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Leptin as a neuroprotective agent in glaucoma

Ankur Gupta *

Royal Derby Hospital, Uttoxeter Road, Derby, UK

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ABSTRACT

Glaucoma is a disease characterized by progressive optic nerve degeneration and is the leading cause of irreversible blindness worldwide. More than 60 million people globally are affected by glaucoma, of which 8 million people suffer from bilateral blindness, making glaucoma the second leading cause of bilateral blindness worldwide. Current management of glaucoma is aimed at reducing intraocular pressure via a number of different strategies. Current treatments do not attempt to correct the underlying pathology of glaucoma, which is the cell degeneration and ultimate death of retinal ganglion cells, thereby limiting their clinical efficacy.

A neuroprotective approach to glaucoma management would address the underlying pathology and would, in theory, be beneficial to all patients regardless of risk and causative factors. Here it is proposed that leptin could be used as a potential neuroprotective agent in the management of glaucoma. Leptin has shown neuroprotective promise in a number of neurodegenerative diseases, and there has been increasing evidence that glaucomatous neurodegeneration is analogous to other neurodegenerative diseases in the central nervous system. Leptin could target retinal ganglion cell death by a number of mechanisms, namely apoptosis, oxidative stress and excitotoxicity reduction. This article presents evidence linking current understanding about leptin's neuroprotective effect and the molecular mechanisms underlying glaucoma.

Glaucoma

Glaucoma is characterized by progressive optic nerve degeneration and is the leading cause of irreversible blindness worldwide. More than 60 million people around the world are affected by glaucoma, and it has been estimated that 8 million suffer from bilateral blindness caused by this disease, making it the second leading cause of bilateral blindness worldwide [1,2].

The pathophysiological feature of glaucoma is the degeneration and gradual loss of retinal ganglion cells (RGC) [3]. RGC death by apoptosis has been detected in human glaucomatous eyes [4], in human optic neuropathy [5] and in animal models of glaucoma and optic nerve injury [6–11]. These neurons link the retina to the optic nerve. It is the loss of this neuronal function that allows glaucoma to be considered alongside other neurodegenerative diseases such as Alzheimer's and Parkinson's disease [12]. Cell death mechanisms in these neurodegenerative diseases have shown great similarity with that of glaucoma [13–16].

Leptin

Leptin, and the human obese (OB) gene that it comes from, were discovered and characterised in 1994 [17]. It is primarily synthesized in adipose tissue and subsequently transported to the brain via the blood brain barrier [18,19]. Initially its only known function was to inhibit the arcuate nucleus in the hypothalamus – in feeding and homeostatic energy control. However in recent years other varying roles for leptin have been elucidated in: reproduction [20], thermogenesis [21], synaptic plasticity [22], glucose homeostasis [23,24], bone formation [25,26], tissue remodelling [27] and inflammation [28], as well as in other elements of the endocrine [29,30], immune systems [31] and neuroprotective activity in a number of brain regions [32–34].

Hypothesis

Leptin is proposed as a potential neuroprotective agent in the clinical management of glaucoma. Leptin has shown promise as a neuroprotective agent in a number of other neuronal disorders such as Parkinson's Disease, Alzheimer's Disease, ischaemic stroke and epilepsy [32,33,35–38].

Leptin neuroprotection in glaucoma

There are a number of proposed mechanisms for the neurodegeneration of retinal ganglion cells typical in glaucoma [3]. Leptin acts on a number of these pathways [38] and this forms the basis of the hypothesis for leptin as a neuroprotective agent in glaucoma management. Neuroprotection specifically refers to a strategy which protect neurons from apoptosis or degeneration. As the

* Corresponding author. Tel.: +44 07946835759.
E-mail addresses: ankur.gupta1@nhs.net, a.gupta98@gmail.com

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RGCs are the primary cell involved in glaucoma, this paper will focus on the potential neuroprotective effects of leptin on these cells.

Attenuating RGC cell death seems a logical step in the management of glaucoma. A neuroprotective strategy would hypothetically benefit all sufferers, regardless of the pathophysiology of RGC degeneration or risk factors present. Factors implicated in RGC death in glaucoma include elevated intra-ocular pressure (IOP), decreased neurotrophin support, glutamate-associated excitotoxicity, hypoperfusion and vasospasm [39,40]. These risk factors, amongst others, would affect the degree of benefit leptin could potentially bestow. A neuroprotective approach will tackle the underlying pathology. This is something current glaucoma management strategies do not address. There are no neuroprotective strategies against glaucoma available for use in the clinic today. The mainstay of current glaucoma management is lowering the intraocular pressure via medication, laser treatments or surgery. In combination with current therapies, leptin treatment could potentially enhance the clinical management of glaucoma.

Leptin receptors have been labelled on radially orientated RGC axons [41]. Leptin receptors have also been identified in the neovascular tufts within the retinal ganglion cell layer [42], as well as in the retinal pigment epithelium [43]. However, detailed data on the subtype representation of leptin receptors in RGCs remains limited.

Mechanisms by which leptin could act as a neuroprotective agent in glaucoma

There are multiple mechanisms by which RGCs die in glaucoma. Apoptosis, oxidative stress and excitotoxic damage are the mechanisms pertinent to this hypothesis. I will provide a very brief overviews of these mechanisms prior to an explanation of how leptin could act on these pathways to act as a neuroprotective agent in glaucoma.

