HHS Public Access

Author manuscript

J Nat Sci. Author manuscript; available in PMC 2016 October 14.

Published in final edited form as:

J Nat Sci. 2016 ; 2(9): .

Role of Calpain in Pathogenesis of Human Disease Processes

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Abstract

Calpains are a 15-member class of calcium activated nonlysosomal neutral proteases which are involved in a broad range of cellular function. Calpains are usually localized to the cytosol and within mitochondria. Calpastatin is an endogenous protein that specifically binds to and inhibits calpain. Overactivation of calpain has been implicated in a number of disease processes of the brain, eyes, heart, lungs, pancreas, kidneys, vascular system and skeletal muscle. Therefore, calpain may serve as a potential therapeutic target for a wide variety of disease processes. This review briefly outlines the current literature regarding the involvement of calpain overactivation in the pathogenesis of almost every organ in the body.

Keywords

Calpain; Pathogenesis; Human Disease

Introduction

Calpains are a class of calcium activated nonlysosomal neutral proteases which are involved in a broad range of cellular function. Overactivation of calpain has been implicated in a number of disease processes ranging from neurodegeneration to muscle atrophy. Inhibition of calpain overactivity has been found to be beneficial in a number of animal models. Therefore, calpain serves a potential medical target for a wide variety of disease processes. This review discusses the current literature regarding the effect of calpain overactivity on the pathogenesis of almost every organ in the body.

Background

Calpains are a 15-member class of calcium activated nonlysosomal neutral proteases which are localized to the cytosol and mitochondria. [1] Some calpains are ubiquitously expressed (1, 2, 4, 5, 7, 10) but others are thought to be localized in specific tissues as follows: 1+2: endothelial cells, 3: skeletal muscle, 6: placenta, 8: smooth muscle, 9: stomach, 11: testes, 12: skin, 13 testes and lung. Calpastatin is an endogenous protein that specifically binds to and inhibits calpain. Interestingly, calpastatin is thought to bind to calcium activated calpains suggesting that it does not interfere with basal calpain activity in the cell. [2]

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Brain

Baseline calpain function is thought to be neuroprotective while over-expression of calpain activity is associated with neurologic dysfunction.[3] Calpain overactivation is linked to the synaptic plasticity and neurodegeneration associated with Alzheimer's disease.[4,5] Calpain mediated proteolysis regulates the activity of important disease associated proteins including tau kinase, cylin dependent kinase 5 and glycogen kinase synthase 3.[5] Calpain inhibition has been shown to beneficially moderate the abnormal synaptic plasticity and memory produced by excess amyloid β in patients with Alzheimer's disease.[6] Calpains are also thought to be mediators of neuronal damage after traumatic and ischemic neural injuries.[7] Most of the research regarding calpain and neurologic decline focuses on calpain 1 and 2. For example, mutations in calpain 1 have been shown to cause autosomal hereditary spastic paraplegia and spastic ataxia. [3] Excessive activation of calpain 2 has been linked to oligomer induced neuronal cell death leading to the dysfunction seen in patients with neurodegenerative diseases. [8] It is clear that overactivity of calpain is associated with neurological decline; more research is needed to determine the mechanism through which this dysfunction occurs.

Eyes

In situations of stress, overactivity of calpain in retinal cells is thought to cause retinal cellular dysfunction leading to vision loss. Ischemic injury in the retina leads to overactivity of calpain which causes the breakdown of α spectrin and results in cellular death in the hypoxic retinal cells. Inhibition of calpain activity in these cells is associated with decreased cell death. [9]

Overactivation of calpain is also thought to cause aberrant neogenesis which leads decreased blood flow and subsequent retinal dysfunction. In ischemic retinopathy, hypoxia leads to vascular endothelial growth factor-A (VEGF) induced abnormal neovascularization that in turn causes damage to the retina and results in blindness. This abnormal neovascularization is associated with increased calpain activity in the retinal endothelial cells and disrupts the actin cytoskeleton and microtubule strength leading to defective neo vessel formation. Calpain inhibition has been shown to reduce VEGF induced neovasculature architectural abnormalities, vascular leakage and retinal hypoxia. Calpain inhibitors are thought to work by improving the organization of the actin cytoskeleton in retinal endothelial cells and improving the stability of actin cables in new blood vessels. [10,11]

Interestingly, calpain has also been found to be upregulated in human lens epithelial cells in patients with diabetic retinopathy. Expression levels of calpain are highest in patients with 1) longer duration of diabetes mellitus 2) higher hemoglobin A1c levels and 3) a diagnosis of advanced diabetic retinopathy. [12]

Taken together, these data suggest that overactivation of calpain both in the retinal and lens epithelial cells and in the endothelial cells of the eye lead to reduced vision.

