Manuscript Type: Commentary

Retinal Focus on Relationships between Diet-Induced, Advanced Glycation End Products and Supplemental Estradiol

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Received: 3 December 2024; Accepted: DMY; Published: DMY

ABSTRACT

Neurodegeneration of retinal tissue leads to progressive vision loss in millions of working age adults each year. Metabolic alterations caused by modern diets that are high in fats and sugars contribute to development of diabetic retinopathy. Chronic, diet-induced metabolic changes are linked to, both, high glucose and harmful, pro-inflammatory compounds in the blood, called advanced glycation end products (AGEs), that can alter the integrity of neurovascular barriers. AGEs-induced changes to the permeability of the inner blood retinal barrier can lead to progressive vision loss with disparate impacts in patients with low estrogen, such as via natural aging processes, chronic illness, or aggressive medical interventions. Application of supplemental estradiol has been shown to ameliorate degeneration across the cardiovascular, intestinal, and nervous systems. This commentary describes potential benefits of estradiol-based therapies on the visual health of older women with progressive diabetic retinopathy.

Diet-Induced Neuroinflammation

Degenerative vision loss is an escalating global challenge as millions of adults will lose their sight with aging due to retinal disease, such as age-related macular degeneration, glaucoma, and diabetic retinopathy [1,2]. A dramatic rise in progressive vision loss from diabetic retinopathy is driven by rising incidence of Type II diabetes mellitus (T2DM), associated with metabolic alterations from the excess intake of calories [3,4]. Modern day ultra-processed foods, high in fats and sugars, can also stimulate neuroinflammation via altered balance of intestinal microbiota leading to the elevated neuronal metabolism [5], and persistently activated inflammatory signaling pathways [6]. The contributing mechanisms to these chronic, diet-induced metabolic changes are linked to the accumulation of harmful, pro-inflammatory compounds in the blood, called advanced glycation end products (AGEs). Many AGEs are produced from the Maillard reaction, which is the browning process during cooking or baking to enhance the color and taste of food. Alarmingly, AGEs can alter protein structure and function and work in concert with high blood glucose to promote inflammatory signaling and neurodegeneration [7]. Moreover, non-nutritive additives used extensively in the global food supply chain, such as anti-microbials, synthetic preservatives, and artificial sweeteners [8], bind to ingested proteins, adhere onto the extracellular matrix, and interact with surface receptors to create inclusion complexes that impact ocular outcomes [9]. As a result, research into the metabolic and neural impact of diet compositions and non-nutritive additives has been at the forefront of nutritional neuroscience, as shown in **Fig. 1**.

