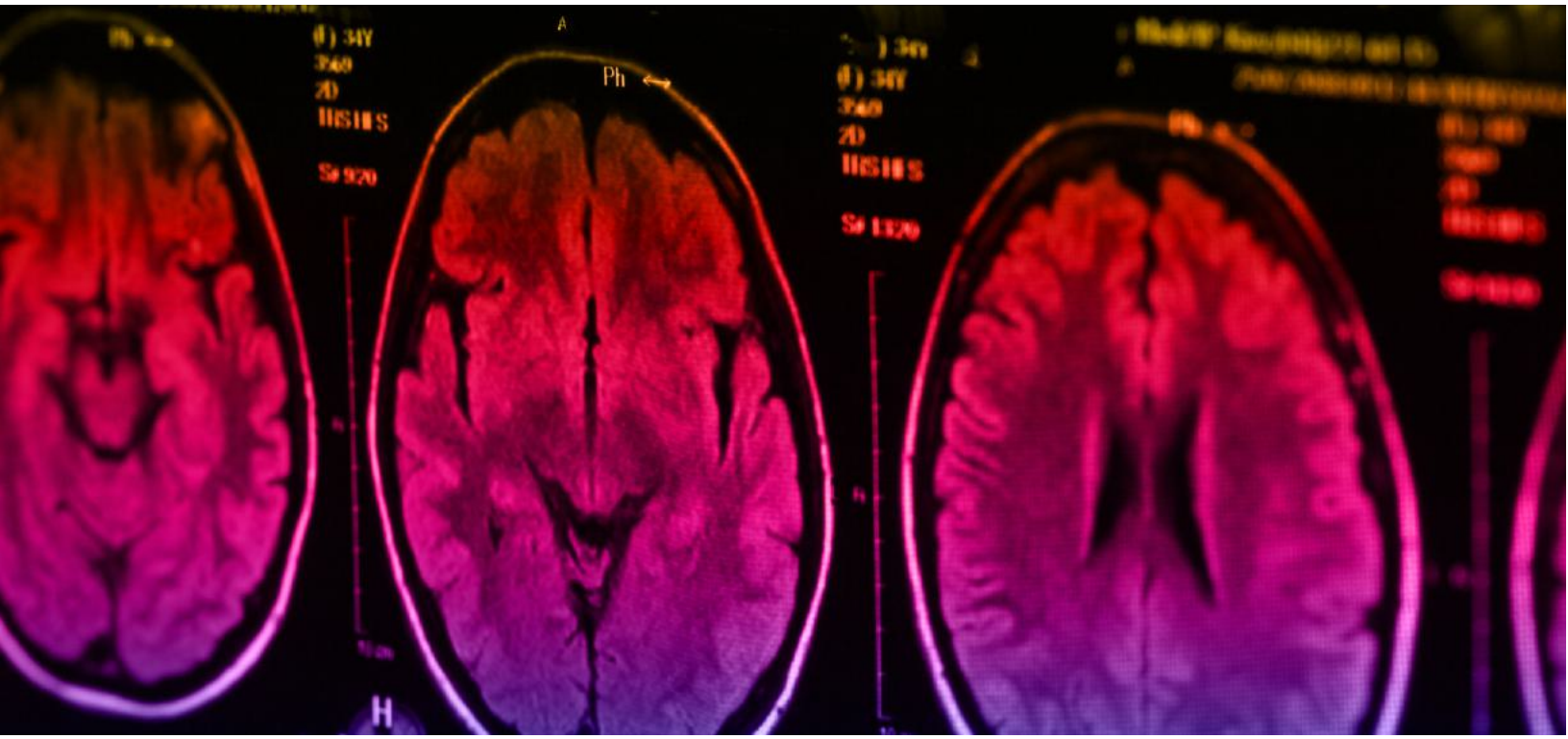
BLAIR MEDICAL GROUP

Research Summary

NEURODEGENERATIVE DISEASES & BETA CARYOPHYLLENE

Potential Applications of Endocannabinoid Treatment Modalities



Presented by Dr. Philip Blair

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Research Overview

Medical research has shown that a compound called β-Caryophyllene (BCP) has been extensively studied in relation to neurodegenerative disorders. BCP acts as an agonist on a specific receptor called CB2R. (An agonist is a chemical compound that binds to a receptor, producing a similar response to the intended chemical and receptor). CB2R has also been found to have various effects on the body that can potentially help prevent or treat conditions that cause the degeneration of nerve cells in the brain, such as Alzheimer's Disease (AD), Parkinson's Disease, Multiple Sclerosis (MS), Friedreich's ataxia, Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS).[1]

Besides CB2R activation BCP works through multiple pathways that include reducing oxidative stress (which is harmful to cells), reducing inflammation in the brain, protecting cells from damage, promoting the process of cleaning up damaged cells (autophagy), supporting the immune system, improving the function of mitochondria (the energy centers of cells), regulating metabolism, reinforcing blood brain barrier function, and preventing the misfolding of proteins (which can lead to neurodegeneration).

