

Involvement of Endothelin-1 in the Pathophysiology of Normal-Tension Glaucoma

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ABSTRACT

In this review, the involvement of endothelin (ET)-1 in the pathophysiology of normal-tension glaucoma (NTG) is summarized. Several ETs were first isolated in Japan in 1988, and were identified as some of the most potent vasoconstrictors. The roles of ETs in the eyes and ocular diseases have been investigated worldwide. ET-1 is a potential participant in the local regulation of several fundamental processes, including intraocular pressure (IOP), ocular blood flow, axonal transport, and neural degeneration. Of these, the effects on IOP are not addressed in this review, and we instead focus on the pathophysiology of NTG. Several studies have reported abnormal plasma ET-1 levels or their response to postural changes in NTG. As a chronic ischemic optic nerve head model induced by ET-1 injections produces retinal ganglion cell-specific cell death and many cellular changes similar to glaucoma, many studies have been conducted on neuroprotection for glaucomatous optic neuropathy using this animal model. Genetic studies on ET receptors have provided evidence that polymorphisms of ET_A and ET_B receptors may be associated with increased NTG risk. In vitro studies have suggested that ET-1 may cause the death of retinal neurons through glutamate and nitric oxide synthase. ET-1 further affects the functions of glial and lamina cribrosa (LC) cells, and may contribute to remodeling of the extracellular matrix at the LC level in glaucoma. Although few studies have yet obtained promising results showing

that ET receptor antagonists can be clinically useful for NTG, blockade of ET receptors is a potentially attractive target for treating this critical ocular disease.

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Key words: Endothelin-1; Normal-tension glaucoma; Optic nerve head; Ocular blood flow; Glutamate; Nitric oxide synthase; Extracellular matrix collagen; Glial cells

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INTRODUCTION

Endothelins (ETs) were first isolated and identified as potent vasoconstrictors by a Japanese research group in 1988^[1]. The ET family comprises three isoforms: ET-1, ET-2, and ET-3. ET-1 appears to be the most biologically potent and predominant member of the ET family, and is produced by endothelin-converting enzyme (ECE) from a precursor of ET-1, Big ET-1, in vascular endothelial cells. The production of ET-1 is stimulated by several factors, including tumor necrosis factor- α , thrombin, and transforming growth factor- β 1. There are at least 4 known ET receptors: ET_A, ET_{B1}, ET_{B2}, and ET_C. ET_A is a subtype for vasoconstriction that is found in the smooth muscle tissues of blood vessels. ET_{B1} is located in vascular endothelial cells and mediates vasodilation through the release of other bioactive substances such as nitric oxide. ET_{B2} mediates vasoconstriction^[2]. The function of ET_C has not yet been clearly defined. ET receptors are also found in the nervous system where they may mediate neurotransmission. ET-1 has been reported to participate in diverse biological activities, including local blood flow regulation, cell growth, embryonic development, tissue remodeling, inflammation, renal functions, pain, cardiovascular homeostasis, pulmonary functions, and in the release of other active substances^[3-6].

Whether ET-1 can penetrate through the blood–ocular barrier has yet to be determined, although the susceptibility of the blood–brain barrier to ET-1 was shown to differ between juveniles and adults in pathological conditions^[7].

A few years after ETs discovery, their roles in the eyes were reported by several other research groups^[8–10]. One such report revealed the production of ET-1 by cultured bovine retinal endothelial cells and the presence of ET receptors on associated pericytes^[8]. Further, another report suggested ET-1 as a potential participant in the local regulation of intraocular pressure (IOP), ocular blood vessel tone, and iris smooth muscle tone, suggesting that it may be an important mediator in the development of ocular pathologic conditions^[9].

Subsequently, many studies have been conducted regarding the role of ET-1 in ocular blood flow, glaucomatous optic neuropathy (GON) with normal IOP, as well as in IOP control and glaucoma with high IOP. However, this review will focus on the former role, and will not address the latter.

