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Review

Role of the calpain on the development of diabetes mellitus and its chronic complications

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ABSTRACT

Diabetes mellitus (DM) is associated with acute and chronic complications that cause major morbidity and significant mortality. Calpains, a family of Ca(2+)-dependent cytosolic cysteine proteases, can modulate their substrates' structure and function through limited proteolytic activity. Calpain is a ubiquitous calcium-sensitive protease that is essential for normal physiologic function. However, alterations in calcium homeostasis lead to pathologic activation of calpain in diabetes mellitus. Since not much is known on the relationship between calpain and diabetes mellitus, this review outlines the contribution of calpain to chronic complications of diabetes mellitus, such as diabetic cardiomyopathy, diabetic nephropathy and diabetic retinopathy.

Contents

1. Introduction

The calcium ion is essential to the normal function of all living cells. In the human, some 99% of total body calcium resides in the skeleton, and 1% is distributed in the soft tissues and extracellular fluids. The concentration of free calcium ions in the cytoplasm of resting cells and in the extracellular fluids is rigidly maintained, in keeping with the critical physiological importance of calcium to a wide variety of biological processes. Ca^{2+} is such an important signaling molecule, mutations causing drastic functional changes in intracellular Ca^{2+} homeostasis are most likely not compatible with life [1].

Calpains are a family of calcium-activated proteases involved in a number of cellular functions including cell death, proliferation and exocytosis [2]. In the human genome, there are 15 calpain genes. Two of the best characterized calpain species are μ-calpain (calpain-1) and m-calpain (calpain-2). These isoforms are heterodimers consisting of 80 kDa catalytic subunits and a 30 kDa regulatory subunit [3]. The regulatory subunit is essential for μ- and m-calpain stability and catalytic activity [4]. The 80 kD subunit has four domains: domain I is important for regulating the activity and dissociation of the subunit; domain II, a catalytic domain, has two subdomains in the absence of Ca^{2+}; domain III binds Ca^{2+} and phospholipids; and domain IV, is important for dimer formation. The 30 kD regulatory subunit of calpains 1, 2, and 9 consists of two domains: domain V and domain VI, which is similar to domain IV of the catalytic subunit [5]. Calpain-1 and calpain-2 activities are

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tightly controlled by the endogenous inhibitor calpastatin. Calpastatin appears to be specific for these two calpain isoforms but does not inhibit any other protease [6].

2. Calpain and diabetes mellitus

In the pancreatic β-cell, cytoplasmic calcium ($Ca^{2+}{}_c$) levels rise as a direct consequence of glucose metabolism, via closure of K_{ATP} channels, triggering Ca^{2+} entry and subsequent Ca^{2+}-mediated exocytosis of insulin granules [14]. Therefore, partial inhibition of any protein involved in the removal of $Ca^{2+}{}_c$ during β-cell excitation should augment insulin secretion only when β-cells are stimulated. Calpain-10 protein may play a role in glucose metabolism, pancreatic β cell function, and regulation of thermogenesis [7]. Calpain 10 has been implicated in both insulin-stimulated glucose uptake and insulin secretion in islet cells [8–10]. SNP-43 in calpain 10 is involved in many of the phenotypes associated with type 2 diabetes mellitus (T2DM), such as insulin resistance, lipogenesis, insulin secretion and microvascular function, while SNP-44 has been associated with increase risk for T2DM [11,12]. Beta-cell function was lower in subjects without T2DM that carried the at-risk genotypes G/G at SNP-43 and T/C at SNP-44 [2]. In subjects with T2DM, the influence of the genotype on beta-cell function was not evident because the level of function of these pancreatic cells is already altered due to the disease per se and to all the factors that contributed to the onset of it; therefore, the influence of the genotype has been lost. Once the disease has been established, which not only involves the dysfunction of beta-cells but also other events, it is likely that at-risk variants in calpain 10 are not more associated with the level of beta-cell function [13].

3. Calpain and diabetic cardiomyopathy

Diabetic cardiomyopathy has been defined as ventricular dysfunction that occurs in diabetic patients independent of a recognized cause such as coronary artery disease or hypertension [14]. The mechanisms of diabetic cardiomyopathy are multifaceted, involving increased oxidative/nitrosative stress, accumulation of advanced glycation end products, enhanced receptor for advanced glycation end product and angiotensin II receptor type 1 signaling, activation of various proinflammatory and cell death signaling pathways polymerase, mitogen-activated protein kinases, coupled with consequent changes in the composition of extracellular matrix with enhanced cardiac fibrosis, myosin heavy chain isoform switch, and decreased activity of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase [15–19].

