A Collection of Studies

TB4-FRAG

National Academy of Hypothyroidism
and Integrative Sciences

Important Disclaimer

All studies have limitations, and there is no perfect study. As with other studies, the studies mentioned below have limitations that should be considered when evaluating the efficacy of TB4 Frag and determining the appropriateness of TB4 Frag for consumer use. A short summary, the abstract and the entire study is provided for your review. It is strongly recommended that you read each study in its entirety to best understand the uses, risks, effects, and limitations of the data on TB4 Frag. While studies suggest that these are possible outcomes, The National Academy of Hypothyroidism does not endorse the use of TB4 Frag for any of these conditions. These are provided for educational use only.

Some limitations of many or all the studies provided may include: The use of animal studies; being foreign studies; having variable TB4 Frag administration, including oral, intraperitoneal, intravenous, local injection and transdermal; use of induced disease models on animals; use of variable treatment protocols and dosing; use different forms of outcome assessment, including clinical response, histopathological, postmortem, gross pathology, and microscopic; variable methods of statistical analysis; no study is currently of the actual brand being marketed; variable sizes and selection methods of treatment and control groups; some may have no control group, or subjects may serve as their own controls; variable study designs; wide-range of conditions tested; and small treatment and control groups. There, of course, might be other study limitations. If you find any issues or concerns that you wish to report or have any questions, please contact The National Academy of Hypothyroidism (nahypothyroidism.com). The National Academy of Hypothyroidism can put you in contact with our chief medical/scientific officer (CMO) for clarifications.

We look forward to your feedback.

Ac-SKP ameliorates the progression of experimental autoimmune encephalomyelitis via inhibition of ER stress and oxidative stress in the hippocampus of C57BL/6 mice

Link: https://pubmed.ncbi.nlm.nih.gov/31589901/

Publication Date: October 2019

Journal Name: Brain Research Bulletin

Synopsis: The pathophysiology hallmarks of multiple sclerosis are inflammatory lesions that lead to damaged myelin sheath, axonal degeneration, and subsequent neurological dysfunction. The central nervous system inflammation present in this disorder is associated with endoplasmic reticulum stress and oxidative stress. In this study, Ac-SKP was used to test its anti-inflammatory properties in experimental autoimmune encephalomyelitis mice, a comparable animal model for multiple sclerosis. The results of the study suggest that Ac-SKP could be used as a therapeutic strategy for attenuating the oxidative stress and endoplasmic reticulum inflammation associated with neurodegenerative disorders. The study suggests that Ac-SDKP may work to inhibit ER and oxidative stress in the hippocampus through (1) decreasing pro-inflammatory cytokine activation, (2) reducing reactive oxygen species and nitric oxide production, and (3) weakening the expression of CHOP and capase-12 induced ER stress in microglia, astrocyte, and oligodendrocyte cells.

N-Acetyl-Seryl-Aspartyl-Lysyl-Proline Prevents Renal Insufficiency and Mesangial Matrix Expansion in Diabetic*db/db* Mice

Link: https://pubmed.ncbi.nlm.nih.gov/15734863/

Publication Date: December 2004

Journal Name: American Diabetes Association

Synopsis: Diabetic nephropathy (DN) is characterized by four main stages, (1) the thickening of the glomerular basement membrane, (2) mild to severe mesangial expansion, (3) nodular sclerosis, and (4) the presence of tubulointerstitial and vascular lesions. Hyperglycemia is commonly seen in animal models and patients with diabetes which is closely associated with the upregulation of glucose transport-1 and the subsequent upregulation of transforming growth factor-b (TGF-b) in mesangial tubular cells.

In this study, Ac-SKP was used to treat diabetic mice to evaluate its ability to inhibit physical manifestations of DN such as renal insufficiency and injury, excessive mesangial expansion, and over expression of extracellular matrix proteins. The results of this study suggest that Ac-SKP may be a useful novel strategy for treating diabetic nephropathy as it displays in this application to (1) attenuate glomerular hypertrophy and mesangial expansion, (2) reduce the overexpression of fibronectin and type IV collagen in the glomeruli of diabetic mice, and (3) inhibit TGF-b signaling via the Smad pathway in mesangial cells.