Additionally, BCP has been found to have positive effects on the way genes are expressed in the body. It regulates certain nuclear receptors and enzymes that control gene activity, leading to beneficial changes in the body's cells. Furthermore, BCP has been shown to stimulate the growth of new nerve cells (neurogenesis) and the development of nerve cell extensions (neuritogenesis).

As a result of these effects, BCP has the potential to be used as a therapeutic agent for the prevention and treatment of the various neurodegenerative conditions, previously mentioned. This research summary explores the findings of selected preclinical studies on neurodegenerative diseases treated with BCP.[2]

BCP is found in many herbs, vegetables and fruits that offer many health benefits and augment the body's natural endocannabinoid system. A normal amount of BCP in the diet amounts to between 10-200mg from various sources including basil, oregano, and cloves. BCP is also found in mango, grapefruit, and guava. But the amounts of BCP are quite low

requiring ingestion of a large quantity of these foods to get a therapeutic effect. Even the FDA has approved BCP as a food flavoring.[3]

RESEARCH SUMMARIES

NEUROPROTECTIVE REVIEW

β-Caryophyllene is classed as a chemical compound known as a sesquiterpene (meaning 15 carbon atoms), which is a member of the terpene family. These compounds may play an important role in regulating and protecting our health, due to their potential for the treatment of numerous health conditions, including cardiovascular disease and cancer.[4]

β-Caryophyllene has multiple important pharmacological effects, including activities as antioxidant, anti-inflammatory, anticancer, cardioprotective, hepatoprotective, gastroprotective, nephroprotective, antimicrobial, and immune-modulatory activity. But more on-target with Alzheimer disease, a recent review of 41 experimental studies suggests that BCP also possesses neuroprotective effects.[5]

CB2 RECEPTOR

The CB2 receptor is a component of the endogenous cannabinoid system and plays a role in Alzheimer's disease (AD), as the levels of CB2 receptors are increased in AD brains and are correlated with β-amyloid plaque deposition.[6] Ojha et al. reported that naturally occurring β-caryophyllene works as a CB2 receptor agonist and exerts neuroprotection by attenuating glial activation, neuroinflammation, and oxidative stress,[7] leading to the reversal of amyloid-induced memory deficit.[8]

PROTEINOPATHIES

Proteinopathies are neurodegenerative disorders that are characterized by the accumulation of specific proteins within neurons or in functional brain tissues. Some of the most prevalent and well-known neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, are classified as proteinopathies. For example, In Alzheimer's, amyloid-

beta protein accumulates in the form of insoluble clumps called plaques. These clumps can trigger a response from the immune system. This immune response can cause ongoing inflammation in the brain, which contributes to the development and worsening of neurodegenerative diseases.

Researchers have found that activating the CB2 receptor can help reduce the clumping of proteins and decrease inflammation in the brain. This, in turn, can alleviate some of the symptoms associated with dementia and other neurodegenerative diseases.[9]

NUCLEAR TRANSCRIPTION

Nuclear transcription is the process by which a cell makes an RNA copy of a piece of DNA. This RNA copy, called messenger RNA (mRNA), carries the genetic information needed to make proteins in a cell. These proteins are signaling molecules for key operations in the cell that can have good or adverse effects. BCP modulates several key nuclear factors coordinating gene products, including NRF2, PPAR's, sirtuin 1 (SIRT1), PGC1a, BDNF, and NF-κB. Several of these signaling molecules are discussed in this section with the remainder being referenced later in this document.

Nuclear factor kappa-enhancer of activated B cells (NF-κB) is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is involved in cellular responses to stimuli such as stress, cytokines, oxidized LDL, and bacterial or viral antigens. NF-κB plays a key positive role in the immune response to infection but when dysregulated NF-κB has been linked to cancer, chronic inflammation, autoimmunity, and neurodegeneration.

