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Diabetes & its Complications

Ocular Surface Complications in Type 1 Diabetes and Dysregulation of the Opioid Growth Factor (OGF) – OGF Receptor (OGFr) Regulatory Pathway

Patricia J McLaughlin[1]*, Joseph W Sassani[2], Allison K Krebs[1] and Ian S Zagon[1]

[1]*Departments of Neural and Behavioral Sciences and, Pennsylvania State University College of Medicine, Hershey, USA.*

[2]*Ophthalmology, Pennsylvania State University College of Medicine, Hershey, USA.*

***Correspondence:**
Dr. Patricia J McLaughlin, Department of Neuroscience and Experimental Pharmacology, Pennsylvania State University College of Medicine, 500 University Drive, MC H109, Hershey, USA, Tel: 717-531-6414.

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ABSTRACT

Ocular surface complications are prevalent in diabetes. For example, up to 54% of persons with diabetes have some form of dry eye disease (DED) and others have decreased corneal sensitivity and delayed epithelial wound healing. Although not life-threatening, these complications can be painful and lead to loss of work productivity, increased healthcare costs, and distorted vision or loss of vision. DED is classified as being either aqueous deficient or evaporative in nature, with the latter form related to environmental conditions such as heat, smoking, low humidity, and the former condition being attributed to Type 1 diabetes (T1D). DED can develop in animal models of T1D without surgical intervention or exogenous drugs and is a naturally occurring complication of hyperglycemia. Investigations have associated the onset of DED in T1D with the dysregulation of the Opioid Growth Factor (OGF) – OGF receptor (OGFr) regulatory pathway with upregulation of the peptide and receptor. This regulatory pathway is a tonically active, inhibitory pathway that is an important regulator during homeostasis and re-epithelialization, and plays a role in the onset and progression of autoimmune diseases. Blockade of the pathway using the opioid receptor antagonist naltrexone (NTX) rapidly reverses dry eye and corneal surface insensitivity in male and female rats with T1D within 5 days. This review focuses on our investigations of mechanisms related to the rapid reversal of diabetic DED and decreased corneal sensitivity following topical administration of NTX.

Keywords

Enkephalins, Cyclin-dependent Inhibitory Kinases, DNA synthesis, Naltrexone, Dry Eye, Wound repair, Cancer.

Incidence, prevalence, and characteristics of Type 1 diabetic ocular complications including dry eye and corneal insensitivity

Estimates of diabetes approach 38 million people in the United States and 98 million have prediabetes[1]. Diabetes mellitus is a leading cause of ocular complications worldwide [1]. Associated healthcare costs in the United States are more than $413 billion, with approximately $307 billion spent on direct medical care [1,2]. Dry eye disease (DED), also known as keratoconjunctivitis, is a prevalent complication of diabetes characterized by loss of tears and eventual damage to the ocular surface; loss of vision and total blindness may develop. It is accompanied by reduced corneal sensitivity and delayed epithelial wound healing. An estimated 54% of diabetic persons suffer from DED episodes [3]. Diabetes arises from multiple origins including lifestyle factors and genetic traits, and is classified into categories of insulin deficiency (Type 1), insulin resistant (Type 2), and gestational diabetes [4]. Type 1 diabetes (T1D) is further classified as severe autoimmune (SAID) and severe insulin-deficient diabetes (SIDD). Although more persons have Type 2 diabetes, T1D usually lasts from childhood to adulthood, making it a long-term autoimmune disorder requiring exogenous insulin [5]. Both forms of diabetes have associated complications that impact nearly every organ system in both sexes and all ethnic groups [6-8]. This review focuses on T1D

and complications of DED and corneal surface insensitivity which appear to arise from dysregulation of the Opioid Growth Factor (OGF) – OGF receptor (OGFr) regulatory pathway [9-12].