C-terminal variable AGES domain of Thymosin β4: the molecule's primary contribution in support of post-ischemic cardiac function and repair

Link: https://pubmed.ncbi.nlm.nih.gov/26255251/

Publication Date: August 2015

Journal Name: Journal of Molecular and Cellular Cardiology

Synopsis: Currently, myocardial infarction is the most common form of heart failure, however there are limited treatments available. The remodeling process due to myocardial cell death after an infarction poses long-term risks that impact principal roles of the heart such as left ventricular function, electrical conduction, and overall pumping capabilities. This study tested the efficacy of various fragments of thymosin-b4 to increase and support cardiac function in mice and pigs after a myocardial infarction.

The results reveal that the C-terminal tetrapeptide, AGES, increases embryonic cardiac cell migration, myocyte communication and beating in culture, stimulates coronary vessel growth, and inhibits inflammation following cardiac ischemia, improving heart function following ischemia. AGES is orally bioavailable and readily taken up by cardiomyocytes. AGES improved cellular communication, which promotes proper cardiac function and prevents A-fib and other arrythmias. The actin binding domain of TB4 was shown to promote myocyte fibrillation due to the lack of effect on the restoration of intracellular communication, as AGES is shown to correct. AGES was the only fragment to improve cardiac function in hypoxic adult pigs.

Closer analysis of the molecular and physiological distinctions between the two constructs concluded that besides positively affecting myocyte death, coronary growth and inflammation, the restoration of intercellular communication in the myocardium (particularly via connexins) is equally critical to achieve sufficient functional recovery in large size mammals, such as pigs.

N -acetyl-seryl-aspartyl-lysyl-proline treatment protects heart against excessive myocardial injury and heart failure in mice

Link: https://pubmed.ncbi.nlm.nih.gov/30998852/

Publication Date: November 2019

Journal Name: Canadian Journal of Physiology and Pharmacology

Synopsis: According to the American Heart Association, acute myocardial infarction and chronic heart disease remains the underlying cause of one in every 2.7 deaths in the United States. Excessive inflammatory response, insufficient myocardial capillary density, cardiomyocyte apoptosis, and long-term complications such as heart failure are few of the numerous critical consequences of a myocardial infarction. In this study, Ac-SKP was used to evaluate its ability to (1) reduce the incidence of cardiac rupture during MI, (2) reduce cardiac fibrosis, and (3) inhibit endoplasmic reticulum (ER) stress in mice. The findings show that the antifibrotic and anti-inflammatory abilities of Ac-SKP reduced interstitial fibrosis, increased capillary density in the myocardium, and decreased the expression of an ER stress marker, displayed pro-angiogenic effects, and improved overall cardiac function. The study suggests that Ac-SDKP could potentially be used as a therapeutic treatment to protect patients with acute myocardial infarction from cardiac injury.

Peptide Fragment of Thymosin b4 Increases Hippocampal Neurogenesis and Facilitates Spatial Memory

Link: https://pubmed.ncbi.nlm.nih.gov/26363149/

Publication Date: December 2015

Journal Name: Elsevier Neuroscience

Synopsis: Previous studies have suggested that thymosin b4 (Tb4) has neuroprotective effects on the central nervous system due to the likely role it plays in synaptogenesis, axon growth and cell migration. Likewise, Ac-SKP, a peptide fragment of Tb4, has been speculated to display similar angiogenic effects. In this study, mice were treated with Ac-SKP to evaluate the effects of neural proliferation and survival. The results showed that the Ac-SKP treatment positively regulated neural proliferation, increased the generation of new neurons, and enhanced spatial memory. This study suggests that Ac-SKP could be used as a potential therapy to increase adult neurogenesis and replenish damaged neurons by vascular endothelial growth factor (VEGF) mediation via P13K/GSK-3b/b-catenin signaling pathways. Ac-SKP could be a useful therapeutic candidate for the regeneration of damaged tissues in various pathologies and neurological disorders such as addiction, depression, epilepsy, and schizophrenia.