This study showed that BCP was able to reverse the negative effects caused by overexpression of Aβ 1-42 that induces transcriptional activity of nucleic factor NF-κB involved in inflammation.

One of the molecules that is also affected by BCP is nuclear factor kappa B (NF-κB), which plays a role in the development of various diseases, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and neurodegenerative conditions. BCP was able to prevent the activation of NF-κB and its movement into the cell nucleus, which in

turn reduced the inflammatory response. The 2017 study also found that BCP could inhibit neuroinflammation caused by Aβ oligomers in a type of brain cell called BV-2 microglial cells.[10]

A standardized black pepper seed extract containing β-caryophyllene was shown to improve cognitive function in scopolamine-induced amnesia model mice via regulation of brain-derived neurotrophic factor (BDNF) and mitogen-activated protein kinase (MAPK) proteins.[11] The BDNF protein is encoded by a gene found in humans on chromosome 11. There are multiple mechanisms through neuronal activity that can increase BDNF gene specific expression.

BDNF helps to support survival of existing neurons and encourages growth and differentiation of new neurons and synapses. In the brain it is active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking. BDNF itself is important for long-term memory and stimulates neurogenesis, a key factor in prevention of dementia. The BCP provided neurological protection against oxidative damage as well as histopathologic changes in the brain.

BCP stimulates sirtuin 1 (SIRT1) deacetylase activity leading to increased levels of deacetylated PGC-1α. SIRT 1 activity plays an important role in the inflammatory pathway of dementia development, particularly in AD.[12] Peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) strongly increases the ability of hormone nuclear receptors PPARα and Estrogen-Related Receptor alpha (ERRα), to drive transcription of fatty acid oxidation enzymes. ERRα activates mitochondrial genes as well as increased mitochondrial biogenesis. This use of BCP increases the expression of genes linked to the fatty acid oxidation pathway in a SIRT1/PGC-1α-dependent mechanism and drastically accelerates the rate of complete fatty acid oxidation. Furthermore, the strongly selective activation of CB2R by BCP promotes lipid oxidation through a signaling/transcriptional pathway.[13]

Thus, BCP has a broad range of cascading effects through activation of CB2R but also independent signaling properties ranging from neurotransmitter, immune, endocrine, and metabolic modulation that have been documented in AD.

CEREBRAL BLOOD FLOW

Vascular dementia occurs due to reduced blood flow to the brain, resulting in cognitive impairments. In a study titled "BCP/HPβCD Improves Cognitive Deficits in Rats with Vascular Dementia through the Cannabinoid Receptor Type 2-Mediated Pathway," researchers investigated the effects of a complex called β-Caryophyllene/Hydroxypropyl-β-Cyclodextrin Inclusion Complex (BCP/HPβCD) on learning and memory deficits in rats with vascular dementia caused by an ischemic insult to cerebral blood flow. The researchers found that treatment with BCP/HPβCD resulted in the reduction of learning and memory deficits in the rats. The group receiving the highest dose of HPβCD/BCP demonstrated the fastest recovery of cerebral blood flow, reaching approximately 75% of the sham group (the group without vascular dementia).

The study also revealed an increase in the levels of cannabinoid receptor type 2 (CB2R) in the treated rats. CB2R is a receptor found throughout the brain in neurons, interneurons, and immune cells. The activation of CB2R in this study was clearly associated with neuroprotection and anti-inflammatory effects. Furthermore, the researchers observed an upregulation of phosphoinositide 3-kinase (PI3K) and Akt in the treated rats specifically involved in cell survival and synaptic plasticity, which are essential for learning and memory. The findings suggest that BCP/HPβCD treatment improved cognitive deficits in vascular dementia through CB2R activation that regulates neuroinflammatory processes and enhancement of cell survival. These pathomechanisms (the mechanism by which a pathological condition is created) that were corrected by BCP are consistent with various types of dementias.[14]

IMMUNOLOGICAL SHIFT

Microglia are immune cells in the central nervous system. When exposed to compounds such as lipopolysaccharide (LPS), microglia can become imbalanced, leading to inflammation and oxidative stress.

A study called "The protective effects of BCP on LPS-induced microglia imbalance" investigated the effects of β-Caryophyllene (BCP) on microglia. The researchers found

that BCP treatment shifted the microglia away from inflammation mode (M1) towards a healing phenotype called M2. This shift resulted in the release of important anti-inflammatory substances like IL-10, Arg-1, and urea, as well as antioxidants like GSH (glutathione). At the same time, BCP reduced the levels of inflammatory substances such as IL-1β, TNF-α, PGE2, iNOS, and NO (nitric oxide), as well as oxidative biomarkers like ROS (reactive oxygen species).