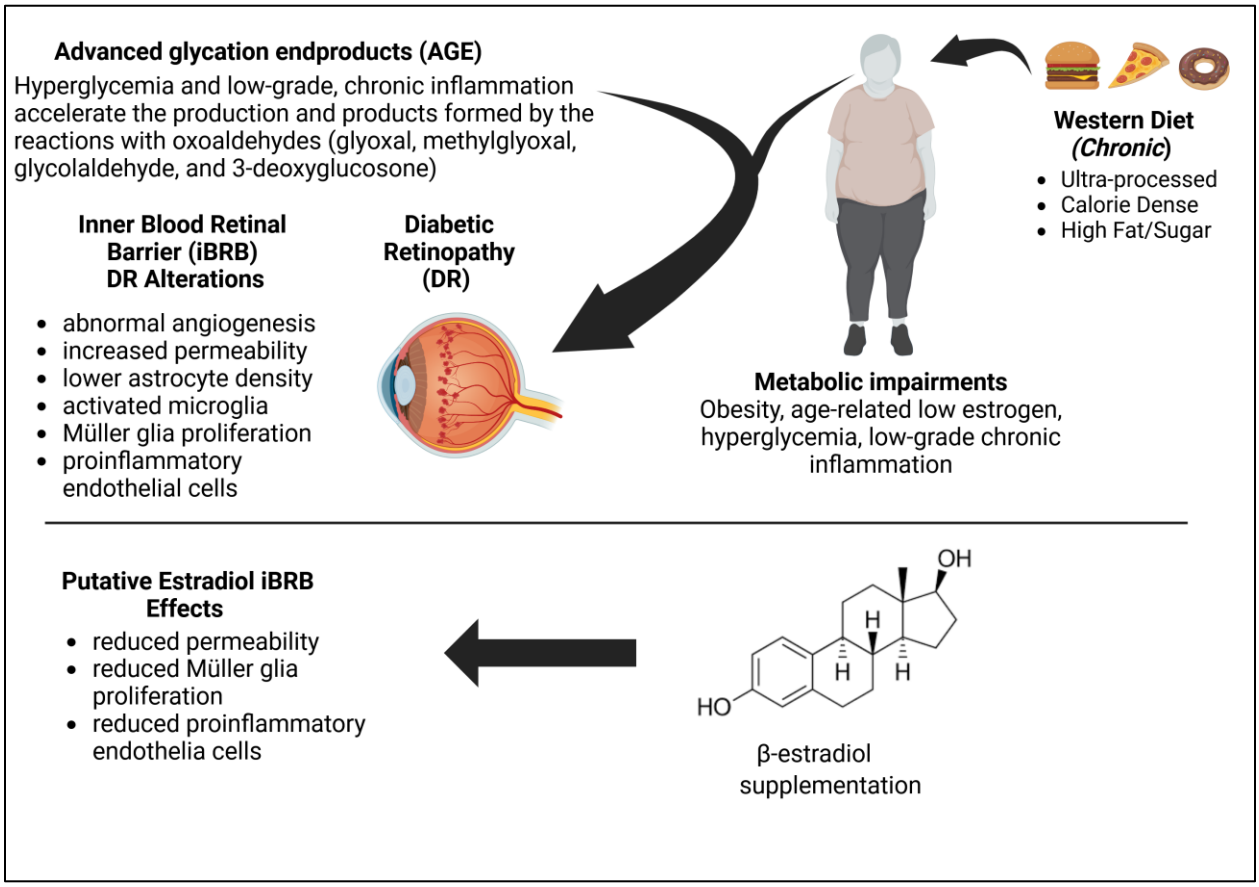

Figure 1: Schematic description of the impacts of diet-based, advanced glycation end products (AGEs) on inflammatory pathways, metabolic alterations, and the inner blood retinal barrier (iBRB).

Neurovascular Barriers

Inflammation-induced changes can be critical for influencing the permeability of neurovascular barriers, such as the blood brain barrier (BBB) and inner blood retinal barrier (iBRB), that regulate transport from circulating blood. Indeed, inflammatory-induced vascular changes can impede clearance of metabolic waste allowing harmful, blood borne molecules and cells to enter the brain. *In vivo* study of high fat diets has implicated excess consumption with cognitive decline, which is due, in part, to insulin resistance (Reviewed in [10]). In line with these findings, our group has reported high fat diet-induced changes in rodent sensorimotor gating of the acoustic startle

response [11] that reflects similar data gathered from non-human primates and clinical patients with neurovascular disorders of the prefrontal and visual cortex [12,13]. Analogous alterations can be involved in the diet-induced, metabolic changes associated with other vascular barriers. The iBRB of the eye is a vision-critical, semi-permeable membrane that regulates transport of molecules and ions between retinal capillaries and the neuroretina. The iBRB is comprised of endothelial cells and pericytes, alongside Muller glia and astrocytes that communicate via junctional, gap, and adhesion proteins, among others (**Fig. 2**). Molecules, such as zonula occludens, facilitate formation of monolayer barriers of endothelial cells to provide resistance to the transport of harmful compounds from circulating blood to neural tissue. Endothelial cells respond collectively with neuroglia in barrier tissues, as these retinal cells are key regulators of oxygen, toxins, and nutrients needed to support neuronal synapse for vision [14, 15]. Neuroglia, thereby, exhibit bi-directional communication with endothelial cells via gap junctions as well as with one another through gliotransmitters, such as glutamate [16]. AGEs are well-known to cause pericyte death and stimulate astrogliosis in patients with chronic, diabetic retinopathy [17], indicating that collective response from barrier cells are significant but understudied components of emerging therapies.

