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Involvement of growth factors in diabetes mellitus and its complications: A general review

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ABSTRACT

Diabetes mellitus (DM) is a major endocrine metabolic disease and is marked by a lack of insulin. The complication of DM is one of the most difficult problems in medicine. The initial translational studies revealed that growth factors have a major role in integrating tissue physiology and in embryology as well as in growth, maturation and tissue repair. In some tissues affected by diabetes, growth factors are induced by a relative deficit or excess. Fibroblast growth factor 21 (FGF21) is a promising regulator of glucose and lipid metabolism with multiple beneficial effects including hypoglycemic and lipid-lowering. Vascular endothelial growth factor (VEGF) is a potent angiogenic and vascular permeability factor and is implicated in both of these complications in diabetes. Increase or decrease in the production of transforming growth factor-β1 (TGF-β1) has been associated with diabetic nephropathy and retinopathy. The insulin-like growth factor-I (IGF-I) is a naturally-occurring single chain polypeptide which has been widely used in the treatment of diabetic glomerular and renal tubular injuries. This review summarizes the recent evidences for an involvement of growth factors in diabetic complications, focusing on their emergence in sequence of events leading to vascular complications or their potential therapeutic role in these diseases. Growth factor therapy in diabetic foot ulcers is already a clinical reality. As methods to finely regulate growth factors in a tissue and time-specific manner are further developed and tested, regulation of the growth factor to normal level in vivo may well become a therapy to prevent and treat diabetic complications.

1. Introduction

Diabetes mellitus (DM) is essentially a metabolic insult characterized by chronic hyperglycaemia. Its underlying features are an absolute or relative deficiency in insulin secretion and/or insulin action in the or by the pancreatic β cells [1–4]. According to the International Diabetes Federation, an estimated 382 million people lived with diabetes in 2013, and this figure is expected to reach over 592 million in 2025 [2]. Clinical evidences [5,6], experimental models [7], and epidemiological studies [8] suggest that all forms of diabetes mellitus might target specific organs and systems in the body, resulting in progressive hyperglycemia and consequent tissue complications. The UK Prospective Diabetes Study [9,10] has demonstrated that progressive hyperglycemia or its metabolic consequences leads to a remarkably similar

Abbreviations: AGE, Advanced glycation end-product; AR, Aldose reductase; ACR, Albumin/creatinine ratio; CTGF, Connective tissue growth factor; DM, Diabetes mellitus; DAG, Diacylglycerol; DN, Diabetic nephropathy; DR, Diabetic retinopathy; DCM, Diabetic cardiomyopathy; DFU, Diabetic foot ulcerations; DNU, Diabetic neuropathy; EGF, Epidermal growth factor; ET-1, endothelin-1; EPO, Erythropoietin; FGF, Fibroblast growth factor; IGF-1, Insulin-like growth factor–1; MAPK, Mitogen-activated protein kinase; NF-kB, Nuclear factor kappaB; NO, Nitric oxide; NADPH, Nicotinic acid adenine dinucleotide phosphate; OS, Oxidative stress; PARP, Poly (ADP-ribose) pathway flux; PDGF, Platelet derived growth factor; PKC, Protein kinase C; ROS, Reactive oxygen species; RAS, Renin-angiotensin system; STZ, Streptozotocin; SDH, Sorbitol dehydrogenase; TGF-ß, Transforming growth factor ß; VEGF, Vascular endothelial growth factor

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increased risk of diabetic end-organ complications in both type 1 and 2 diabetes. The Diabetes Control and Complication Trials have clearly established that tighter blood glucose control is helpful in preventing the onset and development of these microvascular complications [3], involving mainly the retina [11], renal glomeruli, peripheral nerves [12] and the cardiovascular system [13]. Thus, the degree of chronic hyperglycemia is a major cause of diabetic complications, which also is an instrumental factor in developing diabetic microvascular complications. Before the arrival of insulin clinical therapy in the 1920s, type 1 diabetic patients rapidly died from severe catabolic dysfunction, such as absolute insulin deficiency and diabetic ketoacidosis [14]. After the discovery of insulin, it became clear that despite insulin treatment, tissue structure damage and organ dysfunctions are expected to occur in diabetic patients. In the current absence of a cure for diabetes, much effort is concentrated on the prevention of diabetic complications. After several decades of trial and error, traditional natural medicines and folklore worldwide have used numerous medicinal plants to manage the various diabetic complications because bioactive phyto-constituents are abundant in many places [1]. Unfortunately, there is still no therapeutic medicine specifically for diabetic complications and the mechanisms underlying the beneficial effects of most medicinal plants or their products on these diseases are unclear. For most people with diabetes, hyperglycemia persists and tissue complications become a reality. Because of the difficulty in achieving complete euglycemia, a new approach to preventing diabetic complications is required. Thus, based on an in-depth understanding of how these complications arise, rational molecular interventions can be developed. Over time, researchers have come to believe a number of aberrantly expressed growth factors play a role in the development of structural changes characterizing diabetic microangiopathy, which may be referred to as abnormal growth and impaired regeneration. Recently, attention has focused on the direct effects of protein and peptide drugs, such as different kinds of growth factors, on diabetic complications in human beings and animal models, some of which appear to mark a brand new direction in diabetic complication treatment.