Heart

There is a large amount of research to suggest that calpain activity is overexpressed in myocardial tissue that is stressed (ie acute infarct, from high glucose levels, oxidative stress, right heart failure, chronic ischemia, sepsis and atrial fibrillation). [13]

Calpain activity is increased in myocardial cells after an acute myocardial infarct. This activation leads to post-myocardial infarction remodeling by disrupting N-cadherin and α-fodrin based cell adhesions. Inhibition of calpain attenuates this post-myocardial infarction remodeling. [14,15] Calpain inhibition after acute ischemia and reperfusion decreases myocardial infarct size and improves left ventricular contractility and myocardial hemodynamic function. [16,17]

High glucose levels induce apoptosis by both mitochondrial dependent and independent mechanisms. Both mechanisms result in calcium overload which leads to activation of calpain 1. Calpain 1 activation induces caspase 3 and poly ribose polymerase and cleaves apoptosis inducing factor. [1] This increased calpain activity results in increased cardiomyocyte oxidative stress and apoptosis. The final result is hypertrophy of the cardiomyocytes resulting in diabetic cardiomyopathy. [13,18] Calpain inhibition has been shown to attenuate the myocardial hypertrophy and fibrosis associated with diabetes. [19]

Right heart failure results from a number of disease processes which lead to acute right ventricular overload and contractility dysfunction. This ventricular contractile dysfunction has been associated with disruption of the focal adhesion proteins; talin, vinculin and α-actinin. Interestingly, calpain inhibition in the setting of right heart overload has been shown to preserve the organization of talin, vinculin and α-actinin resulting in the attenuated severity of right heart failure. [20]

Calpain inhibition has been shown to increase myocardial blood flow and vascular density in the setting of chronic myocardial ischemia.[21,22] GSK-3β is a known substrate of calpain which has been shown to play a dominant role in cardiomyocyte death.[23–25] Interestingly, GSK-3β inhibition in the same chronic ischemia model has been shown to have similar beneficial effects on myocardial blood flow.[26] Troponin T is an important sarcomeric protein that is involved regulation of cardiac muscle contraction. In chronically hypoxic cardiomyocytes calpain is thought to induce the breakdown of troponin T. [27,28]

Additionally, sepsis has been shown to cause overactivation of calpain in cardiomyocytes leading to increased caspase-3 activation and TNF-α expression. Inhibition of calpain activation in cardiomyocytes improves the myocardial dysfunction associated with endotoxaemia. [29,30]

Interestingly, calpain 2 protein levels have been found to be increased in the atrial tissue of patients with atrial fibrillation, valvular heart disease and diabetes. [31]

There is a large amount of research to suggest that calpain overactivity in stressed myocardial tissue leads to cardiac dysfunction and that inhibition of calpain activity is beneficial to cardiac function.

Lungs

Calpain is thought to play a critical role in the pathogenesis of the tissue remodeling associated with a number of pulmonary diseases. Calpain augments collagen-1 synthesis in patients with pulmonary fibrosis. [32] Inhibition of calpain has been found to ameliorate pulmonary fibrosis by decreasing expression of interleukin-6, transforming growth factor-β1, angiopoietin-1 and collagen-1 in lung tissue. [33]

Calpain overactivity has also been implicated in the pathogenesis of asthma through a similar mechanism. Calpain is thought to mediate cytokine induced collagen-1 proliferation by upregulating the mTOR/Akt signaling pathway. This results in the airway smooth muscle remodeling that occurs in patients with asthma. [34] Taken together, research suggests that calpain overactivity leads to pulmonary disease by upregulating collagen proliferation.

Pancreas

Calpain-10 gene expression has been found to be associated with the pancreatic insufficiency that occurs in patients with obesity and diabetes mellitus. [35–37] Beta cell dysfunction is a major cause of the pathogenesis of type 2 diabetes mellitus (T2DM). Calpain has been found to contribute to beta cell dysfunction and apoptosis in the setting of T2DM. [8]

One mechanism through which calpain may lead to beta cell dysfunction is thought to occur through the endoplasmic reticulum. Obesity and T2DM result in increased levels of plasma free fatty acids. These free fatty acids have been shown to lead to increased calcium ion expression and calpain activation that induces major endoplasmic reticulum stress markers in beta cells resulting in cellular apoptosis.[38]

Finally, current research suggests that variation of the calpain 10 gene impacts a variety of the clinical metabolic derangements related to type 2 diabetes mellitus.[39] However, the exact mechanism through which calpain works is currently unknown.

