An evaluation of progressive amyloidogenic and pro-inflammatory change in the primary visual cortex and retina in Alzheimer’s disease (AD)

James M. Hill1, Prema Dua2, Christian Clement3 and Walter J. Lukiw1,4*

1 Louisiana State University Neuroscience Center and Departments of Ophthalmology and Pharmacology, Louisiana State University Health Science Center, New Orleans, LA, USA
2 Department of Health Information Management, Louisiana State University, Ruston, LA, USA
3 Department of Natural Sciences, Infectious Diseases, Experimental Therapeutics and Human Toxicology Lab, Southern University at New Orleans, New Orleans, LA, USA
4 Department of Neurology, Louisiana State University Health Science Center, New Orleans, LA, USA
*Correspondence: wluikw@lsuhsc.edu

Edited by:
Delia Cabrera DeBuc, University of Miami, USA
Reviewed by:
Delia Cabrera DeBuc, University of Miami, USA
Gábor Márk Somfai, Semmelweis University, Hungary

Keywords: Aβ42 peptides, Alzheimer’s disease (AD), amyloid, inflammatory signaling, retina, spreading, visual system

OVERVIEW
Sporadic Alzheimer’s disease (AD; idiopathic, of unknown origin) is associated with dysfunctional gene expression in the limbic system and entorhinal cortex of the brain that drives amyloidogenesis, pro-inflammatory signaling, alterations in innate-immunity and related AD-type neuropathology (Colangelo et al., 2002; Lukiw, 2004; Ginsberg et al., 2012; Kikuchi et al., 2013). While the primary visual cortex (Brodmann Area 17) and the retina appear to be initially spared of AD-type changes that devastate the hippocampal CA1 and temporal lobe neocortex (Brodmann Area 22), these primary sensory and signal processing elements of the visual system become more involved as AD progresses. Recent data indicate that in moderate to late-stage AD, pro-inflammatory and amyloidogenic pathway spreads along the entorhinal-primary visual sensory cortex-thalamic-retinal axis, and this may be responsible in part for the complex visual disturbances, such as spatial and visual agnosia, facial identification problems, perceptual disturbances, and visual hallucinations, associated with end-stages of the AD process (Cui et al., 2007; Dehabadi et al., 2014; Tzekov and Mullan, 2014; Zhao et al., 2014). This “Opinion paper” will comment on current trends in our understanding of specific amyloidogenic and pro-inflammatory changes in the human primary visual cortex and retina as AD advances with particular reference to: (i) the expression of the pro-inflammatory marker cyclooxygenase-2 (COX-2); (ii) the appearance and aggregation of Aβ42 peptides; (iii) epigenetic mechanisms involving microRNA (miRNA) signaling that appear to be associated with disease propagation; and (iv) how direct and non-invasive analysis of the retina may help to detect and diagnose AD.

COX-2 AND BRAIN AND RETINAL DEGENERATION
A family of cyclooxygenase (COX) enzymes in the brain and retina constitutes a group of prostaglandin-endoperoxide synthases (PTGSs) responsible for the formation of several prostanoid-types of pro-inflammatory mediators including prostaglandins, prostacyclins, thromboxanes, and leukotrienes (Yang and Chen, 2008; Cudack et al., 2014). Cyclooxygenase-2 (COX-2; EC 1.14.99.1; 72 kDa) is the inducible, NF-kB-regulated isotype of the PTGSs, and as the rate-limiting enzyme of the arachidonic acid cycle is up-regulated in anatomical regions of AD brain where it potentiates inflammatory neuropathology (Lukiw and Bazan, 1998; Bazan and Lukiw, 2002; Hoozemans et al., 2008; Lukiw et al., 2012a,b; Cudack et al., 2014). COX-2 expression, mean abundance, activity, and signaling is significantly up-regulated in both AD and age-related macular degeneration (AMD), a progressive degeneration of the human retina pathologically similar in many ways to the neocortical degeneration observed in AD neocortex (Hoozemans et al., 2008; Dinet et al., 2013; Rodriguez Diez et al., 2013). Notably, sub-retinal injection of Aβ42 peptides using C57BL/6J mouse models was found to significantly induce COX-2 expression up to 6-fold while compromising the integrity of the blood-brain barrier and inducing retinal inflammation, photoreceptor cell death and driving a progressive retinal degeneration (Dinet et al., 2013). While COX-2 remains a major player in the generation of oxygen radicals and lipid mediators in propagating inflammation in degenerating neocortex and retina, a third COX enzyme cyclooxygenase-3 (COX-3) may play ancillary roles in membrane-based COX signaling, however the role of COX-3 in AD and progressive neocortical and retinal disease is understudied and not well-understood (Cui et al., 2004; Wu and Wan, 2010). Importantly, pathogenic factors associated with aging or the later stages of both brain and retinal degenerative disease may be important in the course, development and progression of each disease and what cell types, tissues, or pathways may be preferentially affected (Cui et al., 2007; Cao et al., 2013; Dehabadi et al., 2014). It is interesting that as AD advances there is a progressive and sequen-
tial elevation in the pro-inflammatory gene expression marker COX-2 from the limbic system (where AD originates) into the primary visual cortex and retina, and this is accompanied by parallel elevations in Aβ42 peptide abundance and inflammation across the entire entorhinal-primary visual cortex-thalamic-retinal axis (Cui et al., 2007; Kruck et al., 2008; Fang et al., 2009; Alexandrov et al., 2011; Cao et al., 2013; Cudaback et al., 2014). This is highly suggestive that soluble, pathogenic signaling factors such as COX-2, Aβ42 peptides or other relatively small and mobile molecules such as miRNA (see below) may be important intercellular carriers of disease signals that eventually connect the brain and retina (Zhao et al., 2006; Tzekov and Mullan, 2014; Zhao et al., 2014).