Excessive production of NO and expression of iNOS are implicated in the development of various diseases, including inflammatory conditions, cancer, multiple sclerosis (MS), asthma, and neuronal toxicity in cortical and striatal neurons. Lowering the levels of iNOS has been shown to promote recovery and improvement in diseases where the M1/M2 ratio is imbalanced, by shifting the M1 phenotype towards the M2 phenotype.

In summary, BCP demonstrated neuroprotective effects by modulating microglia towards the healing M2 phenotype while reducing inflammation and oxidative stress.[15]

EPIGENETIC MODULATION

In Chinese herbal medicine the substance Acori Tatarinowii Rhizoma (ATR) is used to treat Alzheimer's disease (AD). Results from a recent study showed that BCP, an active component of ATR, participated in related biological defensive processes against cancer, inflammation, cellular metabolism, and metabolic pathways through protein-protein interaction and core target genes. ß-caryophyllene significantly reduced the mRNA expression levels of amyloid-β protein precursor and TAU proteins that are intimately associated with pathologies and dementias of Alzheimer's disease aggregating into disruptive neurofibrillary tangles.[16]

CHOLINESTRERASE INHIBITION

Acetylcholinesterase and butyrylcholinesterase (BChE) inhibitors are the only available drugs proven to slow the progression of Alzheimer's disease (AD). This study aimed to assess the levels of acetylcholine, a key neurotransmitter, in neuronal tissue using essential oils from plants rich in β-Caryophyllene (BCP). Acetylcholine plays a vital role in various

brain functions, including memory, attention, and motivation. Damage to the cholinergic system in the brain is associated with memory deficits in Alzheimer's disease. Inhibiting the breakdown of acetylcholine raises its levels and prolongs its effects.

One study showed that BCP specifically inhibited BChE thereby increasing acetylcholine levels. BCP easily passes through the blood-brain barrier due to its low molecular weight. Supplementation with BCP-rich fruit pulp protected mice against age-related cognitive deficits by reducing oxidative stress and inhibiting acetylcholinesterase activity.[17]

DNA ANTI-OXIDATION

Aging is associated with detrimental cellular and cognitive changes, making it an important dementia concern; yet many of these changes may be influenced by nutritional interventions. The natural sesquiterpene β-caryophyllene has promoted neuroprotection in different animal models that involve cognitive damage. BALB/c mice were administered D-galactose that induces mitochondrial dysfunction, a common abnormality in the aging brain and long-term memory and cognitive flexibility were evaluated.

In addition, immunohistochemistry was performed on brain slices to detect glial acidic fibrillary protein and DNA oxidation. D-galactose caused elevation of astrocytes with inflammatory interactions in the hippocampus, and increased DNA oxidation in the prefrontal cortex. BCP administration impeded the DNA oxidation thus showing a neuroprotective effect at the molecular and cellular level.[18]

NEUROINFLAMMATION INHIBITION

Neuro-inflammation is another common cause of various types of dementia. β-caryophyllene (BCP), has shown potential neuroprotective effects in cerebral ischemia and neuro-inflammation. In this study citation, BCP was evaluated for its impact on memory performance in animal models of dementia associated with neuro-inflammation, specifically in doxorubicin-induced neuro-inflammation in a chemo-brain model.

In the chemo-brain model, BCP effectively reduced lipid peroxidation compared to the disease control. Additionally, in the novel object recognition task, BCP enhanced

recognition and discrimination, accompanied by increased catalase levels and decreased lipid peroxidation in the hippocampus and frontal cortex. Catalase that decomposes hydrogen peroxide to water and oxygen is an important enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS).

Based on these findings, the authors concluded that BCP has a protective effect against dementia caused by neuro-inflammation.[19]

AMYLOID β INHIBITION

Alzheimer's disease (AD) is characterized by the presence of amyloid β (Aβ) plaques and neurofibrillary (TAU) tangles, which contribute to synaptic and neuronal cell loss. To study AD, PC-12 cells, derived embryologically from neural crest, were used to overexpress amyloid-β protein precursor.

