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Review

Role of leukotrienes in diabetic retinopathy

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ABSTRACT

The pathophysiology of diabetic retinopathy is highly complex and encompasses the detrimental roles of numerous factors/mediators in inducing various molecular pathological alterations. Although the roles of many inflammatory mediators, involved in the progression of this complication, have been thoroughly researched and studied, the part played by leukotrienes remains widely neglected. This review focuses on leukotrienes-induced mediation and aggravation of the pathological pathways, such as inflammation, oxidative stress and retinal angiogenesis, responsible for exhibition of various characteristic events including leukostasis, macular edema, retinal neovascularization and vitreous hemorrhages, hence, marking the advent of diabetic retinopathy. Acknowledging these roles, it might be possible to potentially utilize leukotrienes antagonists for suppressing or reducing the intensity of the mentioned pathological alterations. Hence, leukotrienes antagonists may act as an effective adjuvant therapy either along with other developing novel therapies (such as anti-VEGF or anti-TNF-α therapy), or with the established conventional laser photocoagulation treatment, to provide additional symptomatic relief or, possibly prevent the progression of diabetic retinopathy.

Contents

1. Introduction

Diabetic retinopathy, a microvascular complication, associated with sight threatening consequences, is initiated due to several hyperglycemia-induced pathological events such as inflammation, oxidative stress, accumulation of advanced glycation end products (AGEs), overactivation of protein kinase C (PKC), increased flux of polyol pathway, alterations in renin-angiotensin-aldosterone system (RAAS), disturbances in the hemodynamic environment of retinal vasculature, pathological angiogenesis and apoptosis of retinal neuronal and endothelial cells. Involvement of numerous mediators in the progression of this complication has been demonstrated. Many studies attempted to illustrate the complex interplay between the various mentioned pathways involved. However, its exact pathophysiology cannot be elucidated under a single mechanism [1–3].

Interdependence among the etiologies of various pathological events, such as inflammation, oxidative stress, cellular apoptosis and angiogenesis has been described by several studies. Its manifestation has become possible due to the involvement of various mediators in inducing more than one pathological pathway. Most prominent role in this interlinked bridging is exhibited by inflammatory mediators. Other than inducing inflammatory response, almost all inflammatory mediators involved in the

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pathophysiology of diabetic retinopathy play numerous additional pathological roles. Studies have now established confirmative role of major inflammatory mediators, including VEGF (vascular endothelial growth factor), COX-2 (cyclooxygenase-2), NF-κB (nuclear factor-kappa B), TNF-α (tumor necrosis factor-alpha) and other cytokines in the pathophysiology of diabetic retinopathy; however, leukotrienes have been least focused upon in this respect [4–7]. The role of leukotrienes in the progression of this complication is highly neglected. This review intends to discuss different leukotrienes-induced alterations which aggravate hyperglycemia-induced pathological conditions, thereby leading to diabetic retinopathy.

2. Pathogenesis of diabetic retinopathy

The prime reasons for the etiology of diabetic retinopathy are the alterations in the retinal blood vessels. These changes are the aftermath of several pathological changes induced by high blood glucose levels. Endothelial cells are, peculiarly, the most vulnerable target of hyperglycemia-induced molecular alterations in several physiological pathways, leading to pathological demonstrations, including increased flux of the polyol pathway, accumulation of advanced glycation end-products, activation of protein kinase C, hemodynamic changes and involvement of 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. The mentioned pathological changes severely damage the retinal endothelial cells, which then act as harbinger for the induction of numerous other downstream pathways leading to overexpression of various growth factors, activation of cytokines, induction of hypoxia, oxidative stress-induced damage, retinal angiogenesis and various other hemodynamic changes, which ultimately result in epithelial dysfunction. This hyperglycemia-induced epithelial dysfunction is regarded as the prime reason for the advent of diabetic retinopathy. These retinal changes are then succeeded by thickening of the basal endothelial membrane, increased permeability of endothelial cells (leading to vascular leakage), stimulation of a robust inflammatory response, induction of ischemic conditions, and mediation of apoptosis of endothelial cells. The collective impact of the above mentioned changes in retinal vasculature results in the exhibition of certain clinical presentations, namely microaneurysms, macular edema and neovascularisation. Microaneurysms are the characteristic features of the primitive stage of diabetic retinopathy, namely non-proliferative diabetic retinopathy. They are defined as small abnormal dilatations in retinal blood vessels and, probably, are caused due to the release of various angiogenic factors during hyperglycemia-induced inflammatory response. Macular edema also occurs as a consequence of retinal inflammation, during which the permeability of retinal blood vessels increases manifold and the consequential leakage results in pooling of vascular contents in the macular tissue. The microaneurysms particularly act as hot-spots for further vascular damage, following which the inflammatory responses aggravate and lead to a cascade of other molecular changes which arbitrate the conversion of non-proliferative diabetic retinopathy into proliferative diabetic retinopathy, the advanced stage of this complication. It is significantly characterized by neovascularization, a process of sprouting of new blood vessels from the pre-existing vasculature (due to the stimulation of various pro-angiogenic factors). The new blood vessels particularly sprout from retinal blood vessels and their growth progresses onto the posterior wall of the vitreous chamber. The fragile and immature blood vessels get exposed to the prevailing hyperglycemia-induced pathological conditions and get damaged, further increasing the vascular leakage. This event is clinically addressed as vitreous hemorrhage. Persistent stress on retina due to hyperglycemia-induced hyperosmolarity, coupled with other pathological conditions described above, results in retinal detachment, the ultimate reason for vision loss [8–11].