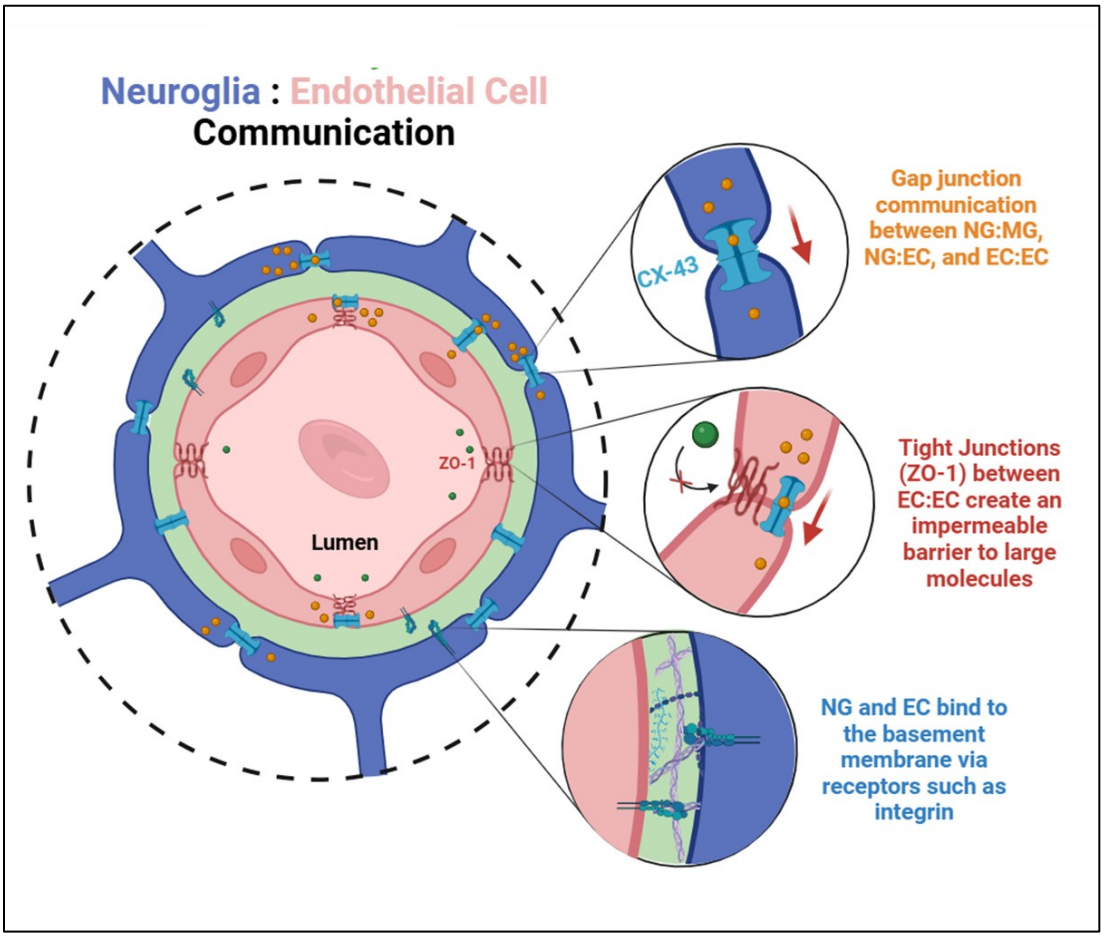

Figure 2: Structure of the inner blood retinal barrier (iBRB) and communication between endothelial cells (ECs) and neuroglia (NG). The inner blood retinal barrier is comprised of endothelial cells that line the inner lumen of retinal capillaries, pericytes that wrap around the capillaries, and neuroglia of the retina that communicate via synapse with retinal neurons to facilitate vision [with permission from 15] These cell types form a dynamic tissue barrier and collectively communicate with one another across a basement membrane comprised largely of collagen IV and laminin. Neuroglia cells primarily communicate with each other, and with endothelial cells, via gap junctions formed by connexin 43 (CX-43) proteins, to enable the passage of small molecules via juxtracrine communication. In complement, endothelial cells form tight junctions, most notably zonula occludens-1 (ZO-1), that selectively regulate transcellular transport across the cell barrier. When the integrity of the iBRB is comprised, higher permeability across the vascular wall leads to unregulated molecular transport of water, toxins, and cytokines that disrupt cell signaling and lead to the dysfunction and eventual death of retinal neurons.