DED is classified as aqueous–deficient or evaporative dry eye. The latter form occurs in 85% of affected persons and results from Meibomian gland dysfunction related to environmental factors that cause tears to evaporate quickly due to poor glandular secretions of oil [13-15]. Aqueous deficient dry eye is associated with T1D and is characterized by failure to produce adequate amounts of tears. This form is also characterized by deficits in lacrimal gland function, which in turn may be altered by inflammation and autoimmune disorders.

Extensive studies of DED in various rodent models have associated dysregulation of the Opioid Growth Factor (OGF) – OGF receptor (OGFr) regulatory pathway with the onset of diabetic DED, at least in Type 1 diabetic rodent models [9-12,16-19]. Our investigations have included mouse, rat, and rabbit, with hyperglycemia created by injection of streptozotocin (STZ) and/or alloxan to destroy insulin-producing beta islet cells of the pancreas [16-18]. These models do not precisely mimic the human condition but do provide a consistent landscape for the study of diabetic DED [20,21]. Elevated blood glucose levels after a single injection of STZ, and increased urine output throughout the duration of disease are hallmarks of T1D in rodents that parallel findings in humans [21]. The STZ model is easily reproduced, does not result in death of study animals, and dry eye and corneal insensitivity spontaneously occur without additional surgical manipulation or environmental intervention. Prolonged hyperglycemia may also result in malfunction or loss of corneal sensory nerve fibers, resulting in diminished corneal sensitivity that contributes to decreased tear production [22].

Dysregulation of the OGF-OGFr regulatory pathway in rodents

The OGF-OGFr regulatory pathway plays a role in the onset and progression of ocular surface complications in T1D rodent models [9-12]. The OGF-OGFr regulatory pathway includes the endogenous opioid peptide [Met^5]-enkephalin (OGF) and a specific nuclear-associated receptor, OGFr. The small, five amino acid peptide OGF is distributed throughout the body and has been detected in the visual, cardiovascular, and gastrointestinal systems [23]. [Met^5]-enkephalin was initially discovered as a neurotransmitter and involved in pain regulation, but this neuropeptide also has been shown to have roles in stress and non-pain related cellular homeostasis. As an inhibitor of cell replication, [Met^5]-enkephalin regulates cellular homeostasis when binding to the OGFr [24]. Thus, to distinguish the roles, the chemical [Met^5]-enkephalin was renamed OGF. OGF is a potent, reversible, tissue-nonspecific negative growth regulator that is conserved across species, and acts at a receptor located on the outer-nuclear envelope [25]. Upon cloning and sequencing, this receptor had little proteomic or genomic similarity with the classical opioid mu, delta, and kappa and thus was termed OGFr. It does maintain some pharmacological properties shared with other opioid receptors in that the antagonist is naltrexone or naloxone [26,27].