3. Leukotrienes and retina

Biologically produced by leukocytes, mastocytoma cells, macrophages, and other tissues and cells of the body, leukotrienes are conjugates of arachidonic acid, a 20-carbon polyunsaturated omega-6, essential, fatty acid. Arachidonic acid, after being acted upon by the enzyme lipoxygenase, yields 5-hydroxy-eicosatetraenoic acid (5-HETE) and a number of members of leukotrienes family. The known members include LTA_4, LTB_4, LTC_4, LTD_4, LTE_4 and LTF_4. Among these, LTC_4, LTD_4 and LTE_4 were discovered as unknown compounds capable of inducing contractions in the smooth muscles of guinea pig ileum, and were awarded with the name—slow reacting substances of anaphylaxis (SRS-A). The SRS-A were found to be three-to-four times more potent, and capable of producing longer lasting contractions than histamine. Subsequent studies discovered other compounds, such as the epoxide intermediate (LTA_4) and its open chain congener (LTB_4), having similar properties and were finally designated a separate class—the leukotrienes. Excluding LTA_4 and LTB_4, all other mentioned compounds are known as peptido-leukotrienes. Sometimes, LTC_4, LTD_4, LTE_4 and LTF_4 are also, collectively, addressed as cysteinyl leukotrienes (cysLTs). However, due to its least potency, LTF_4 holds no physiological/pathological significance [12,13]. The peptido-leukotrienes are quite different in their biological actions from LTB_4, besides having different cellular targets. The difference can be easily noticed from their response in gastrointestinal mucosa, where the peptido-leukotrienes act as potent vasoconstrictor whereas LTB_4 shows little or no such effect [14]. Other bioactions of peptido-leukotrienes include contraction of bronchial and vascular smooth muscles, increasing the permeability of small blood vessels, inducing exudation of plasma, enhancing secretion of mucus in airway and gut, and recruiting leukocytes at the site of inflammation, whereas LTB_4 is primarily involved in inducing and aggravating the inflammatory responses. LTB_4 acts as a potent chemotactic agent for the recruitment of several pro-inflammatory cells, namely neutrophils, eosinophils and monocytes. It also prolongs the survival of eosinophils by preventing their apoptosis. It also mediates adhesion and extravasation of the mentioned inflammatory cells across endothelium. Besides, several studies have also reported their role in upregulating the secretion of reactive oxygen radicals, lysosomal enzymes and cytokines (such as interleukins) from pro-inflammatory cells and immune cells. The evidence of involvement of LTB_4 in immune responses was given by Costa et al. in their study which described the critical role of LTB_4 in enhancing the mobilization of T lymphocytes in response to several stimuli. LTB_4 may also produce bronchoconstriction but it is accompanied by tachyphylaxis, a response not observed during peptido-leukotrienes-induced bronchoconstriction. Vascular permeability changes induced by LTB_4 are usually observed only in the presence of a vasodilator prostaglandin [15–17]. Apart from the targets and bioactions, peptido-leukotrienes and LTB_4 also differ from each other in respect of inducing adverse reactions. While the former have been associated with inducing anaphylactic shock (when present in excess amounts), no such response has been reported for the later [18]. Leukotrienes are now widely recognized as potent inflammatory mediators, which exhibit prominent pathological roles in asthma, rheumatoid arthritis and other such