ET-1 AND NORMAL-TENSION GLAUCOMA (NTG)

A few research groups, including our own, have reported that plasma ET-1 levels may be associated with the pathogenesis of glaucoma, particularly normal-tension glaucoma (NTG)^[11–14]. We and Cellini *et al* found that plasma ET-1 levels were significantly higher in patients with NTG without systemic vascular or circulatory disorders than in normal controls^[11,13]. We also demonstrated higher plasma ET-1 levels in NTG patients at the initial stage of visual field loss than in those at the middle stage^[11]. Kaiser *et al* found no physiological increase in ET-1 plasma levels in NTG patients after changing from the supine to upright position, suggesting that vascular dysfunction may be involved in the pathogenesis of optic nerve damage in NTG^[12]. A study using color Doppler imaging revealed vascular insufficiency in NTG patients, particularly in the posterior ciliary arteries that provide the blood supply to the optic nerve head (ONH)^[13]. Another study indicated that resistivity index in the ophthalmic arteries was positively related to plasma ET-1 levels^[14].

Buckley *et al* observed increased sensitivity to ET-1 in arteries dissected from the gluteal fat of NTG patients, which could result in enhanced vasoconstriction and contribute to the vasospasm seen in NTG^[15]. In addition, Nicoleta *et al* demonstrated that glaucoma patients showed abnormally high plasma ET-1 levels after the body cooled+. Recently, Terelak-Borys *et al* provided evidence that

abnormal neuro-endothelial function was related to the effects of ET-1 via a vasospastic mechanism in NTG patients^[17]. The ET-1-dependent vascular dysregulation known as Flammer syndrome^[18] may be one of the important causes of NTG. Moreover, Emre *et al* reported that glaucoma patients (with either normal IOP or normalized IOP after treatment) showing visual field progression had increased plasma ET-1 levels^[19]. However, Chen *et al* found no correlation between plasma levels of ET-1 and the severity of glaucoma^[20]. On the other hand, Lee *et al* indicated that plasma ET-1 levels were associated with heart rate variability in NTG patients, suggesting that the relationship between autonomic dysfunction and autoregulation might play a role in the pathogenesis of NTG^[21].

ET-1-INDUCED MODELS OF GON

We and another research group independently reported that ET-1 administration induced chronic ONH ischemia with enlarged excavation of the ONH in animal eyes^[22–25]. We injected ET-1 into the posterior vitreous of rabbits twice a week for 4 weeks, which induced continuous reduction in ONH blood flow and enlargement of the ONH excavation (Figure 1) as well as axonal loss and demyelination affecting the prelaminar portion of the optic nerve^[22,25]. Cioffi *et al* also observed the ONH excavation and histologic tissue loss in the anterior optic nerve resulting from ischemia induced by ET-1-incorporated mini-pumps in rabbits and primates^[23,24]. Stokely *et al* reported that intravenous ET-1 administration decreased anterograde axonal transport in the rat optic nerve^[26]. Prasanna *et al* further indicated that ET-1 induced astroglial proliferation in cultured human ONH astrocytes through ET receptor activation, suggesting a possible mechanism for the astrogliosis observed in the glaucomatous ONH^[27]. Lau *et al* provided experimental evidence that acute ET-1 injections could produce retinal ganglion cell (RGC)-specific cell death and many cellular changes that are similar to those observed in glaucoma^[28]. Taniguchi *et al* revealed that a single intravitreal injection of ET-1 impaired retrograde axonal transport in the rat optic nerve, which was correlated with the observed histological optic nerve damage^[29]. These various findings suggest that ET-1-induced chronic ONH ischemia could be a candidate model of GON. In fact, many researchers have evaluated neuroprotection mechanisms for GON using this animal model^[25,30–34]. Munemasa *et al* suggested that one of the glaucoma agents, unoprostone, had neuroprotective effects against ET-1-induced neuronal injury through phosphorylation of extracellular signal-regulated kinase. However, a majority of the neuroprotective mechanisms have yet to be determined^[33].

