Life Sciences 135 (2015) 131–137

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Possible role of endostatin in the antiangiogenic therapy of diabetic retinopathy

Tapan Behl *, Anita Kotwani

Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

ARTICLE INFO

Article history:
Received 31 October 2014
Received in revised form 15 May 2015
Accepted 3 June 2015
Available online 2 July 2015

Keywords:
Antiangiogenic
Collagen XVIII
Matrix metalloproteinases
NF-kappa B
VEGF

ABSTRACT

Diabetic retinopathy is one of various complications of diabetes mellitus, which is one of the most prevalent chronic disorders in the modern world. Diabetic retinopathy is one of the secondary complications encountered by the patients suffering from chronic diabetes mellitus. Two major characterizing features of diabetic retinopathy are — macular edema and angiogenesis. It has been noted in the past few years that by controlling or completely inhibiting the factors contributing to the progression of events leading to angiogenesis, there is a noticeable amount of progress seen in the prevention and cure of the animal models of diabetic retinopathy. Endostatin is one such antiangiogenic agent being studied at present. It is a carbon terminal protein fragment obtained after cleavage from the carbon terminus of collagen XVIII. It is one of the most potent inhibitors of angiogenesis known at present and is currently undergoing clinical trials. Although the exact mechanism of action of endostatin is not completely known, various factors which are altered/influenced by the action of endostatin are being studied. These include the downregulation and activation/inactivation of various factors which have been proven to have some role in the progression of angiogenesis. Endostatin could be well exploited as a durable agent in the antiangiogenic therapy, once the clinical trials show positive results.

Contents

1. Introduction . . . 131
2. Diabetic retinopathy . . . 132
3. Angiogenesis as a significant event in diabetic retinopathy . . . 132
4. Endostatin . . . 133
   4.1. Endostatin is responsible for the downregulation of Id1 and Id3 . . . 133
   4.2. Endostatin is responsible for the inhibition of matrix metalloproteinases (MMPs) . . . 133
   4.3. Endostatin is responsible for the modulation of AP-1 transcription factors . . . 134
   4.4. Endostatin is responsible for the modulation of NF-kappa B signaling . . . 134
   4.5. Endostatin is responsible for the downregulation of CXCL1 . . . 135
   4.6. Endostatin is responsible for the downregulation of vascular endothelial growth factor . . . 135
5. Conclusion . . . 136
Conflict of interest statement . . . 136
References . . . 136

1. Introduction

Diabetes mellitus can unmistakably be addressed as one of the most abundantly found endocrine disorders in today's population. It is characterized by the altered levels of glucose in the blood, particularly on the elevated side — a condition, medically termed as, hyperglycemia. The causal factors of diabetes mellitus can be stated in the following two statements. The first form of diabetes mellitus (known of Type I diabetes mellitus) is caused due to the impairment in the normal secretions of the hormone — insulin, which is responsible for the transportation of blood glucose and its conversion into glucagon (a modified form of glucose which stores it in the various body cells, especially liver, adipose tissue and striated muscle cells). The second form of diabetes mellitus (known as Type II diabetes mellitus) is caused due to the peripheral

* Corresponding author at: Department of Pharmacology, Vallabhbhai Patel Chest Institute, Delhi, India.
E-mail address: tapanbehl31@gmail.com (T. Behl).

http://dx.doi.org/10.1016/j.lfs.2015.06.017
0024-3205/

resistance of the receptor cells of insulin — a condition termed as insulin resistance, in which the receptor cells stop responding to the stimulus of insulin [8,9,34].

The disorder of diabetes mellitus is not alone in causing various dysfunctions in the body; it also accompanies several other medical ailments commonly termed as diabetic complications, which contribute to the dysfunctions associated with it. These complications arise due to chronic untreated diabetes mellitus, the cause of which can be broadly stated as the adverse effects of the prevalent hyperglycemic conditions (in the body of a diabetic person) on the various other cells and/or tissues of the body such as neurons (diabetic neuropathy), blood vessels supplying eyes (diabetic retinopathy), blood vessels of kidneys (diabetic nephropathy) and various other small blood vessels of the body (diabetic microangiopathy) [15].

2. Diabetic retinopathy

Diabetic retinopathy is a complication of diabetes mellitus resulting in severe consequences. It is one of the leading causes of preventable blindness in the world. Vision loss in this disorder is attributed to the damage caused to the retinal cells due to the various dysfunctions which have occurred in the surrounding microvasculature. Its prevalence is reported to be very high all over the globe. Numerous data accounts have been presented after researches on various populations [3]. According to a study conducted on 18,891 people (of all age groups) suffering from type I diabetes mellitus, there was an observation that, after suffering from diabetes for 40 years, 50.2% of the patients presented with advanced diabetic retinopathy and 84.1% of the patients suffered from some kind of primitive stages of diabetic retinopathy [26].