"Taken together, these data demonstrate that TB4 frag [Ac-SKP] functions as a regulator of neural proliferation and indicate that Ac-SDKP may be a therapeutic candidate for diseases characterized by neuronal loss. Ac-SKP also increased spatial memory."

"For the first time, we showed that ß-thymosin peptide active fragment, Ac-SKP, could increase adult neurogenesis, which may be highly relevant in preventing various neurodegenerative diseases by the replenishment of damaged neurons."

A Small Peptide Ac-SKP Inhibits Radiation-Induced Cardiomyopathy

Link: https://pubmed.ncbi.nlm.nih.gov/30354563/

Publication Date: August 2018

Journal Name: American Heart Association

Synopsis: Mediastinal radiation therapy is a commonly used treatment modality for a diverse range of neoplasms for targeted areas such as the lungs, breasts, and thorax. However, this existing treatment can result in deleterious cardiac damage induced by inflammation, fibrosis, and cardiomyocyte loss after continuous radiation exposure. In this study, Ac-SKP was used to test its antifibrotic and anti-inflammatory effects in a rat model of radiation-induced cardiomyopathy. This study suggests that Ac-SKP could be used as a future novel peptide treatment for radiation induced cardiotoxicity due to its presented cardioprotective effects. The study presents evidence that Ac-SKP has strong anti-inflammatory, antifibrotic, cardiomyocyte preserving, and Mac-2 inhibitory capabilities. Ac-SKP could be used as a possible treatment to decrease the accumulation of interstitial collagen, myocardial ECM volume, and inflammation associated with cardiomyopathy.

Ac-SKP inhibits transforming growth factor-b1 induced differentiation of human cardiac fibroblasts in myofibroblasts and conditions associated with increased TGFb-1, such as CIRS, chronic Lyme disease, CFS, fibromyalgia, chronic illness, NASH, and aging

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2867434/
Publication Date: February 2010
Journal Name: American Journal of Physiology- Heart and Circulatory

Synopsis: Transforming growth factor-b1 (TGF-b1) is an important fibrogenic cytokine which induces the transformation of cardiac fibroblasts into myofibroblasts, subsequently increasing production of extracellular matrix proteins such as collagen. High concentrations of TGF-b1 are present in fibrotic cardiac tissue and plays a key role in cardiac remodeling under physiological and pathophysiological conditions. In this study, Ac-SKP was used to test its anti-fibrotic properties in human fetal cardiac fibroblasts (HCFs). The results showed that Ac-SKP inhibited all effects of TGF-b1, inhibited endothelin-1 (ET-1) stimulated TGF-b1 production, and suppressed the differentiation of HCFs into myofibroblasts. The study suggests that Ac-SKP worked to inhibit TGF-b1-induced transformation of human fetal cardiac fibroblast to myofibroblasts through inhibiting the TGF-b/Smad/ERK1/2 signaling pathway. These findings suggest that Ac-SKP could be used as an endogenous antifibrotic peptide, and reduces the negative effects of elevated TGFb-1, which is common in a wide range of chronic illnesses, including CIRS, moldtoxicity, Lyme disease, CFS, fibromyalgia, neurodegenerative diseases, chronic kidney, liver, and heart disease, and aging.