**AD AND Aβ42 PEPTIDES**

All forms of AD are characterized neuropathologically by the progressive appearance of intracereellar neurofibrillary tangles and dense, mostly extracellular, insoluble Aβ42 peptide-enriched lesions known as senile plaques (Alexandrov et al., 2011; Sivak, 2013; Hardy et al., 2014). Aβ42 peptides which form the central core of the senile plaque are generated by a complex series of secretase-mediated cleavage events from the neuronal-enriched, polytopic beta-amyloid precursor protein (βAPP; Hardy et al., 2014). The very presence of Aβ42 peptides in any tissue or physiological circuit also implicates the existence of sufficient βAPP precursor and several functional membrane-associated accessory proteins—beta and gamma secretases, presenilin, and nicastrin for example—which are required for efficient Aβ42 peptide generation (Hardy et al., 2014; Zhao et al., 2014). βAPP, the enzymatic machinery required to generate Aβ42 peptides, the Aβ42 peptides themselves, and their fibrillar and/or oligomeric aggregates are considerably enriched in both the hippocampal CA1/association neocortex and sensory retina as AD progresses (Alexandrov et al., 2011; Ohno-Matsui, 2011; Lukiw et al., 2012a,b; Cao et al., 2013; Sivak, 2013; Zhao et al., 2014). Indeed both the progressively deposited senile plaques of AD and the drusen of AMD contain high concentrations of Aβ42 monomers, dimers, and oligomers aggregated at their cores (Alexandrov et al., 2011; Ohno-Matsui, 2011; Lukiw et al., 2012a,b; Sivak, 2013; Zhao et al., 2014). One recent study reported Aβ42 peptides accumulating up to 9-fold and greater over controls in the retina of advanced AD patients, and Aβ42 peptides were found to be increased ~19-fold or greater over controls in the retinas of aging Tg2576 mice (a transgenic amyloid over-expressing murine model of AD; TgAD), and a remarkable 53-fold or more over controls in the retina of the advanced 5xFAD murine TgAD model (Lukiw et al., 2012b; Zhao et al., 2014). From these and other data it is clear that as AD or AMD initiates and progresses, Aβ42 peptides and pro-inflammatory markers (such as COX-2) sequentially populate the hippocampus and neocortex, the primary visual cortex and then the retina. This is further supported by the temporal pattern of progressive Aβ42 peptide deposition in TgAD models as their phenotype develops (Lukiw et al., 2012b; Tzekov and Mullan, 2014). Interestingly, the degree of visual problems reported by AD patients has a strong correlation with the degree of Aβ42 and related amyloidogenic and pro-inflammatory markers in the primary visual cortex when short post-mortem interval brains are examined for the expression of genes involved in inflammatory neurodegeneration. The magnitude of these defects appear to mirror the temporal sequence of declining cognitive status in the AD patients, especially in late-onset AD cases with more rapid progression and in aged AD patients (Jellinger and Bancher, 1998; Thompson et al., 2003; Wilson et al., 2006; Cui et al., 2007; Tzekov and Mullan, 2014; unpublished observations). Again, these findings suggest a progressive and propagating component of AD neuropathology that extends well beyond the anatomical centers of the brain where AD originates.

