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Dysregulation of the OGF-OGFr pathway and associated diabetic complications

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Abstract

Background: Diabetes is a worldwide epidemic with more than 550 million individuals expected to be diagnosed with the disease by 2030. Complications associated with diabetes affect nearly all systems, but more than 54% of diabetic individuals have ocular surface disorders including keratopathy, dry eye or altered corneal surface sensitivity, and nearly 70% experience slow healing foot ulcers which if left untreated, can lead to amputation. There is new information regarding the underlying pathophysiology associated with these complications, as well as potential treatment.

Aim: This commentary assembles data on preclinical studies showing that corneal surface complications such as dry eye and sensitivity, as well as delayed epithelial wound healing in the cornea and skin in diabetic rats and mice, correlate with a dysregulation of the opioid growth factor (OGF)-opioid growth factor receptor (OGFr) regulatory axis. The peptide in this pathway, OGF, chemically termed [Met^5]-enkephalin, is elevated in the serum of humans and animals with either type 1 or type 2 diabetes. The cause for this finding is unknown. However, there are studies that demonstrate that blockade of the interactions between OGF (or elevated levels of OGF) and its receptor can reverse and, in some cases, prevent the onset of diabetic corneal complications. Clinicians and healthcare workers need to recognize this fundamental pathophysiology leading to diabetic complications.

Summary: Dysfunction of the OGF-OGFr growth regulatory system plays a role in the development of ocular surface complications and delayed cutaneous wound healing complications in multiple animal models of both Type 1 and Type 2 diabetes. Modulation of this system may hold promise for reversing or even preventing these diabetic complications in humans. Moreover, monitoring serum levels of OGF should be investigated as an indicator of the development of these and other diabetic complications.

Keywords

OGF serum levels; dry eye; keratopathy; diabetic foot ulcers; naltrexone

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Introduction

Diabetes is a major healthcare concern worldwide [1–5]. In addition to the financial burden estimated at $760 billion, the human suffering related to complications of diabetes as well as the disease itself are immense. Complications associated with diabetes affect both men and women, but there is a higher incidence reported in the aging population, women, and people of color. In particular, abnormalities of the ocular surface including diminished tear production, decreased corneal surface sensitivity, and delayed re-epithelialization of the corneal surface pose health concerns and long-term risks to vision. Slow healing cutaneous wounds, termed diabetic foot ulcers (DFU), account for 4 million patient visits in the US alone, with nearly half being recurring foot ulcers. Estimated healthcare costs for diabetic foot ulcers exceed $40 billion in the United States, supporting the need for new therapeutic approaches to treat delayed cutaneous wound healing. A novel regulatory pathway involving an endogenous peptide and its receptor has emerged as a contributing factor to diabetic complications. The Opioid Growth Factor (OGF) – OGF receptor (OGFr) axis becomes dysregulated in diabetes leading to elevated expression levels of OGF, an inhibitory growth factor that suppresses DNA synthesis [6,7]. Blockade of this regulatory pathway with receptor antagonists can reverse the ocular surface complications and restore wound healing processes [8]. The pharmacological antagonist is naltrexone and warrants further research as a repurposed therapeutic for diabetic complications.

Nature of the Problem and Mechanism

An underlying pathophysiological problem associated with diabetes is the dysfunction of the OGF-OGFr regulatory pathway. OGF, chemically termed [Met^5]-enkephalin, is an endogenous pentapeptide that binds to OGFr, a nuclear-associated receptor. This pathway is responsible for homeostasis of cell replication and renewal. OGF maintains cellular homeostasis by inhibiting cell replication [9]. The pathway is dysregulated in diabetes. OGF is overexpressed in diabetic humans [10,11] and animal models of diabetes [12–14]. Dysregulation of the OGF-OGFr regulatory pathway has been shown to appear within weeks of chemical induction of hyperglycemia in both male and female diabetic rats [6,7]. Overexpression of both OGF and OGFr has been reported in tissues and serum of male and female type 1 diabetic rats [6,7]. The cause of the dysregulation is currently a topic of investigation. There are several possible events that would result in elevated serum OGF levels including greater production of peptide or slower degradation of the peptide. The peptide is produced by post-translational modification of the prohormone preproenkephalin A and is predominately produced in the hypothalamus and pituitary, although there is support for autocrine production of the peptide throughout the body.

Research has shown that the OGF-OGFr pathway can be modulated in diabetes. The scientific concept underlying this potential therapy is that continuous blockade of this pathway using naltrexone, a potent opioid receptor antagonist, prevents the inhibitory peptide OGF from interacting with its receptor OGFr. This biological mechanism is based on pharmacological studies [15]. The duration of blockade defines the response. Complete receptor blockade using a high dose of naltrexone or multiple doses of naloxone (a shorter

acting receptor antagonist) or lower doses of naltrexone results in sufficient blockade of OGF interaction enabling increased cell proliferation. If the receptor blockade is intermittent or incomplete, the result can be inhibition of DNA synthesis.