In broad terms, growth factors are endogenously produced polypeptides that affect cellular functions, most commonly by inducing cell hyperplasia and/or tissue hypertrophy, resulting in growth of the organism [15]. Growth factors exert physiological effects in virtually every organ and tissue, but a number of molecular perturbations that occur in diabetes may cause, in genetically susceptible subjects, imbalances of their expression leading to derangements of cellular metabolism and proliferation [16]. In the microcirculation of diabetes, there may be interplay of metabolic and haemodynamic pathways, leading to an increase in growth factors in the target tissues [17]. Because diabetes is a state of chronic hyperglycaemia, it is possible that glucose-dependent processes are involved in these mechanisms: in vitro studies over the past 5 years clearly established a role for hyperglycaemia in stimulating the expression of growth factors such as transforming growth factor ß (TGF-ß) [18], fibroblast growth factor (FGF) [19,20], platelet derived growth factor (PDGF) [21] and vascular endothelial growth factor (VEGF) [22]. There is an evidence to support a potential role for a particular growth factor in causing diabetic complications in a tissue [15]. Many studies, both in diabetic people and animal models, indicate that the growth factor is abnormally regulated in the tissue involved in the diabetic complication [23]. Moreover, in vitro cell and tissue mechanistic studies show that intervention and returning the abnormal level and function of a growth factor in diabetes towards normal will lead to a reduction in, or may even prevent, tissue pathology and dysfunction [24,25]. To examine the role of growth factors in the main diabetic complications, these sources of evidence used to implicate growth factors in diabetic complications will be referred to. Knowledge of the involvement of growth factors in diabetic microangiopathy opens the way to new therapeutic interventions aimed at blocking the deleterious actions of several growth factors.

The present review summarizes recent research findings of the growth factors on the diabetic complications which include diabetic kidney disease (nephropathy), diabetic eye disease (retinopathy) and diabetic neuropathy in both diabetic men and experimental diabetic animals. In addition, we also highlighted the mechanism of the prophylactic role of growth factors against these diseases via in vivo and in vitro studies, describing the ameliorative effects of these cytokines especially on diabetes and its complications for providing a systematically in-depth basis to deepen the understanding for the origin of diabetic tissue damage, and encouraging the experimental and clinical results of using growth factors as a new alternative to treatment with diabetic complications.

2. The main mechanisms of diabetes caused by complications

2.1. The mechanism of glucose metabolism disorder in diabetes and its complications

Diabetes, as a metabolic disorder, a condition that disrupts cellular function, or as a pathological entity causing specific tissue and organ functional and structural damage, has aroused a worldwide alert. Epidemiological and clinical intervention studies in diabetes have shown that hyperglycemia impacts in a major way on both micro- and macro-vascular disease, as do lipid abnormalities. Sustained hyperglycemia causes severe diabetic micro-vascular complications such as retinopathy, nephropathy, autonomic neuropathy, cardiovascular symptoms, etc. Hyperglycemia is the major causal factor in the development of diabetic vascular complications and can mediate their adverse effects through multiple pathways. Four main hypotheses about how hyperglycaemia causes diabetic complications have generated a large amount of data, as well as several clinical trials based on specific inhibitors of these mechanisms. Four hypotheses are: increased Poly (ADP-ribose) pathway flux (PARP); increased advanced glycation end-product (AGE) formation; activation of protein kinase C (PKC) isoforms; and increased hexosamine pathway flux. Up to now, these mechanisms are still under constant exploration. There is no unifying hypothesis linking these four mechanisms.

2.1.1. Activation of protein kinase C (PKC) isoforms

PKC, a family of serine-threonine kinases, plays a key role in regulating endothelial cell permeability, promoting cell proliferation and vascular growth [3]. PKC-β, which is activated in diabetic animals and in vascular cells exposed to elevated glucose levels, is one of the targets for improving diabetic complications [24,26–28]. Recent studies have identified that hyperglycemia-induced PKC activation and diacylglycerol (DAG) levels increased in a variety of tissues are involved in diabetic vascular complications [29,30], including retina, aorta, heart, and renal glomeruli from diabetic animal models and patients. Interestingly, hyperglycemia-induced oxidative stress may also mediate the adverse effects of PKC- isoforms by the activation of the DAG-PKC pathway [31]. The amount of clinical and animal experimental material indicated that excess glucose directly stimulates activation of the polyol pathway and also the activity of mitochondria, PKC and NADPH oxidase [32,33], which results in the massive production of reactive oxygen species (ROS). Many kinds of tissue lesions are associated with these changes in retinal, renal, and cardiovascular tissues. In addition, sustained activation of PKC in turn contributes to the activation of several growth factors such as TGFß, VEGF and PDGF in cultured mesangial cells [34] and in glomeruli of diabetic rats [35]. This may be an important research field in the future. Hyperglycaemia-induced activation of PKC has also been implicated in the overexpression of the fibrinolytic inhibitor, the activation of NF-kB in cultured endothelial cells [36] and vascular smooth muscle cells [37]. The above conditions give rise to occlusion of blood vessels or capillaries, which will lead to more severe complications. In early experimental diabetes [38], activation of PKC-β isoforms has been shown to mediate various vascular function changes including retinal and renal blood flow abnormalities,