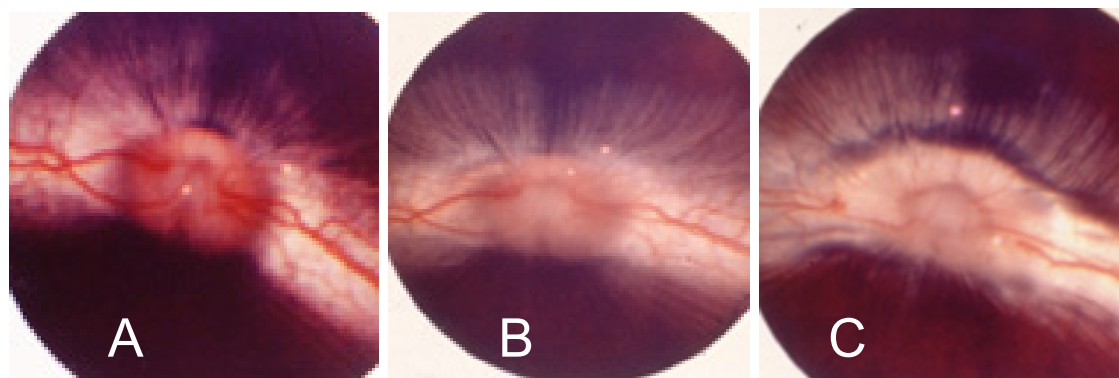


Figure 1 Representative photographs of changes in the optic nerve head (ONH) of a rabbit that received intravitreal injection of endothelin (ET)-1 at 10 pmol twice a week for 4 weeks (A: pretreatment, B: 2 days, C: 4 weeks). Obvious enlargement in excavation of the ONH was observed 4 weeks after injection (C).

ET RECEPTORS AND GON IN NTG

As described in the Introduction, ET_A and ET_B receptors seem to be critical receptors for ET. ET_A receptor plays an important role in vasoconstriction. ET_B receptors mediate both vasodilation (ET_{B1}) and vasoconstriction (ET_{B2}), and some of these effects are due to the release of other bioactive substances such as nitric oxide, prostaglandins, and cytokines. Since ET_B receptors are clearance receptors for ET-1, their expression levels are important determinants of the plasma ET-1 concentration^[35].

Researchers in Japan investigated whether gene polymorphisms of ET-1 and its receptors ET_A (*EDNRA*) and ET_B (*EDNRB*) were associated with glaucoma phenotypes and clinical features^[36]. The GG genotype of *EDNRA*/C+70G was associated with worse visual field defects in NTG patients, suggesting that this polymorphism of the ET_A receptor may be related to NTG risk. Another study conducted in Korea also revealed that a polymorphism of the ET_A gene was associated with NTG^[37]. Furthermore, a multi-center study conducted in the United States revealed that *EDNRB* was associated with early paracentral loss in glaucoma patients, suggesting that genes for the ET_B receptor may also be related with a certain type of glaucoma^[38].

Henry *et al* reported that NTG patients have reduced vasodilatation in response to ET_A receptor antagonism, which could be due to attenuated ET_A receptor-mediated tone and/or increased ET_B receptor-mediated contraction^[39]. Resch *et al* indicated that dual inhibition of ET receptors by bosentan increased ocular blood flow both in patients with glaucoma and in healthy subjects^[40]. On the other hand, we suggested that ET-1 may act synergistically with glutamate to damage retinal neurons under hypoxic conditions through ET_A receptors^[41]. In addition, we verified that ET-1 caused the death of retinal neurons through activation of nitric oxide synthase and production of superoxide anions, which were upregulated by ET_A receptor-mediated activation of NADPH oxidase^[42,43]. Furthermore, Wang *et al* demonstrated the immunoreactivity of ET_B receptor in GON and its association with astrocytes, suggesting that the glia-ET system may be involved in the pathologic mechanisms of neuronal degeneration in glaucoma^[44]. We also reported that blocking the ET_B receptors by the selective antagonist BQ-788 rescued RGCs from optic nerve injury, most likely by attenuating neuroinflammation^[45]. In addition, Rao *et al* reported that human lamina cribrosa (LC) cells expressed functional ET_A and ET_B receptors, and their expression and function were altered in response to prolonged exposure to ET-1, suggesting that elevated ET-1 levels could impact LC function, including extracellular matrix (ECM) collagen synthesis, and may contribute to ECM remodeling at the LC level in glaucoma^[46,47]. Based on these findings, I summarize the probable involvement of ET-1 in the pathophysiology of NTG as a schema in Figure 2.