Diabetic retinopathy is particularly initiated by the vascular changes in the blood vessels supplying blood to the retinal cells of the eyes. These changes are attributed to the molecular alterations made by high glucose levels in the blood and its effects on the endothelial cells via various mechanisms such as increased flux of the polyol pathway, accumulation of advanced glycation end-products, activation of protein kinase C, hemodynamic changes and involvement of the renin–angiotensin–aldosterone system, oxidative stress and involvement of various growth factors such as basic fibroblast growth factor (bFGF), insulin-like growth factor-1 (IGF-1), angiopoietin-1 and -2, stromal-derived factor-1, epidermal growth factor (EGF), transforming growth factor-beta 2 (TGF-beta 2), platelet derived growth factors (PDGFs), vascular endothelial growth factor (VEGF) and erythropoietin [3]. These microvascular changes are followed by various other events which characterize the advanced stages of diabetic retinopathy. These events are — macular edema and neovascularization [27]. The former is caused due to the obstruction caused in the blood–retinal barrier, which arises because of the various vascular and other pathological changes (such as increase in the permeability of the endothelium, activation of cytokines, alterations in the blood flow, hypoxia and inflammation) that have been induced in that area as a result of the abnormal blood glucose levels. The consequence of this occlusion is the leakage of the surrounding plasma constituents into the retinal cells, ultimately leading to retinal/macular edema [14]. Neovascularization is a process of formation of new blood vessels from pre-existing ones. It is primarily initiated by the events of capillary occlusion caused due to various microvascular changes, particularly by activated leukocytes — a characteristic inflammatory event, along with cellular endothelial damage. Neovascularization is significant in deciding the stage of diabetic retinopathy. According to a clinical classification, diabetic retinopathy is divided into two subclasses — non-proliferative diabetic retinopathy (in which no signs of neovascularization are seen) and proliferative diabetic retinopathy (the one presented with neovascularization). Non-proliferative diabetic retinopathy is the early stage of this diabetic complication which ultimately progresses to get converted into proliferative diabetic retinopathy (the advanced stage of this disorder). The event of retinal neovascularization is primarily responsible for the visual loss caused in diabetic retinopathy [23].

3. Angiogenesis as a significant event in diabetic retinopathy

Angiogenesis (or neovascularization) is the formation of new blood vessels from the existing vasculature as a result of various inflammatory responses occurring due to elevated blood glucose levels in the body of a diabetic patient. It occurs in response to the aftermath of the concessions of growth factors, vascular endothelial cells, extracellular matrix molecules, chemokines and cell signaling molecules. The process of angiogenesis is quite complex and takes place in response to the activation of vascular endothelial cells, proteolytic degradation of the endothelial basement membrane, degeneration of the extracellular matrix, relocation of endothelial cells, vascular proliferation, recruitment of pericytes, and deposition of new basement membrane, closing off the newly formed arteriovenous collateral vessels [5].

The process of angiogenesis is under the critical control of the proangiogenic and antiangiogenic factors which maintain a censorious balance during the normal physiological conditions of the body. The proangiogenic factors are responsible for the upregulation of the process of angiogenesis, which is required during the growth and development of various tissues of the body e.g., during embryonic development, in the process of wound healing, tissue repair and organ regeneration. This differentiation and growth of the cells is kept under check by antiangiogenic factors which are responsible for the downregulation of the process of angiogenesis. This kind of downregulation is required mainly during the pathological conditions where the proangiogenic factors are getting overexpressed, resulting in unchecked cell growth, ultimately leading to tumor progression. In diabetic retinopathy (and many other tumors where the process of angiogenesis is causing tumorigenesis), this subtle balance between the proangiogenic factors and antiangiogenic factors gets abruptly disturbed [22]. The various pathological conditions which contribute to the destruction of the balance between stimulating and dissuading angiogenic factors include chemical, mechanical, degenerative or infectious stimuli. Anatomically, the ophthalmic artery (which supplies blood to the corneal region) is divided into smaller arteries known as ciliary arteries which are further subdivided into even more smaller capillaries. These capillaries form a network like structure in the retinal region referred to as pericorneal limbal plexus. During the process of angiogenesis in pathological conditions, the overstimulated proangiogenic factors cause the endothelial cells of the pericorneal limbal plexus region to proliferative in an abnormal manner resulting in the sprouting of new blood vessels in that area, resulting in neovascularization [39].

The various proangiogenic factors of angiogenesis include Vascular Endothelial Growth Factor (VEGF), Platelet Derived Growth Factor (PDGF), basic Fibroblast Growth Factor (bFGF), acidic fibroblast growth factor (aFGF), Thymidine phosphorylase (TP), Hepatocyte Growth Factor (HGF), Transforming Growth Factor-beta (TGF-beta), Placental Endothelial Cell Growth Factor (PlGF), Connective Tissue Growth Factor (CTGF), activating protein-1 (AP-1), Inhibitor of differentiation proteins 1 and 2 (Id1 and Id2), tumor necrosis factor-alpha (TNF-alpha), epidermal growth factor (EGF), Granulocyte colony-stimulating factor (GCSF), erucamide, Urokinase plasminogen activator, platelet activating factor (PAF), nuclear factor- kappa B (NF-kappa B) angiopoietin-1 (Ang1), prostaglandins E1 and E2, interleukin 8 (IL-8) and angiogenin. Some molecules which generally come under scanner during disease mechanisms include —, angiopoietins, protein kinase C (PKC), ephrins, interleukins, leptin, angiotensin, monocyte chemotactic protein (MCP), vascular cell adhesion molecule (VCAM), tissue plasminogen activator (TPA), and extracellular matrix metalloproteinases (ECM-MMPs) whereas the various antiangiogenic factors known are — angiostatin, endostatin, Platelet factor 4 (N-terminal processed form), 16 kDa prolactin fragment, thrombospondin, vasostatin, interferon-alpha,