The molecular mechanisms of diabetic cardiomyopathy are not well understood; however, impairment of Ca^{2+} homeostasis is a significant feature of type 1 and type 2 diabetic cardiomyopathies [20,21]. Studies have shown promising improvements in cardiac function after inhibition of calpain activity whether in infarction or ischemia/reperfusion models [22,23]. Pharmacological inhibition of calpain reduced apoptosis in both treatments. Furthermore, research has uncovered vital roles for calpain in regulating the activity of nuclear factor of activated T cells (NFAT) and nuclear factor-κB (NF-κB), two transcription factors frequently implicated in the promotion of hypertrophy and fibrosis [24,25]. Calpains may play a role in cardiac hypertrophy of diabetic cardiomyopathy. A recent study reported that transgenic overexpression of calpastatin reduced myocardial hypertrophy in a mouse model of angiotensin-II–induced hypertension, suggesting that calpain may be a contributing factor to cardiac hypertrophy. Calpain activation correlated with increased NFAT and NF-κB activity, each of which mediates prohypertrophic signaling pathways [26–28]. Indeed, calpain has been identified as a key activator of the NF-κB pathway leading to myocardial hypertrophy in angiotensin-II–induced hypertension [26]. Furthermore, cardiomyocyte-expressed calpain may contribute to fibrosis via indirect or direct mechanisms. Cultured cardiac fibroblasts undergo significant hyperplasia in response to high glucose, and that was reduced by the inhibition of calpain. Fibroblast proliferation is induced by a number of factors, including possibly NF-κB [29]. Evidence suggests the IκB–NF-κB complex is influenced by calpain activation, which may contribute to the development of diabetic cardiomyopathy through the promotion of fibrosis [30]. Specifically, NF-κB is required for the induction of proinflammatory cytokines such as TNF-α, which is also overexpressed in the diabetic heart [31]. Specifically, calpain inhibition also reduced matrix metalloproteinase-2 (MMP-2) and MMP-9 activities in the diabetic heart. Prior work suggests that calpain induces MMP-9 activity in homocysteine-stimulated cardiac microvascular endothelial cells [32].

4. Calpain and diabetic nephropathy

Diabetic nephropathy (DN) is the leading cause of end stage renal diseases worldwide [33]. DN is characterized by morphological and ultrastructural changes in the kidney including expansion of the molecular matrix and loss of the charge barrier on the glomerular basement membrane [34,35]. DN is a multifactorial progressive disease where the pathogenesis of the disease is extremely complex involving many different cells, molecules, and factors [36]. Renal calpain 10 protein and mRNA decrease with chronic elevated glucose, both in vitro and in vivo, a decrease that correlates with increased calpain 10 substrates resulting in mitochondrial dysfunction and apoptosis [37]. Loss of renal calpain 10 by siRNA in vivo results in renal dysfunction and apoptosis, suggesting a direct relationship between loss of calpain 10 protein expression and renal dysfunction. These data collectively indicate that the loss of calpain 10 in vivo results in renal apoptosis and renal dysfunction, underscoring that the loss of calpain 10 causes mitochondrial dysfunction leading to cell death in diabetic nephropathy [38].

Previous studies have also demonstrated that calpastatin administration prevents fibronectin degradation by externalized calpains in postischemic kidney [39]. Externalized calpains may accelerate tubule repair in ischemic acute renal failure is supported by the demonstration of persistent lesions of tubules after administration of calpastatin domain I [39]. The decreased level of fibronectin breakdown product in urine of mice given calpastatin indicates clearly that calpastatin reached tubule lumens and effectively targeted externalized calpains [40]. By contrast, a recent report shows that two cell-permeable calpain inhibitors, PD 150606 and E-64, reduce the renal dysfunction and injury caused by ischemia reperfusion [40]. Altogether, this is good evidence that extracellular calpains triggered by calpastatin domain I contribute to tubule repair, partly by inducing epithelial cell migration, whereas intracellular calpains triggered by PD 150606 and E-64 participate in tubule injury, partly by increasing oxidative stress [39].

5. Calpain and diabetic retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes and a leading cause of visual impairment and blindness [40]. Patients with DR may irreversibly lose sight as a result of the development of diabetic macular edema and/or proliferative diabetic retinopathy; retinal blood vessel dysfunction and degeneration plays an essential role in their pathogenesis [41]. Although the selective loss of retinal pericytes has long been known to be one of the earliest histopathological findings in diabetic retinopathy, only limited information is available concerning their function and cell biology. Recently, it has been shown