

Objectives/Goals
Amyloid-beta peptide (Aâ) is a potential cause of Alzheimer's disease, in which it accumulates in the brain, increasing monocyte migration across the blood brain barrier (BBB). Since the mechanisms of Aâ-mediated migration are not fully known, this project attempts to study some of those direct and indirect mechanisms. First, Aâ was confirmed as an augmenter of transmigration via interaction with its receptor advanced glycation end products (RAGE) and platelet endothelial cell adhesion molecule (PECAM-1). Furthermore, endothelial receptor polarity was examined. Next, Aâ was examined as an indirect regulator of migration, one that may increase the expression of chemotactic factors. Aâ regulation of placental growth factor (PlGF) mRNA expression was the specific focus, as its role in PlGF expression is unknown.

Methods/Materials
Human brain endothelial cells cultured in Transwell chambers were used to model the BBB in vitro. Monocytes were added to the top compartment medium, representative of the luminal side, and allowed to migrate across the monolayer to the abluminal side, where medium was removed for cell counting. In gene expression experiments, THP-1 monocytic cells were cultured in medium containing Aâ. RNA was subsequently collected and RT-PCR procedures were performed to analyze mRNA expression.

Results
Aâ was shown to increase HL-60 monocytic cell migration across the endothelial monolayer, and RAGE and PECAM-1 were shown to be involved. Aâ on both sides of Alzheimer's endothelium was able to induce migration, but only on the luminal side in normal endothelium. The peptide was shown in RT-PCR results to increase the mRNA expression of PlGF as well as its receptor Flt-1, but not vascular endothelial growth factor (VEGF), a sister molecule of PlGF.

Conclusions/Discussion
Results suggest that Aâ binds to RAGE, initiating possible signaling leading to increased membrane permeability involving PECAM-1 and increased monocyte migration. The absence of this effect in normal endothelium exposed to abluminal Aâ suggests that Aâ receptor RAGE is not present on that side, while present on both sides of Alzheimer's cells. RT-PCR experiments suggest that Aâ interaction with THP-1 monocytes increases expression of PlGF and its receptor Flt-1. Since expression of VEGF was unchanged, the induction of the two chemokines may take place through separate pathways.

Summary Statement
Amyloid peptide, a potential cause of Alzheimer's disease, increases the migration of monocytes into the brain, leading to the destruction of brain tissue by the cells after differentiation.

Help Received
Used lab equipment at USC under the supervision of Dr. Vijay Kalra