RGCs have been shown to die by apoptosis in a number of studies, via both the intrinsic and extrinsic apoptotic pathways [12,41–48]. In very basic terms the intrinsic pathway involves non-receptor–mediated intracellular signals, inducing activities in the mitochondria that initiate apoptosis [49]. Multiple stimuli, such as cell stress, activate the intrinsic pathway of apoptosis. Numerous molecules convey this signal to the apoptotic machinery, for example JNKs – which are a form of stress activated protein kinases (SAPKs) [50], which has been studied in glaucoma [51]. Other pro-apoptotic molecules include Bcl-2-associated death promoter (BAD) [52] and Bim-EL [53]. These stimuli induce changes in the inner mitochondrial membrane that result in the loss of transmembrane potential, which ultimately leads to the release of pro-apoptotic molecules (namely cytochrome c) into the intracellular fluid [49,54] activating the apoptosis cascade via the activation of a variety of caspases, including caspase 9 and 3 [49]. The extrinsic pathway of apoptosis involves a number of 'death-receptor' ligands binding to cell surface receptors to induce cell death via in the induction of caspases, including caspase 8 and 3 [49,54–56]. This pathway has been shown to be involved in glaucoma [57].

It has been shown that the extracellular-signal-regulated kinases (ERK) 1/2 signalling pathway plays a critical role in leptin-mediated neuroprotection in other neuronal diseases [32,33]. ERK signalling may confer neuroprotection via a number of mechanisms including both direct inhibition of cell death machinery and transcriptional regulation of cell death/survival factors [58]: ERK-1/2 can phosphorylate a series of pro-apoptotic molecules: BAD at Ser-112 [59–61], causing inhibition of its apoptotic activity [58] Bim-EL at Ser-69, facilitating its degradation [62,63] and caspase-9 at Thr125, blocking its cleavage and activation [64,65]. Caspase-9 is important in the intrinsic pathway of apoptosis in RGC cell death [66]. Numerous studies have investigated inhibition of caspases to prolong RGC cell survival, with many showing beneficial effects [67–69]. The inactivation of caspase-9 might lead to decreased activation of caspase-3; caspase-3 representing a major downstream substrate of caspase-9 [66]. Inhibition of caspase-3 has shown neuroprotective effects in RGCs, again via the intrinsic pathway of apoptosis [67–69]. Leptin therefore could have a significant neuroprotective benefit in RGCs via the attenuation of apoptosis, which is a significant mechanism of RGC cell death in glaucoma [3].

ERK-1/2 can also phosphorylate and activate several transcription factors such as cAMP response element-binding protein (CREB), and then up-regulate brain-derived neurotrophic factor (BDNF) [32,58,70,71]. BDNF is a 14-kDa neuroprotective protein [72] that binds to the high affinity TrkB32 receptor with subsequent activation of signalling cascades that include the ERK and phosphatidylinositide 3-kinases (PI3K) pathway [73]. Delivery of additional BDNF has been demonstrated in a number of models, including those in primate sized eyes, to preserve the retina and optic nerve structure [74–79]. Leptin has been shown to increase BDNF levels in the hypothalamus [80]. If BDNF levels are increased in the retina via similar mechanism, this will have clear beneficial neuroprotective effects. If leptin can mimic even part of BDNF's effect on the retina it could function as an effective neuroprotective agent.

Animal studies suggest the retrograde axoplasmic supply of BDNF is an important factor in the survival of RGCs [81]. Raised IOP is thought to be a major risk factor in developing glaucoma in a large proportion of individuals, and it has been shown that an elevated IOP reduces BDNF axoplasmic delivery to RGCs [82]. It would be of obvious benefit if leptin could support some of the downstream mechanisms of BDNF in this large group of individuals.

Oxidative stress to RGCs has been shown to greatly impact their survival in times of stress, and it has been shown that certain reducing agents have survival benefit in RGCs [83]. Oxidative stress is the imbalance between the production of reactive oxygen species (ROS) and their elimination by antioxidants. Neuronal death by ROS occurs via a number of mechanisms, including protein modification and DNA damage [12,84]. There is evidence for oxidative stress resulting in RGC death in glaucoma [85]. A ROS superoxide burst has been proposed as an RGC apoptosis trigger in glaucoma [86–90]. Superoxide dismutase (SOD) is a natural antioxidant, with SOD1 knockout mice being characterized by loss of RGC function [91,92].

Interestingly it has been shown that certain reducing agents act through the ERK pathway, suggesting that there could be some cross-talk between the mechanisms preventing apoptosis and reducing oxidative stress [12]. Experimentally, ferrous ions have been shown to induce anti-oxidant sensitive neuronal death in RGCs [93] and it has been demonstrated that leptin significantly improves neuronal survival of rat hippocampal neurons after exposure to ferrous iron [94]. This suggests leptin could also relieve oxidative stress on RGCs, which would enhance it's potential neuroprotective effect.

Activation of signal transducer and activator of transcription 3 (STAT3) is well known to mediate neuronal cell survival [95]. Leptin is known to activate STAT3 [96]. Activation of STAT3 includes its dimerization, which then allows it to translocate to the nucleus and influence the expression of a number of genes [38,97]. The findings that intravitreal injection of ciliary neurotrophic factor (CNTF) induces phosphorylation of STAT3 in RGCs [98], and that CNTF protects RGCs [99] and promotes neurite outgrowth in culture RGCs [100,101], supports a hypothesis that leptin could confer a neuroprotective effect on RGCs via the STAT3 pathway.