Austin Journal of Clinical Pathology

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Austin Publishing Group

Editorial

Blood-Brain Barrier Associated Transport Proteins in Sporadic Alzheimer Disease Pathogenesis

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Received: August 24, 2015; **Accepted:** August 26, 2015; **Published:** August 26, 2015

Keywords

Blood-brain barrier; Alzheimer's disease; Neurofibrillary Tangles; SenLRP; RAGE; P-gp; VEGF; eNOS; ApoE; Claudin

Editorial

Perturbation of the homeostatic roles of Blood-Brain Barrier [BBB] transport proteins is currently a significant hypothesis investigating the pathogenesis of Alzheimer [AD] lesions; Neurofibrillary Tangles [NFTs] and senile plaques [SPs] [1,2]. Specifically, the facilitation of the movement of β-amyloid molecules into and out of the brain parenchyma is likely altered causing an imbalance and accumulation of amyloid resulting in senile plaque development and putatively neurofibrillary pathology. It is these lesions which result in the devastating clinical presentations. This imbalance is thought to be at least correlated, in not caused by, the deleterious expression of one or more of LRP Lipoprotein Receptor-Related Protein, RAGE receptor For Advanced Glycation End Products, P-gp P Glycoprotein, VEGF Vascular Endothelial Growth Factor, ENOS Endothelial Nitric Oxide Synthase, Apo-E Apolipoprotein and / or Claudin.

We summarize here our laboratory investigations examining the relationship between Alzheimer lesion development and the expression of the capillary blood-brain barrier transport proteins listed above. During these investigations we used standardized immunohistochemical techniques and routinely compared results between comparable normative and Alzheimer brain samples in lesion sparse and lesion dense regions; the Superior Temporal Cortex [ST], the Occipital Cortex [OC] and the Brainstem [BS], identifying NFTs, SPs and immune-positive capillary blood-brain barrier proteins.

Both LRP and P-gp facilitate the export of amyloid from the brain across the BBB [3-6]. Our studies demonstrate that these proteins have significant positive correlations with the presence of NFTs in the superior temporal cortex of AD brains. In addition, there is a significant positive correlation between capillary LRP expression and the presence of senile plaques ($A\beta_{42}$) and a significant negative correlation between capillary P-gp expression and senile plaques ($A\beta_{42}$). No such correlations were evident in comparable normative samples. RAGE facilitates the import of amyloid from the vascular compartment into the brain [2,3]. There is a strong positive correlation between positive capillary RAGE expression and the presence of both NFTs and senile plaques ($A\beta_{42}$) in the superior temporal cortex of AD samples. No such correlations were evident in comparable normative samples. Both VEGF and ENOS capillary expressions are negatively correlated with senile plaques ($A\beta_{42}$) in the superior temporal cortex. ENOS is negatively correlated with NFTs in the superior temporal cortex. In normative samples both VEGF and ENOS capillary expressions are positively correlated with senile plaques ($A\beta_{42}$) [7-10] with respect to claudin BBB capillary expression preliminary study indicates that there is a significantly positive correlation with NFT presence in the superior temporal cortex in normative samples and a significantly negative correlation with the presence of senile plaques ($A\beta_{42}$) in comparable AD samples.

The results of these investigations clearly demonstrate the central role of the blood-brain barrier on the regulation of the transport of β-amyloid into and out of the brain. Dysfunction of the barrier can result in an accumulation of pathogenic levels of amyloid in specific and predictable regions of the brain. These aberrant levels of amyloid are significantly correlated with the pathogenesis of senile plaques, and putatively neurofibrillary tangles. We suggest that the mechanisms for the BBB dysfunction likely include:diminished LRP and P-gp expression thus retarding the elimination of amyloid from the brain; over-expression of RAGE facilitating an increase in amyloid transport into the brain; reduced VEGF and ENOS expression contributing to an BBB endothelium less able to maintain its' functional capacity; and diminished expression of claudin, thus impairing the barrier function of the BBB and potentially allowing an increase in the influx of amyloid.

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Citation: Jeynes B and Provias J. Blood-Brain Barrier Associated Transport Proteins in Sporadic Alzheimer Disease Pathogenesis. Austin J Clin Pathol. 2015; 2(1): 1026.

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Austin J Clin Pathol - Volume 2 Issue 1 - 2015
ISSN : 2381-9170 | www.austinpublishinggroup.com

Citation: Jeynes B and Provias J. Blood-Brain Barrier Associated Transport Proteins in Sporadic Alzheimer Disease Pathogenesis. Austin J Clin Pathol. 2015; 2(1): 1026.