ET ANTAGONISTS FOR NEUROPROTECTION IN GLAUCOMA

There have been several reports that ET antagonists, particularly ET_A receptor antagonists, might be useful for neuroprotection in cerebral ischemic injury^[48-52]. The ET_A receptor antagonist BQ-123 increased rat hippocampal CA1 neuron survival in gerbils subjected to transient global ischemia^[48]. The selective ET_A receptor antagonist Ro 61-1790 partially preserved tissue perfusion following focal ischemia, and this effect was associated with significant neuroprotection in a rat model of cerebral ischemia^[49]. Another selective ET_A receptor antagonist,

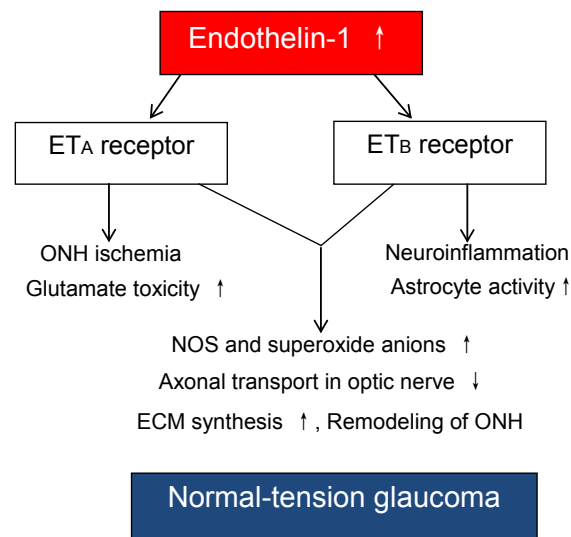


Figure 2 A schematic representation of the involvement of ET-1 in the pathophysiology of normal-tension glaucoma (NTG). NOS: nitric oxide synthase, ECM: extracellular matrix.

SB 234551, reduced neurological deficits in rat models of closed head injury and focal stroke^[50]. The ET_A receptor antagonist BSF-208075 reduced the post-ischemic leukocyte activation and showed a neuroprotective effect^[51]. Another specific ET_A receptor antagonist, S-0139, provided neuroprotection by suppressing ischemia- and rtPA-triggered molecules in a rat model of middle cerebral artery occlusion^[52].

On the other hand, there have been few reports regarding the neuroprotective effects of ET antagonists for glaucoma. Syed *et al* provided evidence that the non-selective ET receptor antagonist sulfoxazole could protect the retina from ischemic-like insults similar to those occurring in glaucoma^[53]. Howell *et al* showed that a novel, orally administered, dual ET receptor antagonist, macitentan, inhibited neurodegeneration in a mouse model of glaucoma^[54]. Therefore, considering the current knowledge on the potential involvement of ET-1 in the pathogenesis of NTG, the use of a blockade of ET receptors may be an attractive target for NTG treatment, although further studies are required to confirm these effects and mechanisms. However, it should be noted that ET antagonists might induce side effects, including hepatic dysfunction, peripheral edema, and interstitial pneumonia, when applied systemically^[55], although the toxicity of their topical application remains to be verified. In addition, ECE inhibitors might also be potential candidates for glaucoma therapy, although their neuroprotective effects remain to be investigated.

CONCLUSION

In this article, the involvement of ET-1 and ET receptors in the pathophysiology of NTG was summarized, and the potential of the application of ET antagonists for NTG treatment was discussed.

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CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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