Estrogen as a Retinal Neuroprotectant

A growing body of evidence demonstrates that estrogen decline during natural aging processes or medically treated conditions drives a systemic inflammatory state [18]. This low-grade chronic inflammation can compromise the iBRB to make the retina more susceptible to neurodegenerative disease [19]. Clinical data illustrate that women are less disposed to effects of neurodegeneration before menopause transition [20], suggesting that rising, worldwide incidence in women as they age may be related to decreasing levels of circulating estrogen. The neuroprotective effects of beta-estradiol in the nervous system are well-established, including major anti-inflammatory effects on microglia. Estrogen also facilitates higher cognitive functions by inducing spinogenesis and synaptogenesis in the visual cortex and hippocampus [21], which play important roles in vision and learning. Moreover, supplemental estrogen improves memory and reduces accumulation of amyloid-beta prodromal to Alzheimer's disease in female mice after ovariectomy [20].

Estrogen receptors are present on endothelial, pericyte, and neuroglial cells of the iBRB, where recent studies suggest that hormonal imbalance may serve as global markers for inflammation and metabolic syndromes that impact neurovascular outcomes [22]. Moreover, activated receptors are shown to prevent oxidative stress and stimulate production of neurotrophic factors that attenuate retinal degeneration. Recent work from our own group illustrates that supplemental estradiol was able to increase resistivity of cell barriers formed by, both, endothelial and neuroglial cells of the iBRB [23] by impacting gap and tight junctional communication [15].

Significant biological sex-based, health disparities have been recorded in vision loss [24], where women experience disparate impacts and poorer outcomes of retinal disease as they grow into mature adulthood. Globally, women over the age of 55 endure progressive vision loss from diabetic retinopathy at higher rates than their male counterparts. The combination of lifelong AGEs consumption in the form of ultra processed foods and lowered estrogen may produce low-grade chronic inflammation in aging women that fuels retinal degeneration. Our group has developed micro-physiological systems that model molecular transport across retinal tissue and demonstrate that increased concentrations of AGEs elevate production of cell reactive oxidation species, altered cell morphology, and increased formation of blood clots in retinal vascular barriers [25]. Our recent studies have used endothelial-glial bilayers to illustrate that increased AGEs reduce glia-to-glia

and glia-to-endothelial cell communication via decreased expression of the critical proteins connexin 43 (Cx43) and cluster of differentiation 40 (CD40) [15]. Moreover, as patients with diabetic retinopathy are frequently treated with anti-VEGF pharmacotherapies to reduce ocular angiogenesis (e.g., Avastin and Eylea), we tested the effects of anti-VEGF on the resistivity of bilayers of iBRB cells. Our results showed that bilayers of endothelial and glial cells cultured long-term in high glucose and AGEs exhibited greater barrier resistivity (measured via Trans-Endothelial Electrical Resistance, or TEER) after treatment with anti-VEGF than did respective bilayers cultured in normoglycemic medium [15]; suggesting an underexplored method of action for anti-VEGF. Surprisingly, effects of AGEs in all studies were attenuated with supplemental estradiol [23], highlighting understudied molecular relationships between hormones and cells of barrier tissue that are significant to aging as well as to women's health.

Conclusion

In summary, accruing evidence illustrates that supplemental estradiol may have neuroprotective effects throughout aging, such as during menopause transition and chronic illness or treatment. Multiple recent studies suggest direct positive benefits of estradiol in combination with accumulating levels of AGEs consumed in modern high fat diets. These understudied relationships are critical to emerging therapies for women's health as AGEs impact the collective cell behavior of neurovascular barriers and could adversely influence the transport of non-nutritive additives and pharmaceuticals agents across the BBB and iBRB.

Acknowledgement: Not applicable

Funding Statement: This research was funded by a Life Sciences Alliance Pilot Seed Grant from the Rutgers–New Brunswick Office of the Vice Provost for Research, Grant Number OVPR-100 (MV), https://newbrunswick.rutgers.edu/provost/research/life-sciences-alliance.

Author Contributions:

The authors confirm contribution to the paper as follows: Conceptualization, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez; ; investigation, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez; resources, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez; writing—original draft preparation, Maribel Vazquez; writing—review and editing, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez; ; visualization, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez; funding acquisition, Nicholas Bello, Bonnie Firestein, and Maribel Vazquez ; All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: "Not applicable." (This article does not involve data availability, and this section is not applicable).

Ethics Approval: Not Applicable.

Conflicts of Interest: The authors declare no conflicts of interest regarding the present study.

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