Preclinical evidence on delayed cutaneous wound healing and ocular surface complications in Type 1 and Type 2 diabetes

Diabetic cutaneous wound healing

The standard-of-care treatment of DFU consists of basic wound care and unloading of the affected area, but does not address underlying pathophysiology. With nearly 40% of patients having a recurrence within one year of the first ulcer [16], there is an urgent need for new therapies to treat incomplete and/or delayed cutaneous wound healing. During the last 2 decades our laboratory has researched the interactions of the OGF-OGFr regulatory system in wound healing using diabetic animal models [17–20]. Blockade of OGF activity results in accelerated cellular proliferation and reverses delayed cutaneous wound healing by stimulating epithelial healing, angiogenesis, fibroblast proliferation, and collagen formation [18–20]. Laboratory studies in type 1 diabetic rats have confirmed that wound closure is delayed relative to naïve animals, and that administration of topical naltrexone cream healed full-thickness wounds significantly faster than wounds receiving vehicle creams. In some cases, closure rates approached those of non-diabetic animals. The quality of healed skin in the diabetic rats as tested by tensile strength equaled that of non-diabetic naïve rats [18].

To investigate whether naltrexone is an effective therapy for accelerating wound healing in type 2 diabetes, genetically obese mice (*db/db*) and normal C57Bl/6J mice received full-thickness cutaneous wounds [19]. Wounds in *db/db* mice treated with vehicle were 11–92% larger than those in normal mice over the 14 day observation period. Topical naltrexone therapy in the *db/db* model reduced residual wound size by 13–30%, and accelerated re-epithelialization and DNA synthesis relative to *db/db* mice receiving vehicle only,.

Diabetic corneal surface complications

An estimated 70% of diabetic individuals experience keratopathy that includes corneal surface complications such as dry eye, delayed corneal epithelialization, and altered surface sensitivity. Initial treatments begin with over-the-counter eye drops, and most prescriptions target only inflammation. The OGF-OGFr axis functions to maintain cellular homeostasis, and OGF acts to inhibit DNA synthesis in tissues such as the corneal epithelium and other tissues [21]. Studies involving this growth regulatory pathway have shown that in rats, rabbits, and mice with diabetes is associated with decreased corneal epithelial turnover, delayed corneal abrasion repair, reduced tear production, and decreased corneal sensitivity [22]. Treatment of diabetic mice and rats with naltrexone, at dosages known to invoke complete receptor blockade, normalized epithelialization [13–16,18,19] and reversed dry eye [17–19]. These results support our hypothesis that one or more of these factors related to the OGF-OGFr regulatory axis are dysregulated in diabetes.

Recent research has investigated the onset and magnitude of dysregulated OGF and reported that serum levels of OGF and OGFr were evident as early as 2 weeks after the induction

of hyperglycemia [6,7]. Moreover, corneal epithelial tissue had elevated levels of both OGF and OGFr, suggesting that there is a dysregulation of this pathway that delays re-epithelialization following corneal abrasion. The elevated serum levels of OGF correlated with abnormal tear production and abnormal corneal surface sensitivity.

Clinical evidence supporting the use of naltrexone

Two small human phase 1 and proof-of-concept studies have been completed confirming the safety and tolerability of naltrexone eye drops. Dose-escalating applications to normal subjects over a 24 hr period of time provided evidence of tolerability. Thirty-day application of naltrexone-containing eye drops to diabetic individuals resulted in no adverse events, with all recruited patients completing the study. The study was not powered to show statistical differences for any efficacy measure, and is considered exploratory in nature. However, all data indicated that there were no ocular complications.

CONCLUSIONS

The standard-of-care treatment for DFUs is off-loading. The care for dry eye and decreased ocular surface sensitivity is often an over-the-counter eye drop or possibly eye drops with an anti-inflammatory agent. Most of the treatments for these wide-spread diabetic complications do not address fundamental, underlying pathophysiological processes. The importance of early intervention with effective treatments, particularly with regard to DFUs or dry eye, is often not adhered to leaving the patient with larger wounds or more painful ocular complications, respectively.

The OGF-OGFr pathway is dysregulated in diabetes, with reports that humans and animals have elevated serum and/or tissue levels of OGF, an inhibitory growth factor, within weeks of initial diagnosis. These elevated serum levels also may have systemic impact on a variety of physiological pathways that have yet to be identified or studied. Preclinical studies using rodent models of type 1 and type 2 diabetes have demonstrated that blockade of this regulatory pathway with naltrexone can reverse the complications, and in some cases, prevent the onset. Dysregulation of the OGF-OGFr regulatory pathway can be modulated systemically or locally by topical application of receptor antagonists. We believe that these data warrant further clinical study.

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