Kidney

Normal calpain activity is necessary for basic renal cell function. Calpain has been found to be localized to both the cytosol and mitochondria in renal proximal tubule cells. Interestingly, calpain 10 has been shown to be required for renal cell viability. Calpain 10 expression levels have been found to decrease with increasing age and renal dysfunction. [40]

In the setting of renal ischemia, calpains are released into the extracellular environment by tubular epithelial cells. This externalization of calpain increases epithelial cell mobility and helps with tubule repair. Calpains work by cleaving fibronectin and preventing its ability to bind to integrin. In a small animal model of ischemic acute renal failure, cytosolic calpain inhibition was associated with delayed tubule repair. [41]

Calpains are thought to mediate renal proximal tubule injury. [42,43] Calpain overactivation leads to cleavage of paxillin, talin and vinculin in renal proximal tubule cells. This cleavage of cytoskeletal proteins results in increased plasma membrane permeability and caspase activation resulting in renal cell death and necrosis. [1] Calpain inhibition preserves cytoskeletal protein levels and mediates plasma membrane permeability. [44]

In situations of stress, renal cells experience a loss of ATP. This ATP depletion leads to increased release of calcium from the endoplasmic reticulum. This increased calcium release leads to increased calpain activity. Calpain is thought to mediate late stage cell death by inducing a second extracellular calcium ion influx leading to cell swelling and loss of plasma membrane integrity. [45]

Calpain 10 cleaves electron transport chain proteins in the mitochondria of renal cells. This cleavage decreases mitochondrial respiration and leads to mitochondrial dysfunction which results in renal cell death. [1]

Taken together, these data suggest that basal levels of calpain activity play a protective role in the kidney but over-activation in the setting of stress leads to cell death.

Vascular System

Research shows that calpain overactivity results in endothelial dysfunction by a number of different mechanisms.

Endothelial dysfunction is a widely accepted cause of diabetic vasculopathy. Calpain activity has been shown to be increased in the microcirculation of rats with T2DM. Inhibition of calpain is associated with attenuated leukocyte-endothelium interactions, decreased expression of cell adhesion molecules and increased endothelia nitric oxide availability. [46]

In the setting of diabetes, calpain also plays a role in vascular endothelial reactive oxygen species (ROS) production. High glucose levels induce calpain activity leading to cellular apoptosis. Inhibition of calpain prevents high glucose-induced ROS production, mitochondrial superoxide generation and apoptosis in endothelial cells, and attenuates endothelium dependent aortic ring relaxation.[47] Interestingly inhibition of calpain in the setting of diabetes has also been found to prevent upregulation of leukocyte endothelial interactions by increasing the association of hsp90 with endothelial nitric oxide synthase and decreasing endothelial cell surface expression of proinflammatory adhesion molecules (ICAM and VCAM) during hyperglycemia.[48]

Angiongensin II is a critical mediator of cardiovascular remodeling in the setting of hypertension. Angiongensin II activates calpain which lead to vascular media hypertrophy, perivascular inflammation and fibrosis. Calpain inhibition blunts angiongensin II-induced medial hypertrophy, perivascular inflammation and fibrosis in the aorta and small kidney arteries. [49]

Over expression of calpain 1 by angiotensin II induces matrix metalloproteinase type 2 activity which has been linked to extracellular matrix remodeling by promoting collagen I

and III production and inducing vascular calcification. Calpain 1 over expression also induces transforming growth factor-β1/Smad signaling, elastin degradation, alkaline phosphatase activation and increases total calcium content in cultured vascular smooth muscle cells and carotid artery rings. Interestingly, calpain 1 and collagen II protein levels increase with the age in human aortic intima. These same proteins have been found to be over expressed in atherosclerotic plaques. Taken together, this data suggests that calpain mediated extracellular matrix remodeling is associated with hypertension and atherosclerosis. [50]

Oxidized low density lipoprotein is known to contribute to atherosclerosis by inducing apoptosis of endothelial cells. Oxidized low density lipoprotein induces calpain dependent proteolysis of the cytoskeletal protein α-fodrin and anti-apoptotic protein Bcl-2 in endothelial cells. Inhibition of calpain mediates this effect. [51]

In endothelial cells, during situations of stress calcium ion overload leads to mitochondrial calpain 1 cleavage of the sodium/calcium exchanger which results in calcium accumulation in the mitochondria. Calpain 1 activity also cleaves Bid which induces cytochrome c release and leads to endothelial cell apoptosis. [1]

Taken together, research suggests that during stress calpains become overactivated leading to endothelial cell dysfunction and, ultimately, organ dysfunction.