In the study, the PC-12 cells showed increased expression of key pathologic mRNA & proteins involved in AD. BCP treatment, however, increased cell viability and protection of cell morphology. BCP also inhibited the overexpression of amyloid-β protein precursor, JAK2, STAT3 mRNA, and BACE1 protein. These findings suggest that BCP protects neurons and counteracts the neurotoxic effects of Aβ by inhibiting the "JAK2-STAT3-BACE1" signaling pathway. By targeting this pathway, BCP shows potential as a protective agent for neurons and may help mitigate the neurotoxicity associated with Aβ in AD.[20]

NEUROPLASTICITY

Synaptic dysfunction plays a central role in the development of Alzheimer's disease (AD). Neuronal degeneration often follows synaptic breakdown. Enhancing neuroplasticity, which is the brain's ability to adapt and form new connections, shows promise as a therapeutic approach to improve cognition in AD.

In a study exploring the potential of β-caryophyllene (BCP) in this process, it was found that BCP can promote the growth of neurites (extensions of nerve cells) even in PC12 cells that do not have cannabinoid type 2 (CB2) receptors. BCP increased cell survival and activated the nerve growth factor (NGF) receptor called trkA, but in the absence of NGF

itself. BCP also increased the expression of proteins associated with nerve axonal plasticity, such as GAP-43, synapsin, and synaptophysin.

These findings suggest that BCP can act like NGF on trkA receptors and stimulate neuritogenesis through a mechanism independent of NGF or CB2R. This implies that BCP may have a direct impact on neuronal plasticity and the formation of new connections, offering potential benefits for neurodegenerative conditions like AD.[21]

NEUROVASCULAR UNIT

The neurovascular unit (NVU) is a complex network consisting of brain microvascular endothelial cells, neurons, and astrocytes. It plays a crucial role in maintaining a stable environment for neurons in conditions like Alzheimer's disease (AD) and ischemic events. The NVU is often referred to as the blood-brain barrier (BBB), which protects the brain.

Type-2 diabetes (T2D) increases the risk of dementia, and it is associated with inflammation and oxidative stress that can disrupt the BBB. Studies have shown that treatments preventing inflammation in the blood vessels can protect the BBB, potentially slowing down cognitive decline in some cases.

Stroke and AD are cerebral pathologies that can occur together and influence each other. Vascular factors that contribute to cerebrovascular disease are also associated with the development of AD. Acute stroke increases the risk of developing dementia. After a stroke, impaired perivascular space integrity, inflammation, hypoxia, and BBB permeability breakdown can accelerate the deposition of amyloid β (Aβ) in the brain, leading to cognitive decline and dementia. Maintaining the clearance of Aβ after stroke could prevent post-stroke cognitive impairment and dementia.

In an NVU model, the effects of β-caryophyllene (BCP) were investigated on injury caused by a cycle of oxygen-glucose deprivation and re-oxygenation. BCP treatment reduced BBB permeability and neuronal apoptosis (a type of cell death), mitigated oxidative stress damage and the release of inflammatory cytokines, as well as promoting the expression of various tight-junction proteins involved in maintaining BBB integrity. These protective

effects of BCP ultimately lead to a decrease in neuronal cell death. The NVU represents a potential target for BCP as a neuroprotective agent.

In summary, the NVU plays a crucial role in maintaining brain health, and disruptions in its functioning can contribute to neurodegenerative conditions. BCP has been shown to defend the NVU by reducing oxidative stress, inflammation, and BBB breakdown, making it a promising therapeutic option for neuroprotection.[22]

ENDOTHELIAL PERICYTE

The development of Alzheimer's disease (AD) is influenced by the structural components of the blood-brain barrier (BBB), such as astrocytes, vascular endothelial cells, tight junctions and pericytes. In the central nervous system, pericytes wrap around the endothelial cells that line the inside of the capillary where they communicate with endothelial cells by means of both direct physical contact and paracrine signaling. When the BBB is dysfunctional, it triggers neuroinflammation and oxidative stress, which in turn increases the activity of certain enzymes involved in the generation of amyloid β (Aβ), a hallmark protein in AD. The progressive accumulation of Aβ and BBB dysfunction create a feedback loop that leads to cognitive impairment and the onset of dementia.[23]

In the brain, the regulation of cerebral blood flow involves various tightly controlled mechanisms, including myogenic, endothelial, metabolic, and neural pathways. Inflammatory processes can disrupt these pathways and play a significant role in certain central nervous system disorders. Different cell types in the brain, including smooth muscle cells, endothelial cells, neurons, astrocytes, pericytes, microglia, and leukocytes, can produce endocannabinoids or express their target proteins.[24]

Acute subarachnoid hemorrhage, traumatic brain injury, and ischemic brain injury cause proliferation of CB2 receptors awaiting activation. CB2 receptors are highly active in pericytes and endothelial cell as well as all immune cells. BCP as a strong, specific CB2R agonist, appears to improve blood perfusion in the brain by reducing vascular inflammation.