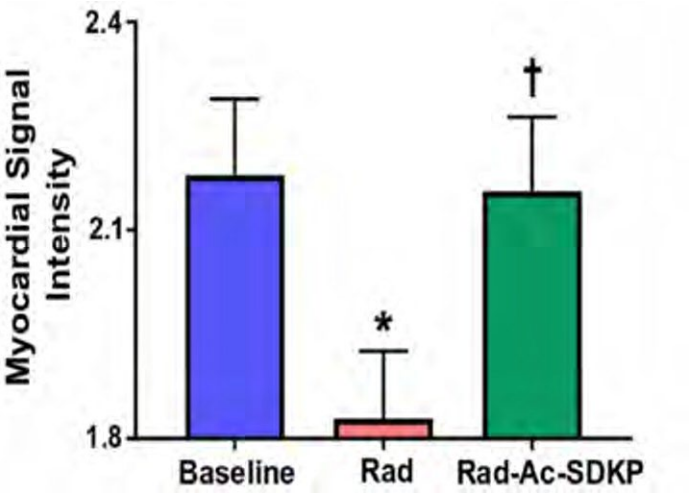
Effects of a novel peptide Ac-SKP in radiation-induced coronary endothelial damage and resting myocardial blood flow.

Link: https://cardiooncologyjournal.biomedcentral.com/articles/10.1186/s40959-018-0034-1
Publication date: December 2018
Journal name: Cardio-Oncology

Synopsis: Cancer survivors treated with thoracic ionizing radiation are at higher risk of premature death due to myocardial ischemia secondary to radiation-induced (secondary to increased ROS generation) coronary arterial endothelial damage, fibrosis and endothelial cell loss, resulting in reduced myocardial blood flow.

Ac-SKP normalized myocardial blood flow, inhibited endothelial cell loss, reversed coronary artery fibrosis, and normalized damaged endothelial tight-junction protein damage, restoring coronary endothelial function and cardiac blood flow.

The effects of AC-SKP on radiation-induced coronary endothelial damage likely has a much broader application in preventing age-associated endothelial damage, as well, as both appear to be mediated by excess ROS formation with age and disease.



Ac-SKP Reverses Inflammation and Fibrosis in Rats with Heart Failure After Myocardial Infarction

Link: https://pubmed.ncbi.nlm.nih.gov/14691195/

Publication Date: December 2003

Journal Name: American Heart Association

Synopsis: Inflammation plays a central role in the pathogenesis of interstitial and perivascular cardiac fibrosis in heart failure post-myocardial infarction. An optimal balance of inflammation is crucial to induce myocardial healing after a myocardial infarction. A defective resolution phase of the inflammatory response can lead to wall thinning, ventricular dilatation, and fibrosis which can cause cardiac dysfunction and mortality. In this study, Ac-SKP was used to test its anti-inflammatory and antifibrotic properties in rats with heart failure after a myocardial infarction. The results of Ac-SKP treatment in the rats attenuated (1) the overall cardiac and perivascular collagen content, (2) the increased macrophage infiltration, and (3) the increased TGF-b-positive cells. The study suggests that Ac-SKP could possibly reduce the accumulation of collagen and other contributing factors of the extracellular matrix in fibrotic disorders. Ac-SKP is thought to be a possible treatment therapy for patients with heart failure post-myocardial infarction to decrease inflammation and fibrosis in the heart for an overall increase in cardiac function.

Acetylated α-Tubulin Regulated by N-Acetyl-Seryl-Aspartyl-Lysyl-Proline (Ac-SKP) Exerts the Antifibrotic Effect in Rat Lung Fibrosis Induced by Silica