Skeletal Muscle

Calpain activity has been found to be upregulated and associated with the muscle fiber atrophy seen in dermatomyositis. This calpain activity is localized to the perifascicular muscle fibers.[52] Calpain is known to cleave transcription factor YY1 which represses muscle restricted expression of sarcomeric α-actin genes.[53]

Conclusion

Calpain overactivity is involved in the pathophysiology of a large number of disease processes. Situations of stress lead to increased calcium ion release causing overactivation of calpain. Calpain then functions to promote cellular apoptosis and degrade cytoskeletal structure resulting in organ dysfunction. (Figure 1) Recent research has started to isolate which specific calpain family member is involved in each of the different disease processes. The next step will be to create a calpain inhibitor that is selective enough to inhibit a specific calpain in a cell- or tissue-specific manner to block the detrimental effects of calpain overactivation.

Acknowledgments

This work was supported in part by the National Heart, Lung, and Blood Institute (R01HL46716, RO1HL128831 Dr. Sellke); NIH/NIGMS GM1P20GM103652 (Project-3) and American Heart Association Grant-in-Aid 14GRNT20460291 (Dr. Abid); NIH/NIGMS Training Grant 2T32 GM065085 (Dr. Potz).

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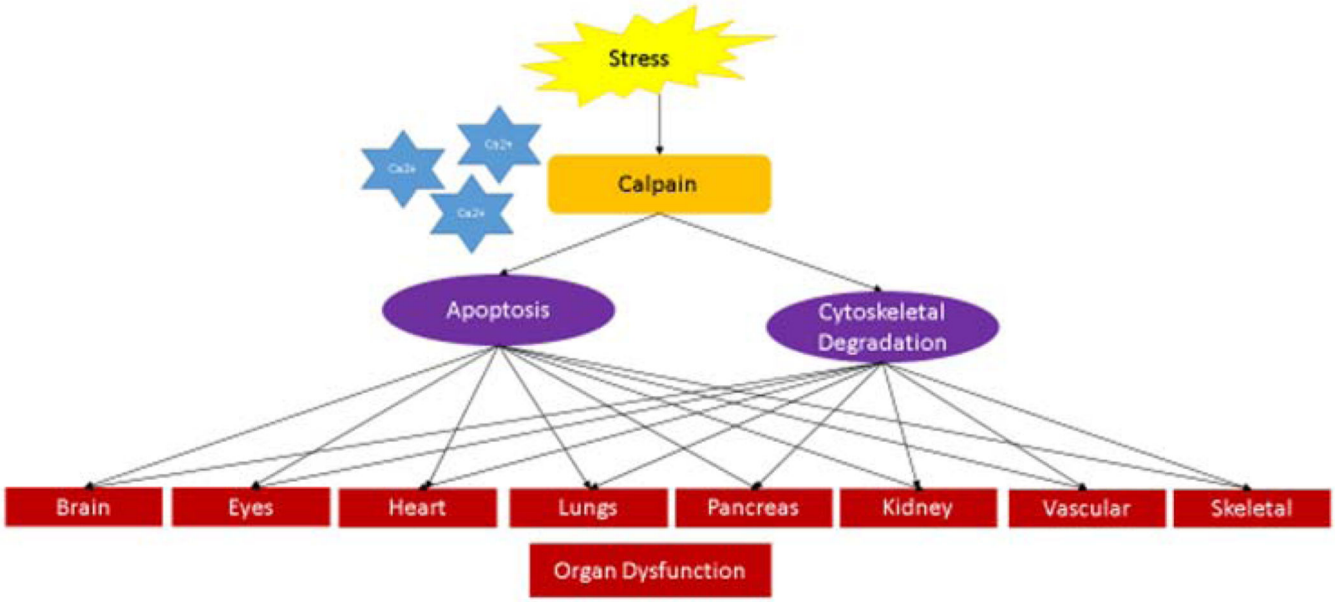

Figure 1. Calpain Activation in Situations of Stress Leads to Organ Dysfunction

Situations of stress lead to increased calcium ion release causing over-activation of calpain. Calpain then acts to promote cellular apoptosis and degrade cytoskeletal structure resulting in organ dysfunction.