In summary, the integrity of the BBB and proper regulation of cerebral blood flow are essential for brain health. Dysfunctions in these processes contribute to the pathogenesis of AD. BCP, through its agonistic effects on CB2 receptors, shows promise in attenuating vascular inflammation and improving blood perfusion in certain cerebrovascular conditions.[25]

MITOCHONDRIA

Alzheimer's disease (AD) is characterized by extensive oxidative stress in the body, including the affected regions of the brain. AD exhibits higher levels of oxidative damage compared to normal aging. Mitochondrial dysfunction and oxidative stress create a harmful cycle that contributes to the development of AD.[26]

Mitochondrial dysfunction in neurodegenerative disorders involves damaged electron transport chains, altered membrane permeability, disrupted calcium homeostasis, and impaired defense systems against oxidative stress. Antioxidants have the potential to stabilize mitochondria and prevent neuronal loss. β-caryophyllene (BCP) has shown the ability to reduce oxidative stress and improve mitochondrial function, suggesting its neuroprotective properties.[27]

The decline in Adenosine triphosphate (ATP) synthesis in skeletal muscle affects protein turnover and is associated with age-related functional changes and insulin resistance. ATP is an organic compound that provides energy to drive and support many processes in living cells. Although this study focuses on muscle, it has implications for the nervous system as well. BCP improves mitochondrial metabolism, specifically in the electron transport chain and ATP synthesis. BCP also mimics the effects of insulin and physical exercise, enhancing glucose metabolism and enzyme activity involved in energy production but without the production of excessive reactive oxygen species.[28]

In summary, oxidative stress and mitochondrial dysfunction play significant roles in the pathogenesis of AD. BCP shows potential in reducing oxidative stress, improving mitochondrial function, and promoting energy metabolism, which may have implications for neuroprotection and overall health.

MITOPHAGY

Mitophagy is a crucial process for maintaining healthy mitochondria by eliminating damaged ones in conditions like cerebral ischemia-reperfusion (CIR) injury and AD. In CIR β-caryophyllene remarkably protected against cell death and apoptosis, and decreased neurologic injury, infarct volume, and the injury of neurons. Surprisingly, the mechanism appears to be promotion of mitophagy. In this study pretreatment with BCP triggered mitophagy, which helps remove damaged mitochondria and reduce brain damage. This protective mechanism involves the recruitment of mitochondrial autophagy marker molecules proteins to the outer membrane of mitochondria. Pink/Parkin plays a crucial role in mitophagy and clearance of reactive oxygen species. Through this process, damaged mitochondria are broken down to generate amino acids and nutrients for neurons.

BCP accelerated mitophagy by regulating expression of mitochondrial autophagy marker molecules and promoting autophagosome formation. Inhibiting this pathway weakened BCP-induced protection against CIR models. Taken together, these results suggest that facilitating mitophagy via Pink1/Parkin2 signaling is essential for the neuroprotective effect of BCP against all CIR injury.

These findings demonstrate that BCP pre-treatment plays a crucial role in facilitating mitophagy and clearing damaged mitochondria in cells affected by oxygen-glucose deprivation/reoxygenation.[29]

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARS)

PPAR-α is a type of nuclear receptor that regulates gene expression by binding to specific regions in the DNA called PPAR response elements (PPREs). It plays a crucial role in oxidative stress, energy balance, mitochondrial fatty acid metabolism, and inflammation in the brain and other organs. PPAR-α is involved in maintaining glutamate balance and regulating cholinergic/dopaminergic signaling in the brain.

It also controls the expression of genes involved in amyloid precursor protein (APP) metabolism. By activating the gene for α-secretase and reducing the gene for β-secretase,

PPAR-α helps prevent the release of amyloid beta (Aβ) peptides, which are associated with Alzheimer's disease (AD). In AD, the expression of PPAR-α and PPAR-γ coactivator PGC-1α is decreased in the brain. Activation of PPAR-α is essential for maintaining brain cell metabolism and cognitive function in neurodegenerative and neurodevelopmental disorders.[30]

PPAR-A

BCP acts as an agonist for PPAR-α in liver cells. It enhances the rate of fatty acid oxidation and upregulates genes and proteins involved in fatty acid uptake and oxidation.[31] In the brain, after transient global cerebral hypoperfusion/reperfusion, BCP modulates the entire endocannabinoid system while preserving the levels of docosahexaenoic acid (DHA) that affects essential membrane-dependent molecular mechanisms. It also inhibits cyclooxygenase-2 (COX2) and increases the levels of PPAR-α protein.