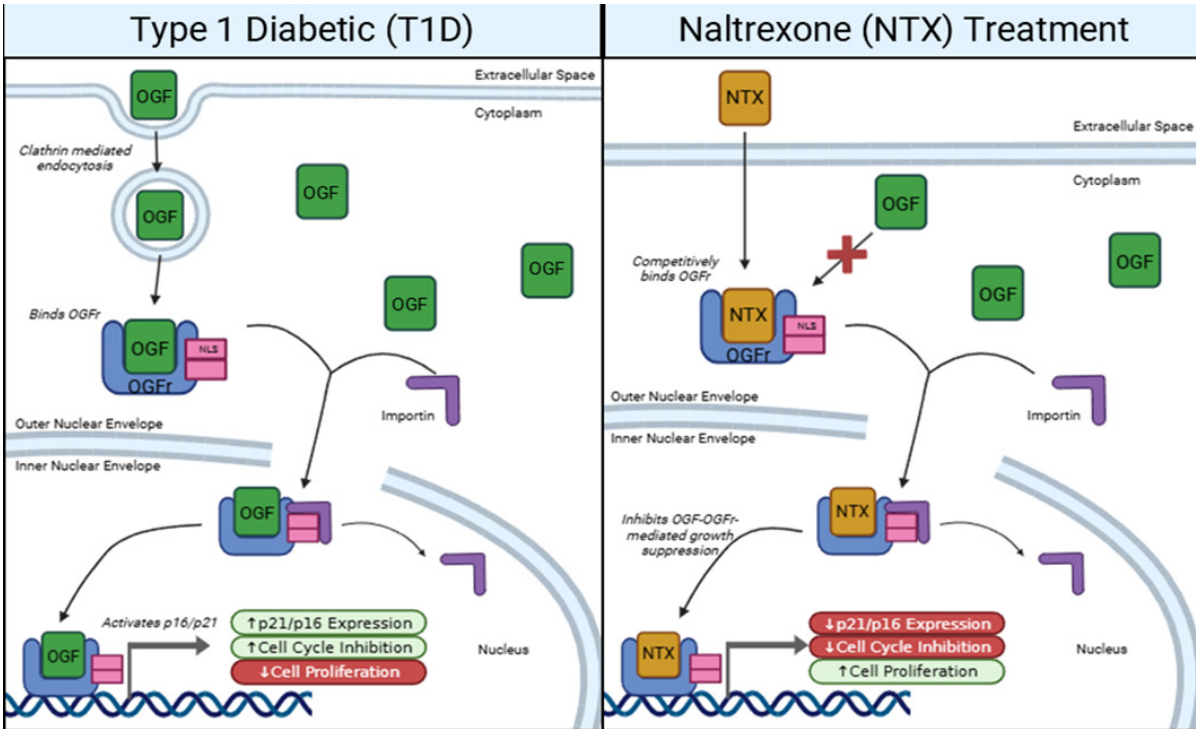

Figure 1: Diagram depicting the excess OGF in T1D and the role of NTX in blocking the OGFr to prevent the inhibitory action of OGF. Prepared with Biorender.

Briefly, OGF enters the cell by passive diffusion, ultimately binding to the nuclear-associated OGFr. Once inside the nucleus via clathrin-mediated endocytosis, OGF utilizes the $p16^{INK4a}$ and $p21^{WAF1/CIP1}$ cyclin-dependent inhibitory kinase pathways to delay the G1-S phase of the cell cycle [28]. The receptor carrying OGF is transported into the nucleus via nuclear localization signals [29] and exported in a CRM1-dependent manner [30]. C-terminal tandem repeats within OGFr are required for the inhibitory activity by OGF [30].

Elevated plasma levels of OGF have been reported in type 1 diabetic individuals [31,32]. In T1D rodents, the peptide and receptor are over-expressed [9-11], and blockade by naltrexone (NTX) rapidly reverses dry eye. (Figure1) summarizes this activity and shows how NTX blocks the binding activity of OGF and OGFr.

Multiple studies have reproducibly documented the spontaneous development of diabetic DED and corneal insensitivity in male and female rats with T1D, and the rapid reversal following topical treatment with NTX [9-11,16]. One drop of NTX re-establishes tear production and corneal sensitivity within 1 hr of administration in T1D rats, with the reversal of dry eye lasting 2-3 days without further treatment and restitution of corneal sensation lasting 4-7 days after termination of NTX treatment [16]. To begin understanding the mechanisms related to the rapid reversal (< 5 days) of diabetic dry eye, dysregulation of the lacrimal functional unit was examined. Morphological comparisons of the external lacrimal glands, Meibomian gland, conjunctiva, and associated nerves between T1D and normal rats of the same sex revealed that diabetes had a deleterious effect on the lacrimal functional unit [33]. Acini in the lacrimal glands of male diabetic animals were fewer ($p<0.05$) in number and smaller in diameter ($p<0.0001$) than those in normal male animals [33]. Female diabetic rats had smaller, but comparable numbers of acini relative to normal female rats. However, the secretions from lacrimal glands, specifically aquaporin 5, were significantly decreased ($p<0.01$ or greater) in T1D rats of both sexes relative to normal animals [33]. Topical administration of NTX for 10 days restored aquaporin 5 expression as measured by immunohistochemistry optical density in both male and female T1D rats, suggesting that diabetes altered morphology and function, but that only the secretory levels of aquaporin were reversed within a 10-day period by topical NTX [33].