Link: https://www.nature.com/articles/srep32257

Publication Date: August 2016

Journal Name: Nature

Synopsis: Silicosis is a long-term, occupational, fibrotic lung disease, classified by areas of hardened and scarred lung tissue due to inhalation of crystalline silica dust in high concentrations. In this study, Ac-SKP was used to explore its antifibrotic effects in a rat model of silicosis. The proteomic profile analysis results showed that the expression of acetylated a-tublin (a-Ac-Tb) was down-regulated and induced by angiotensin II (Ang II) in silicotic rats, suggesting that a-tublin plays a role in silicosis development and progression. The results showed that Ac-SKP attenuated (1) TGF-b-1 and Ang II signaling through the up-regulation of a-Ac-Tb, (2) pulmonary fibroblast proliferation, and (3) collagen synthesis via c-Jun N-terminal kinase signaling. Ac-SKP also regulated myofibroblast differentiation which was found to be related to the progression of silicosis. This study suggests that Ac-SKP could be used as a treatment method for inhibiting fibrosis and inflammation in silicosis as well as other organs including the heart, kidney, and liver. The combination of a reduction of TGFb-1 and inhibition of the negative effects of Ang II makes AC-SKP a good candidate to reduce common age-related illnesses, including cardiovascular disease and hypertension induced chronic illness.

Novel anti-inflammatory mechanisms of N-Acetyl-Ser-Asp-Lys-Pro in hypertension-induced target organ damage

Link: https://pubmed.ncbi.nlm.nih.gov/18178715/

Publication Date: January 2008

Journal Name: American Journal of Physiology- Heart and Circulatory Physiology

Synopsis: High blood pressure is an important risk factor for cardiac, renal, and vascular dysfunction as it acts as a major determinant of endothelial dysfunction and vascular damage. Patients with pre-hypertension and hypertension have increased plasma levels of inflammatory markers inducing excess inflammation which is a major pathogenic mechanism for hypertension-induced target organ damage. In this study, bone marrow stem cells (BMSC) and mice with angiotensin II-induced (Ang II) hypertension were treated with Ac-SKP to evaluate its anti-inflammatory properties. The results of the Ac-SKP treated bone marrow stem cells showed that Ac- SKP inhibited the differentiation of BMSC to mature macrophages and reduce macrophage migration while decreasing collagen deposit in the left ventricle of Ang II- induced hypertensive mice. The results of the study suggest that Ac-SKP could be used as a possible treatment to inhibit hypertension-induced inflammation and fibrosis through preventing collagen accumulation.

Antifibrotic Effects of *N* -Acetyl-Seryl-Aspartyl-Lysyl-Proline on the Heart and Kidney in Aldosterone-Salt Hypertensive Rats

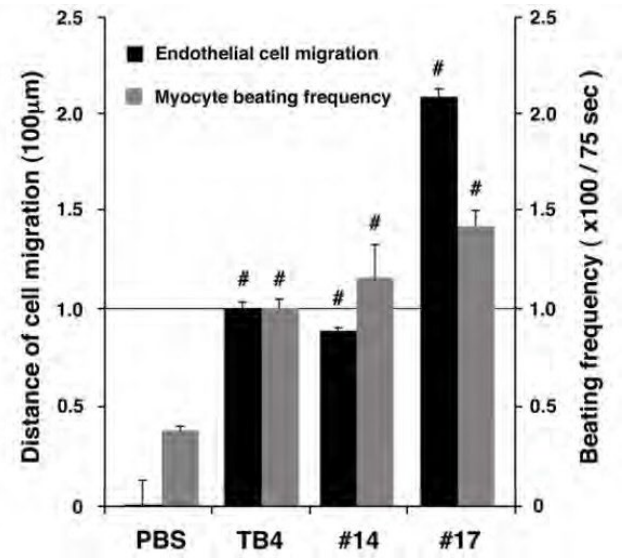
Link: https://pubmed.ncbi.nlm.nih.gov/11230375/