In summary, BCP treatment in a single acute dose exerts significant preventive effects against the tissue and plasma molecular changes triggered by hypoperfusion/reperfusion, i.e., a) modulates the activation of the ECS by increasing basal tissue levels of 2-AG, AEA, PEA, OEA and relative protein levels of CB1 and CB2; b) decreases plasma levels of AEA; c) spares basal tissue levels of DHA.[32]

PPAR-Γ

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists have shown positive effects in treating Alzheimer's disease (AD) by improving learning, memory, and reducing AD-related pathology. PPAR-γ regulates fatty acid storage and glucose metabolism as well as promoting anti-inflammatory M2 macrophage activation and anticancer effects.

PPARγ is expressed in various brain regions and plays a role in regulating lipid metabolism, oxidative stress, and cell apoptosis. It activates transcription factors known to play an important role in the regulation of glucose absorption, lipid metabolism.[33] It also exhibits anti-inflammatory activity and provides neuroprotection. The regulation of Aβ

levels in Alzheimer's disease actually involves cholesterol metabolism and inflammation regulated by PPAR-γ.[34]

β-Caryophyllene (BCP) activates the CB2 receptor, PGC-1α and the PPAR-γ pathway, leading to improved Alzheimer-like symptoms in mice and demonstrating therapeutic potential in AD treatment. BCP given orally to mice improved cognitive function, reduced β-amyloid accumulation, decreased inflammation, and protected against AD-like symptoms. These findings highlight the potential of BCP as a treatment for AD.[35]

SIRTUIN

As people live longer, age-related problems like cognitive decline and dementia are becoming more prevalent. Aging is a significant risk factor for various diseases, but there is a growing interest in living a healthier life. Scientists have studied cellular and molecular mechanisms involved in aging, particularly the AMPK, SIRT1, and mTOR pathways.[36]

In a muscle study, the activation of CB2 receptors by BCP enhanced fatty acid oxidation through the SIRT1/PGC-1α pathway. PGC-1α regulates mitochondrial biogenesis and interacts with the nuclear receptor PPAR-γ, which permits the interaction of this protein with multiple transcription factors.

Sirtuins are a family of signaling proteins involved in metabolic regulation implicated in cellular processes like aging, transcription, apoptosis, inflammation, and stress resistance. BCP treatment increased the expression of genes related to fatty acid oxidation and boosted the rate of fatty acid oxidation in muscle cells. These findings suggest that BCP may have potential benefits for promoting healthier aging throughout the body.[37]

DNA/MRNA EPIGENETICS

Differentially expressed genes induced by β-caryophyllene could play a role in cerebral ischemia-reperfusion injury (CIR) and dementia that frequently follows. In a study using rats with CIR resulting from Middle Cerebral Artery Occlusion (MCAO), BCP intervention significantly reduced neurologic deficits and improved cerebral ischemia outcomes. The study also identified ten hub genes that are closely related to the effects of BCP treatment

on CIR. BCP may exert neuroprotective effects in CIR by reducing the expression of MMP-9 and TIMP-1 and inhibiting the STAT3 signaling pathway, which contributes to neurodegenerative injury following CIR. These findings suggest that BCP could be a potential treatment strategy for stroke and subsequent AD disease.[38]

(SASP) SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE

Aging research has identified natural compounds that can influence the senescence-associated secretory phenotype (SASP), which contributes to inflammation during aging. SASP is associated with DNA damage response, activation of NF-kB and NLRP3 inflammasome pathways, and production of proinflammatory factors.