Aquaporin proteins are important water channels for the function of lacrimal glands by enabling water to move across plasma membranes [34,35]. In Sjögren's syndrome, another autoimmune disorder, aquaporin 5 expression is reduced and/or trapped in cells resulting in reduced tearing rather than moisturization of membranes [36]. T1D also resulted in reduced surface areas of Goblet cells that produce the mucins that help adhere tear film to the cornea and Meibomian glands that produce an oily material that helps decrease tear film evaporation. Together, they comprise two layers of the tear film [37,38]. T1D rats of both sexes had a 27% decrease in surface area of Goblet cells. NTX treatment for 10 days increased the cellular area for both male ($p<0.01$) and female ($p<0.0001$) rats with some sex differences [33]. It was concluded that the rapid reversal of dry eye by topical NTX did not involve structural changes related to diabetes. However, the rapid and robust corrective increase in secretions suggested that inflammation may be suppressed by the NTX blockade and supported a contributing role of stress and/or inflammation in causing the OGF-OGFr dysregulation.

What mechanisms are involved with the rapid reversal of dry eye?

To determine whether the relationship between OGF and OGFr is "causal" in diabetic ocular surface disease, either the peptide or receptor needed to be inactivated and the outcome determined. When the OGF-OGFr pathway is blocked (and inactive) by topical and systemic treatment with NTX, the complications of dry eye and corneal surface insensitivity are reversed. Blockade of the pathway and restoration of tear production to normal suggests that, in fact, the dysregulated OGF-OGFr regulatory pathway causes diabetic dry eye. This relationship appears independent of insulin [39] and estrogen [12]. The timing of upregulation of expression levels of OGF and OGFr in corneal tissue, and higher serum levels of OGF, suggest that dysregulation of the OGF-OGFr pathway precedes other internal pathways (e.g., insulin, estrogen-progesterone) that may provide protection in the hyperglycemic animals.

Biological mechanisms involved in the dysregulation of the OGF-OGFr axis and onset of ocular surface complications in diabetes

Is dry eye reversal due to increased cell proliferation?

The initial observation that the OGF-OGFr axis is involved with cell replication and cellular homeostasis began with experiments involving corneal explants from rats [40] and human donor corneas not suitable for transplantation [41]. Explants treated in culture with various doses of OGF had delayed epithelial outgrowth or none at all, whereas treatment with the OGFr antagonist NTX showed rapid and organized outgrowth. In vivo studies demonstrated that OGF disrupts normal homeostasis of the corneal epithelium, and NTX accelerates re-epithelialization without exuberant granulation tissue formation, neovascularization, or damage to adhesion complexes in normal animal models [42]. Investigations at the limbus revealed that in diabetic rats, proliferation was decreased in the limbal epithelial stem cells, while NTX treatment to the corneal surface restored replication rates to normal [43]. However, these deficits in diabetic animals required longer periods of time for recovery. Thus, cell replication is only one part of the effective mechanism of NTX.

Does inflammation play a role in diabetic dry eye?

Inflammation occurs with diabetes. Altered insulin regulation in both type 1 and type 2 diabetes leads to the formation of advanced glycation end-products (AGEs) that are involved in precipitating inflammation in many disorders including diabetes. AGEs influence other signaling pathways related to oxidative stress. We began investigations into the role of inflammation, particularly reactive oxygen species (ROS) pathways as an intermediary

causing dry eye [44].