**microRNA AND AD PROPAGATION**

One hundred and eight years of AD research has revealed that despite an entorhinal/neocortical origin for AD in the hippocampal CA1 and/or the superior temporal lobe (Brodman area A22), AD neuropathology eventually spreads insidiously into the frontal, parietal and occipital lobes including the primary visual cortex, and then to other susceptible, anatomically-connected regions of the CNS including the retina (Alzheimer et al., 1995; Zhao et al., 2006; Cui et al., 2007; Zhao et al., 2014). The mechanism for this spreading is not well-understood, but the translocation of soluble pathogenic factors including small nucleic acids between human brain cells, and between neural cells and the cerebrospinal fluid have been reported (Zhao et al., 2006; Pogue et al., 2014). The finding that the abundance and complexity of intraneural miRNAs are often contiguous with the extracellular fluid (ECF), and that the ECF and cerebrospinal fluid (CSF) contain many of the same pathogenic miRNAs, such as the inducible, NF-kB-regulated pro-inflammatory microRNAs miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155, suggests that these soluble, degeneration-associated single stranded RNAs are capable of translocating throughout the circulating fluids of the CNS and perhaps into the blood serum. It is our opinion that besides their obvious diagnostic value, pharmacological approaches aimed at down-regulating overly abundant, pathogenic miRNAs by using anti-miRNA strategies may ultimately have application in the clinical management of AD and AMD, and perhaps other diseases with an amyloidogenic and pro-inflammatory component (Cui et al., 2010; Alexandrov et al., 2011; Zhao et al., 2014).

**CONCLUDING REMARKS**

In summary, a picture is emerging of the evolution of the AD phenotype as an advancing, spreading or “propagating” amyloidogenic and pro-inflammatory, ultimately fatal, CNS dysfunction eventually manifesting as a more globalized disorder than previously appreciated, involving the brain’s limbic system, primary visual cortex and eventually the sensory retinal systems, especially in the later stages of AD. It still remains unclear whether AD neuropathology evolves independently in the limbic system, primary visual cortex and retina, but current findings suggest that there is a “continuity” or “spreading” of the pathology from the limbic system to the entorhinal-cortex-visual cortex-retinal circuit. The cellular
linkage of the hippocampal CA1 to the primary visual cortex, from the primary visual cortex to the thalamus, and from the thalamus to the retinal ganglion can involve as few as three neurons and their processes, although many more different types of neurons and complex circuitries in the retinal-primary visual cortex connectome have recently become apparent that are required for homeostatic visual processing (Cui et al., 2007; Masland, 2013; Dehabadi et al., 2014). The common neuroectodermal origins of the neocortex and retina may predispose these highly integrated, multi-neuronal layered structures to AD-type dysfunction, including the involvement of shared pathogenic pathways that drive amyloidogenesis and pro-inflammatory neurodegeneration. Importantly, the retina is the only component of the CNS that can be visualized directly and non-invasively. We propose that rigorous retinal examination including electrocoagulography, high resolution retinal imaging, ophthalmoscopy, optical coherence tomography (OCT) analyzing retinal nerve fiber layer (RNFL) thinning and other parameters, visual evoked potential (VEP) analysis, or combinations of these and other advanced techniques may have considerable value in the estimation and diagnosis of early AD-type change. It is our opinion that the integration of the data obtained from these multiple non-invasive techniques of the retina at various stages of AD may be of useful diagnostic value as they should be reflective of the structural and functional pathologies originating in deeper structures of the AD brain (Koch et al., 2006; Kesler et al., 2011; Vaney et al., 2012; Moreno-Ramos et al., 2013; Chang et al., 2014; Dehabadi et al., 2014; Tzekov and Mullan, 2014).

ACKNOWLEDGMENTS

This research was presented in part at the Society for Neuroscience (SFN) Annual Meeting, San Diego CA, USA, 9–13 November 2013 and at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Orlando FL, USA, 4–8 May 2014. Thanks are extended to Drs. Y. Zhao and S. Bhattacharjee for helpful discussions and to Aileen Pogue and Darlene Guillot for expert technical assistance. Research in the Lukivi laboratory on the innate-immune response, amyloidogenesis, and neuroinflammation in AD, retinal, and prion disease, was supported through Research to Prevent Blindness (RPB) and NIH grants NEI EY006311 and NIA AG038834.

