Is Glaucoma a Neurodegeneration caused by Central Insulin Resistance: Diabetes Type 4?

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How to cite this article: Dada T. Is Glaucoma a Neurodegeneration caused by Central Insulin Resistance: Diabetes Type 4? J Curr Glaucoma Pract 2017;11(3):77-79.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Glaucoma is an acquired multifactorial progressive neurodegenerative syndrome with complex pathogenesis. It is characterized by accelerated retinal ganglion cell (RGC) apoptosis and leads to optic neuropathy with visual field defects, the intraocular pressure (IOP) being a major risk factor. The only therapy currently available is lowering of IOP with medical/laser/surgical therapy; however, many patients continue to progress despite an adequately controlled or apparently “normal” IOP. Recent studies have shown that glaucoma patients have central neurodegeneration involving both the occipital cortex and lateral geniculate body (LGB).1,2 It has been postulated that glaucoma may be a disease initially affecting the central nervous system (CNS) and traveling downstream to the optic nerve and RGCs. Our group recently proposed a novel theory for glaucoma—the brain diabetes theory (describing glaucoma as diabetes type 4).3,4 This theory explains that glaucoma is a CNS condition involving brain insulin resistance or central insulin signaling dysfunction, which leads to transsynaptic neurodegeneration. This proposal has given rise to a new holistic theory for primary open angle glaucoma (POAG)/normal pressure glaucoma and raised the possibility of the development of therapeutic approaches targeting the brain rather than the eye.

Diabetes types I and II are insulin hypofunctionality-mediated systemic syndromes accompanied by hypoinsulinemia (type I) or insulin resistance (type II). But the existence of brain-specific diabetes independent of peripheral diabetes and manifesting as neurodegeneration has been previously reported as diabetes type III—Alzheimer’s disease (AD)5 and recently as diabetes type 4—glaucoma.4

THE ROLE OF INSULIN IN THE BRAIN AND THE EYE

Insulin/insulin signaling is important for neuronal survival, in general,6 and RGC survival, in particular.7 Insulin is present in the brain in very high (10–100 times the level in plasma) quantities,8 indicating local production and its important role in cerebral functions. Additionally, insulin is important in trabecular meshwork (TM) maintenance and aqueous outflow regulation, thereby playing a role in maintenance of IOP. Ameliorating defects in insulin signaling is, therefore, an important therapeutic target to consider for glaucoma therapy.

- Insulin has been found to be important in the production of nitric oxide (NO) by TM cells mediated through de novo synthesis of tetrahydrobiopterin. The NO is important in aqueous outflow regulation and has been reported to increase outflow9-11 and, hence, decrease the IOP. This means insulin resistance may cause elevation in IOP leading to ocular hypertension and POAG, and insulin-based therapy may have role to play in lowering IOP through enhancement of aqueous outflow.
- Mitochondrial dysfunction leading to oxidative stress lies at the center stage of glaucomatous damage and insulin is required for healthy functioning of the mitochondria. An increase in IOP leads to mitochondrial dysfunction,12 and this, in turn, leads to aberrant insulin signaling, which creates a vicious self-perpetuating cycle13 with serious damage to mitochondrial functions and an increase in oxidative injury to RGCs. Elevated IOP also leads to mitochondrial fission and optic nerve head cupping mediated by release of OPA1, an important gene involved in various forms of optic neuropathy14 including optic nerve head atrophy.15
- Insulin induces the expression of GLUT4 in the RGC layer of retina,16 thereby enhancing RGC survival. Insulin deprivation or resistance can, therefore, lead to impaired RGC function and trigger apoptosis and cell death. This can occur independent of any increase in IOP. Since RGC layer of retina is metabolically highly active, its activity and cellular viability...
Insulin plays a key role in the Central Nervous System, Optic nerve head and Retinal Ganglion Cells (RGC)

Insulin is required for Neuronal and RGC survival and normal Mitochondrial function

Insulin has anti-apoptotic and anti-inflammatory activity &

Inhibits Glial activation, Glutamate excitotoxicity & Oxidative stress

Insulin also plays a role in aqueous outflow (via Nitric Oxide) and aberrant insulin signalling in RGCs and their axons can be triggered by a rise in IOP with consequent RGC apoptosis, optic nerve head damage and trans-synaptic CNS degeneration

An IOP independent primary CNS neurodegeneration in the Occipital cortex and Lateral Geniculate body descending to the optic nerve-RGCs, can also be a consequence of central insulin resistance with accumulation of Amyloid beta, Tau and Amyloid Angiopathy – hallmarks of neurodegeneration

Neurodegeneration in the CNS, Optic Nerve and RGCs can be initiated and sustained by an Aberrant Insulin state

Diabetes Type 4

Fig. 1: Role of insulin resistance in glaucoma

Insulin resistance leads to accumulation of amyloid beta (Aβ) in the CNS (Alzheimer’s) and ocular tissues (RGC, occipital cortex). Increased deposition of Aβ-plaques has been observed in retinas of glaucoma patients and associated with an increase in RGC apoptosis. Another pathological change observed in human visual cortex due to accumulation of amyloid is cerebral amyloid angiopathy leading to vascular dysregulation and ischemia. Enhancing insulin function may help in preventing plaque deposition and preserving RGC function.

In summary, the central insulin resistance theory (Fig. 1) explains how insulin dysfunction can specifically cause both forms of glaucoma (high pressure and normal pressure) by afflicting outflow pathways via TM, vascular changes (amyloid angiopathy), and trigger glial activation, central neuronal degeneration, and RGC apoptosis through various molecular pathways. Therefore, aberrant insulin signaling in the CNS and specifically visual pathways (RGC–optic nerve–LGB–occipital cortex) appears to be a cause for glaucoma. Central insulin functional enhancement by giving intranasal insulin therapy may help to lower IOP, enhance blood flow, and ameliorate injury to RGCs, preventing RGC apoptosis by positively modulating several cellular pathways like glial activation, glutamate excitotoxicity, ameliorating amyloidopathy/taupathy, and decreasing mitochondrial dysfunction.

ACKNOWLEDGMENT
The author would like to thank Dr Muneeb A Faiq for the help and kind support.
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