The T1D rats had reductions on the corneal surface of some inflammatory markers such as TNF-α. A proteomic analysis of the corneal epithelium in male and female normal and diabetic rats revealed that diabetes resulted in dysregulation of the inflammatory processes (unpublished data). Additionally, examination of the trigeminal ganglion revealed that the number of calcitonin gene-related peptide-positive neurons was increased after NTX treatment suggesting again, that enhanced cellular proliferation may be involved [33]. Substance P-positive neurons were not changed in diabetic rats after 15 days of treatment. Effects were comparable in male and female diabetic rats.

One pathway for the pathogenesis of diabetic ocular surface disease that currently is being pursued is oxidative stress and inflammation (see Figure 2). Diabetes induces inflammation on the corneal surface and releases pro-inflammatory cytokines that are elevated in the rat model of T1D [45]. Studies on reactive oxygen species (ROS) revealed that diabetic rats had elevated ROS and proinflammatory cytokines in both corneal epithelium and the lacrimal glands [45]. Topical NTX was able to decrease expression levels of these inflammatory mediators including ROS, CHOP protein and NOX-2 protein, as well as proinflammatory cytokines including interleukin (IL) -1β, IL-6, and tumor necrosis factor alpha (TNF-α). Investigations of both lacrimal glands and corneal epithelium from male and female type 1 diabetic rats supported the role of inflammation in contributing to the ocular complications, and the role of NTX in mitigating DED and corneal insensitivity. Another possible mechanism for the rapid reversal of dry eye in diabetics may be reversal of peripheral neuropathy in the cornea, a densely innervated tissue [46,47]. Given that NTX increased proliferation in the corneal epithelium and limbus after 10 -15 days with topical NTX treatment, it is possible that corneal nerve density might increase within 1-2 weeks of topical treatment as demonstrated with other treatments. Of course, this mechanism would not result in the rapid short-term reversal of diabetic decreased tear flow and corneal insensitivity that occurred with topical NTX treatment. Thus, NTX may employ both short-term and long-term mechanisms that serve to ameliorate diabetic ocular surface complications.