REFERENCES

Alexandrov, P. N., Pogue, A. I., Bhattacharjee, S., and Lukivi, W. J. (2011). Retinal amyloid peptides and complement factor H in transgenic models of Alzheimer’s disease. Neuroreport 22, 623–627. doi: 10.1097/WNR.0b013e32834f7334

Alzheimer, A., Stelzemann, R. A., Schnitzlein, H. N., and Murtagh, F. R. (1995). An English translation of Alzheimer’s 1907 paper, “Ueber eine eigenartige Erkrankung der Hirnrinde.” Clin. Anat. 8, 429–431. doi: 10.1002/ca.98080612

Bazan, N. G., and Lukivi, W. J. (2002). Cycloxygenase-2 and presenilin-1 gene expression induced by interleukin-1beta and amyloid beta 42 peptide is potentiated by hypoxia in primary human neural cells. J. Biol. Chem. 277, 30359–30367. doi: 10.1074/jbc.M203201200

Cao, L., Wang, H., Wang, F., Xu, D., Liu, E., and Liu, C. (2013). Aβ-induced senescent retinal pigment epithelial cells create a pro-inflammatory microenvironment in AMD. Invest. Ophthalmol. Vis. Sci. 54, 3735–3750. doi: 10.1167/iovs.13-11612

Chang, L. Y., Lowe, J., Ardiles, A., Lim, J., Grey, A. C., Robertson, K., et al. (2014). Alzheimer’s disease in the human eye. Clinical tests that identify ocular and visual information processing deficits as biomarkers. Alzheimers Dement. 10, 251–261. doi: 10.1016/j.jalz.2013.06.004

Colangelo, V., Schurr, J., Ball, M. J., Pelaez, R. P., Bazan, N. G., and Lukivi, W. J. (2002). Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. J. Neurosci. Res. 70, 462–473. doi: 10.1002/jnr.10351

Cudaback, E., Jorstad, N. L., Yang, Y., Montine, T. J., and Keene, C. D. (2014). Therapeutic implication of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-kappaB in stressed human astroglial cells and in Alzheimer disease. J. Biol. Chem. 285, 38951–38960. doi: 10.1074/jbc.M110.178848

Dehabadi, M. H., Davis, B. M., Wong, T. K., and Cordeiro, M. F. (2014). Retinal manifestations of Alzheimer’s disease. Neurodegener. Dis. Manag. 4, 241–252. doi: 10.2217/nmd.14.7

Dinten, V., Bruhan, J., Chaloult, N., Maoui, A., An, N., Jonet, L., et al. (2013). Distinct effects of inflammation on gliosis, osmohomeostasis, and vascular integrity during amyloid beta-induced retinal degeneration. Aging Cell 11, 683–693. doi: 10.1111/ajc.12201

Fang, I. M., Yang, C. H., Yang, C. M., and Chen, M. S. (2009). Comparative effects of fatty acids on pro-inflammatory gene cyclooxygenase 2 and inducible nitric oxide synthase expression in retinal pigment epithelial cells. Mol. Nutr. Food Res. 53, 739–50. doi: 10.1002/mnfr.200800220

Ginsberg, S. D., Alldred, M. J., and Che, S. (2012). Gene expression levels assessed by CA1 pyramidal neuronal and regional hippocampal dissections in Alzheimer’s disease. Neurobiol. Dis. 45, 99–107. doi: 10.1016/j.nbd.2011.07.013

Hardy, J., Bogdanovic, N., Winblad, B., Portelius, E., Andreassen, N., Cedazo-Minguez, A., et al. (2014). Pathways to Alzheimer’s disease. J. Intern. Med. 275, 296–303. doi: 10.1111/j.1365-2958.2012.12192

Hoozemans, J. J., Rozemuller, J. M., van Haastert, E. S., Veerhuis, R., and Eikelenboom, P. (2008). Cyclooxygenase-1 and -2 in the different stages of Alzheimer’s disease pathology. Curr. Pharm. Des. 14, 1419–1427. doi: 10.2174/138161208784408171

Jellinger, K. A., and Bancher, C. (1998). Neuropathology of Alzheimer’s disease: a critical update. J. Neural Transm. Suppl. 54, 77–95. doi: 10.1007/978-3-7091-7508-8_8

Kesler, A., Vakhashova, V., Korczyn, A. D., Naftaliev, E., and Neudorfer, M. (2011). Retinal thickness in patients with mild cognitive impairment and Alzheimer’s disease. Clin. Neuro Neurosurg. 113, 523–526. doi: 10.1016/j.clineuro.2011.02.014

Kikuchi, M., Ogishima, S., Miyamoto, T., Miyashita, A., Kuwano, R., Nakaya, J., et al. (2013). Identification of unstable network modules reveals disease modules associated with the progression of Alzheimer’s disease. PLoS ONE 8:e76162. doi: 10.1371/journal.pone.0076162

Koch, K., McLean, J., Segev, R., Freed, M. A., Berry, M. J. 2nd., Balasubramanian, V., et al. (2006). How much the eye tells the brain. Curr. Biol. 16, 1428–1434. doi: 10.1016/j.cub.2006.05.056

Kruck, T. P., Percy, M. E., and Lukivi, W. J. (2008). Metal sulfate-mediated induction of pathogenic genes and repression by phenyl butyl nitrite and Feralex-G. Neuroreport 19, 245–249. doi: 10.1097/WNR.0b013e3282fcd57e

Lukivi, W. J., and Bazan, N. G. (1998). Strong NF-KB-DNA binding parallels cyclooxygenase-2 gene transcription in aging and in sporadic Alzheimer’s disease superior temporal lobe neocortex. J. Neurosci. Res. 53, 583–592.