Publication Date: February 2001

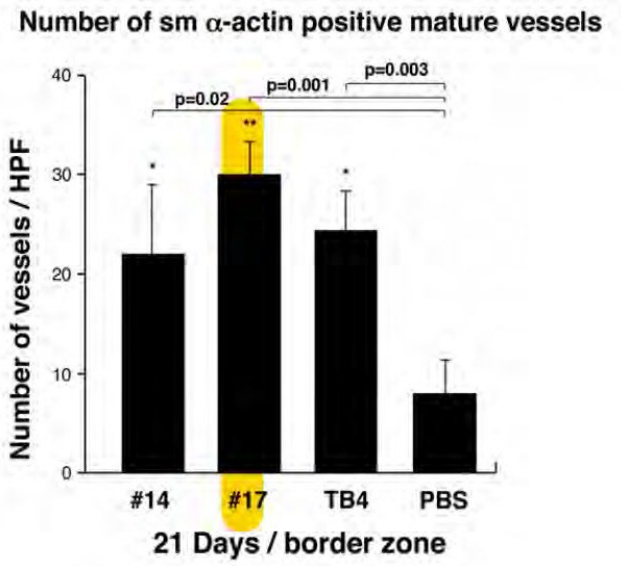
Journal Name: American Heart Association

Synopsis: The broad pathophysiology of renovascular hypertension is defined by decreased blood supply to the kidneys due to renal artery stenosis. The result of the narrowing in the arteries and low blood flow result in an increased production of aldosterone causing sodium and water retention in the body and subsequent elevated blood pressure levels. In this study, the effects of Ac-SKP were evaluated in a hypertensive rat model of cardiac and renal fibrosis to determine its efficacy in inhibiting cardiac and renal fibrosis and hypertrophy. The aldosterone treated rats showed a significant increase in blood pressure levels, renal hypertrophy and injury, and significant increase in collagen content in the right and left ventricle as well as in the kidney. The results of this study showed that Ac-SKP completely prevented an increase in collagen content within the kidney, improved glomerular and tubulointerstitial injury, and significantly decreased collagen content in the left ventricle. This suggests that Ac-SKP could possibly be used as an antifibrotic therapy method to treat renal hypertension.

"In summary, we identified the C-terminal four amino-acid variable end of TB4 as the essential and responsible domain for the molecule's full benefits in the hypoxic heart. Additionally, we introduced AGES as a novel, system-ically applicable drug candidate to aid cardiac infarction in adult mammals."



TB4 = full-length TB4
#14 = Actin binding domain
#17 = AGES



Thymosin b4 and its degradation product, Ac-SKP, are novel reparative factors in renal fibrosis

Link: https://pubmed.ncbi.nlm.nih.gov/23739235/

Publication Date: December 2013

Journal Name: Kidney International

Synopsis: Unilateral ureteral obstruction (UUO) leads to various detrimental events such as reduced renal blood flow and glomerular filtration rate, interstitial inflammation, and fibrosis. In this study, Ac-SKP and Tb4 was used to treat obstructed kidneys in wild-type mice to evaluate the difference of each treatment method's antifibrotic effect. The results showed that while Tb4 alone reduced fibrosis at its later stage, Ac-SKP was consistent in reducing fibrosis and collagen accumulation during each stage of repair. The study suggests that the antifibrotic and protective effects of Ac-SKP could be used as a possible therapy treatment for both early and late stages of renal fibrosis induced by UUO and other similar hypertensive kidney diseases.

A long-acting isomer of Ac-SKP attenuates pulmonary fibrosis through SRPK1-mediated PI3K/AKT and Smad2 pathway inhibition

Link: https://pubmed.ncbi.nlm.nih.gov/33135306/

Publication Date: September 2020

Journal Name: IUBMB Life

Synopsis: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and irreversible lung disease which is commonly characterized by chronic inflammation and excessive production of extracellular matrix proteins. In this study, the antifibrotic properties of Ac-SKP were tested through determining its efficacy in inhibiting the proliferation of collagen production by HFL-1 and evaluating its effect in mice with bleomycin induced pulmonary fibrosis. The results of this study found that Ac-SKP inhibited the proliferation and activation of HFL-1 and significantly ameliorated bleomycin induced pulmonary fibrosis in mice mediated by regulating the TGF-b1 and PIK3/AKT pathway. This study suggests the possible clinical application for Ac-SKP as an antifibrotic polypeptide drug.