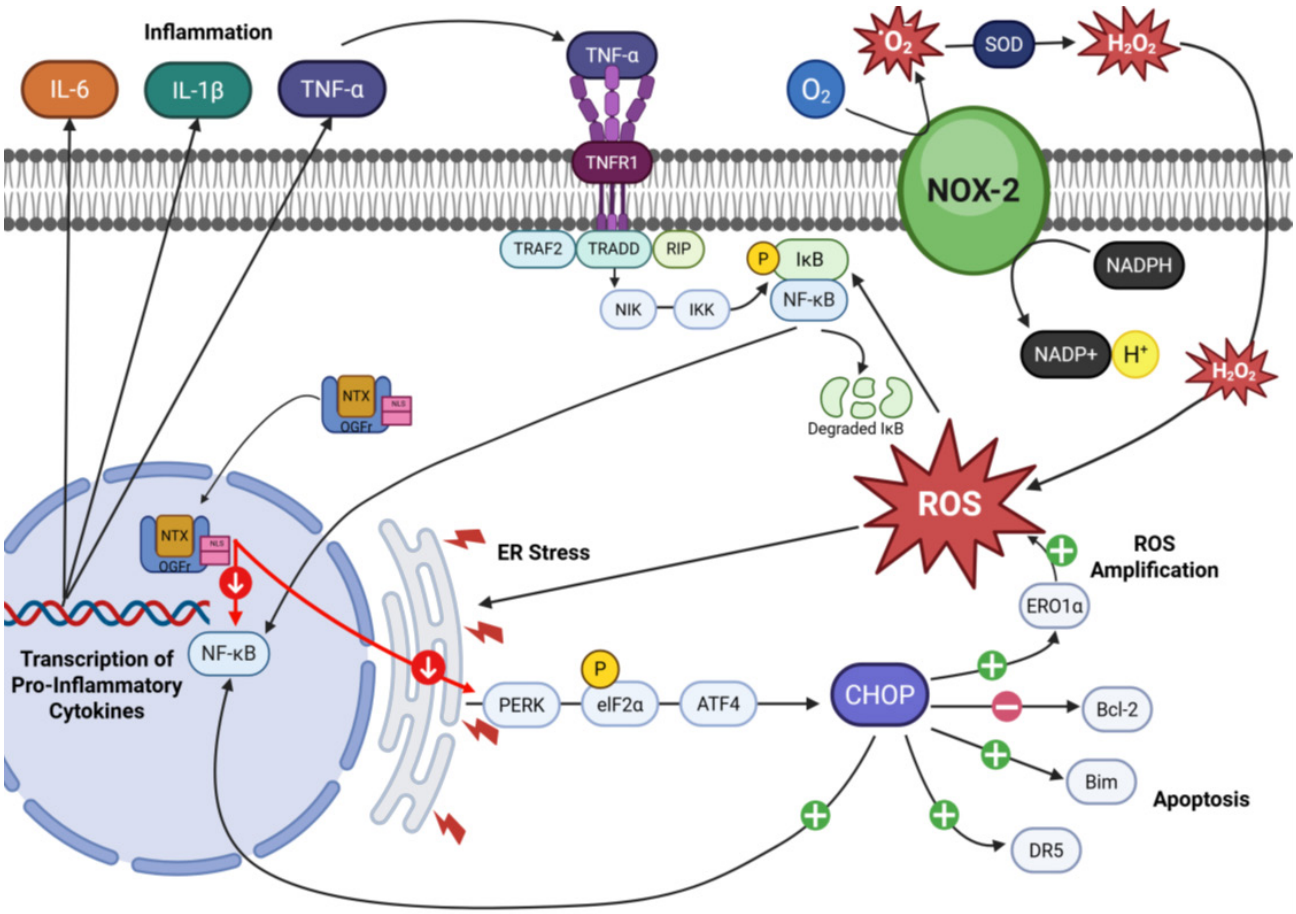

Figure 2: Schematic drawing showing that blockade of the OGF-OGFr pathway by NTX suppresses the reactive oxygen species pathway. Prepared with Biorender.

Discussion, Future Studies

Investigations into mechanisms of how and why topical NTX rapidly reverses diabetic DED and restores corneal surface sensitivity are ongoing. As we have shown, Type 1 diabetes causes many alterations to the corneal surface and lacrimal functional unit contributing to the complications of DED and corneal insensitivity that, if untreated, may result in vision loss. T1D alters the morphology of the lacrimal functional unit including reducing the surface area of tear glands and conjunctival goblet cells. These structures are important for production of the aqueous and mucin layers of the tear film that provide lubrication to the corneal surface and function as a protective barrier against pathogens [34-36,44,45]. Topical treatment with NTX did not change the overall morphological structure of the lacrimal functional unit but did increase the aquaporin expression levels in the lacrimal glands and secretions from the conjunctival goblet cells. Diabetic rats also had smaller acini in Meibomian glands, which are responsible for the lipid layer of the tear film. Lipids in tears prevent evaporative loss of tears, which further contributes to the development of DED. Others have reported atrophied acini in the diabetic lacrimal gland and deficits in secretory function due to size or composition of cations and proteins [46-48].

The specific mechanistic answers as to how topical NTX reverses diabetic DED and decreased corneal sensitivity are not known. Nevertheless, we have shown that topical NTX has both short-term (hours) and longer term (days to weeks) effects that do reverse or ameliorate the adverse effects of diabetic DED and decreased corneal sensitivity. Further research is needed to elucidate the specific mechanisms underlying these effects.

Conflict of Interest

PJM, ISZ, and JSW have intellectual property owned by Penn State Research Foundation that involves naltrexone treatment of dry eye but receive no financial compensation or royalties. AKK declares no competing interests.

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