Lukivi, W. J., Bhattacharjee, S., Zhao, Y., Pogue, A. I., and Percy, M. E. (2012b). Generation of reactive oxygen species (ROS) and pro-inflammatory signaling in human brain cells in primary culture. J. Alzheimer’s Dis Parkinsonism (Suppl. 2):001. doi: 10.4172/2167-0460.S2-001

Lukivi, W. J., Suriyaditpa, B., Dua, P., and Alexandrov, P. N. (2012a). Common microRNAs target complement factor H regulation in Alzheimer’s disease (AD) and in age-related macular...
degeneration (AMD). *Int. J. Biochem. Mol. Biol.* 3, 105–116.

Lukiw, W. J. (2004). Gene expression profiling in fetal, aged, and Alzheimer hippocampus: a continuum of stress-related signaling. *Neurochem. Res.* 29, 1287–1297. doi: 10.1023/B:NERE.0000023615.89699.63

Masland, R. H. (2013). Neuroscience: accurate maps of visual circuitry. *Nature* 500, 154–155. doi: 10.1038/500154a

Moreno-Ramos, T., Benito-Leon, J., Villarejo, A., and Bermejo-Pareja, F. (2013). Retinal nerve fiber layer thinning in dementia with lewy bodies, and Alzheimer’s disease. *J. Alzheimers Dis.* 34, 659–664. doi: 10.3233/JAD-121975

Ohno-Matsui, K. (2011). Parallel findings in age-related macular degeneration and Alzheimer’s disease. *Prog. Retin. Eye Res.* 30, 217–238. doi: 10.1016/j.preteyeres.2011.02.004

Pogue, A. I., Hill, J. M., and Lukiw, W. J. (2014). MicroRNA (miRNA): sequence and stability, viroid-like properties, and disease association in the CNS. *Brain Res.* 1584, 73–79. doi: 10.1016/j.brainres.2014.03.042

Rodríguez Diez, G., Sánchez Campos, S., Giusto, N. M., and Salvador, G. A. (2013). Specific roles for Group V secretory PLA2 in retinal iron-induced oxidative stress. Implications for age-related macular degeneration. *Exp. Eye Res.* 113, 172–181. doi: 10.1016/j.exer.2013.05.019

Sivak, J. M. (2013). The aging eye: common degenerative mechanisms between the Alzheimer’s brain and retinal disease. *Invest. Ophthalmol. Vis. Sci.* 54, 871–880. doi: 10.1167/iovs.12-10827

Wu, M. J., and Wan, J. Y. (2010). COX-3: is it the target of acetaminophen? *Sheng Li Ke Xue Jin Zhan* 41, 40–42.

Yang, H., and Chen, C. (2008). Cyclooxygenase-2 in synaptic signaling. *Curr. Pharm. Des.* 14, 1443–1451. doi: 10.2174/138161208784480144

Zhao, Y., Bhattacharjee, S., Jones, B. M., Hill, J. M., Clement, C., Sambamurti, K., et al. (2014). Beta-amyloid precursor protein (BAPP) processing in Alzheimer’s disease (AD) and age-related macular degeneration (AMD). *Mol. Neurobiol.* [Epub ahead of print].

Zhao, Y., Cui, J. G., and Lukiw, W. J. (2006). Natural secretory products of human neural and microvessel endothelial cells: implications in pathogenic “spreading” and Alzheimer’s disease. *Mol. Neurobiol.* 34, 181–192. doi: 10.1385/MN:34:3:181

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 08 August 2014; paper pending published: 15 September 2014; accepted: 11 October 2014; published online: 12 November 2014.

Citation: Hill JM, Dua P, Clement C and Lukiw WJ (2014) An evaluation of progressive amyloidogenic and pro-inflammatory change in the primary visual cortex and retina in Alzheimer’s disease (AD). *Front. Neurosci.* 8:347. doi: 10.3389/fnins.2014.00347

This article was submitted to Neurodegeneration, a section of the journal *Frontiers in Neuroscience*. Copyright © 2014 Hill, Dua, Clement and Lukiw. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.