A nutritional supplement containing curcumin, polydatin (a precursor of resveratrol), and liposomal β-caryophyllene (BCP) was studied for its anti-SASP and anti-inflammatory effects in human endothelial and monocytic cell models. Senescence was induced in cells using specific triggers, and the natural compounds were individually or combinedly applied. BCP showed significant reductions in the expression of inflammatory factors and miRNA, and activation of caspase-1, along with an increase in SIRT1 protein levels. However, the combined mixture of all three compounds showed the strongest effects.[39]

FERROTOPSIS

Ferroptosis is an iron-mediated, programmed cell death mechanism characterized by phospholipid peroxidation that has been observed in clinical AD samples. In spite of profound investment in numerous clinical trials targeting amyloid-β, none have yielded any clinically success. An extensive body of work links iron dys-homeostasis with multiple aspects of the pathophysiology of AD and in Parkinson's Disease[40 41] Elevated brain iron and cerebrospinal fluid ferritin in AD has been confirmed in numerous studies and was associated with poorer cognition and hippocampal atrophy. There is a complex interplay between amyloid-β, tau, and iron in both physiological and pathological states. Ferroptosis may exacerbate AD by targeting the hypoxia-inducible factor 1α and heme oxygenase-1

(HO-1) pathways along with deficiency of nerve erythroid 2-related factor 2 (Nrf2) that regulates genes involved in the metabolism of glutathione, iron and lipids, and mitochondrial function. Enhancing Nrf2 signaling may hence be neuroprotective.

BCP specifically suppressed ferroptosis in a recent study of cerebral ischemia. BCP enhanced NRF2 nuclear translocation, activated the NRF2/HO-1 pathway, which protected against ferroptosis. In vitro primary astrocytes subjected to oxygen-glucose deprivation/re-oxygenation were pretreated with different concentrations of BCP revealing decreased ROS generation and iron accumulation. Herein, the significant neuroprotective effects of BCP in ischemic injury are correlated with ferroptosis regulation.[42] In ulcerative colitis mice where macrophage lipid peroxidation was observed β-caryophyllene (BCP) had a direct inhibitory effect reversing the inflammatory effects activated by ferroptosis. Further molecular mechanism studies showed that BCP activated the CB2 receptor to inhibit macrophage ferroptosis and its characteristic inflammatory response.[43] Thus, BCP has been documented to inhibit several key mechanisms pertaining to neuroinflammation and ultimately, neurodegeneration caused by ferroptosis.

SUMMARY

This white paper has reviewed many of the known mechanisms of AD where BCP could play a role in mitigating this disorder and reducing the financial burden. The huge costs of dementia worldwide place enormous strains on care systems and families alike. The global cost of dementia for 55.2 million people living with dementia in 2019 was estimated at US $1313 billion.[44]

BCP is a natural product found in thousands of plants, easily extracted, and formulated into highly bioavailable mixtures for delivery by oral, transdermal, or mucosal mechanisms. Despite appeals for research, there are very few clinical trials at this time. Full clinical studies should be initiated as soon as possible to clarify the benefits and limitations of this extraordinary compound.

ABOUT DR. PHILIP BLAIR

Retired Colonel (Dr.) Philip Blair is a board-certified Family Physician licensed in Washington State. He graduated from West Point in 1972 and attended University of Miami School of Medicine and trained as a family physician. He had assignments in Georgia, Louisiana, Washington, Oklahoma, Texas, Hawaii, Kansas, Italy, Korea, Germany, and the Gulf War.

After retiring from the Army in 1996 he became Vice President for Disease Management at AWAC, Inc., a medical management company, where he co-developed a highly successful interventional approach to chronic kidney disease. In 2011 he formed his own company consulting for employer-based health insurers and providing a revolutionary style of chronic disease management achieving success in over 75% of patients with diabetes, kidney disease, heart disease and metabolic syndrome.

In 2014 he was introduced to cannabidiol and became a medical consultant to a large distributor of CBD products. In his clinical practice he has treated several thousand patients with CBD. More recently, he has explored the terpene β-Caryophyllene for adaptogenic properties and developed a series of highly beneficial products for which clinical studies are now being discussed.

ABOUT BLAIR MEDICAL GROUP SPC

Dr. Philip Blair has been providing healthcare consulting as the "AbleDoc" for years.

When Blair Medical Group developed our 'Abledoc's Apothecary' product line, we wanted to convey the trust and familiarity of the corner drugstore/apothecary, where the pharmacist knew everyone by name, and personally cared about their health. Blair Medical Group and our "Abledoc's Apothecary" brand is proud to build on this community tradition.

We are dedicated to supporting our partners and healthcare communities around the world. We follow our core values in all aspects of our work:

Integrity – Compassion – Reliability – Quality – Commitment

Our vision is to make our nutritional supplements, products, and programs universally accessible, creating a healthier, revitalized world for everyone.

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Research summaries courtesy of Dr. Philip Blair, MD

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