A Multi-Domain Approach to Prevention and Reversal of Cognitive Decline

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Abstract

Incidence of dementia has been on the rise over the last few decades and it is projected that more than 130 million people will be affected by dementia worldwide by 2050. The underlying cause remains incompletely determined, and despite numerous clinical trials, no drug to date has proven effective in preventing or reversing symptoms of cognitive decline due to Alzheimer's disease. The amyloid hypothesis as a basis for drug development of Alzheimer's disease has thus far proven to be ineffective, suggesting that perhaps a new approach is required. New studies have shown the efficacy of a multi-domain approach which targets several disease risk factors simultaneously, to achieve a synergistic effect on cognitive impairment. This paper analyzes a multi domain protocol, known as ReCODE protocol, developed to treat and prevent Alzheimer's disease, and provides clinical and experimental research as well as potential mechanisms to support the key elements upon which this protocol is based. Although the results seem promising, more rigorous clinical testing is required to link this approach with prevention and reversal of cognitive decline more definitively.

Acronyms

Alzheimer's disease (AD), amyloid beta (Aβ), β-Amyloid Precursor Protein (APP), Reversal of Cognitive Decline (ReCODE), tumor necrosis factor (TNFα), interleukin-6 (IL-6), interleukin-1β (IL-1β), Apolipoprotein E4 (ApoE4), Positron Emission Tomography (PET), Presenilin 1 (PS1), homocysteine (HC), Beta Hydroxybutyrate (β-HB), ketone bodies (KB), acetoacetate (Ac)

Introduction

Today, nearly 50 million people worldwide are living with dementia (Prince et al., 2016). As one of the leading causes of age-related cognitive decline, Alzheimer's disease (AD) represents a significant health concern for the aging population. The underlying cause remains incompletely determined, and to date no effective treatment has been discovered. Although remarkable progress and scientific breakthroughs in recent decades have led to the development of effective protocols for diseases such as HIV and cancer, treatment therapies for neurodegenerative diseases such as Lewy body dementia and Alzheimer's disease continue to lag significantly behind. Despite billions of dollars funneled into hundreds of clinical trials on various drug modalities, no truly effective etiological treatment or prophylactic medication has been approved by the FDA to date. Of the five drugs that have been approved to treat the cognitive symptoms of Alzheimer's disease, none have been shown to have more than a marginal or sustained effect on symptomatic patients with AD.

The Amyloid Hypothesis

AD onset is associated with a complex neurodegenerative cascade mechanism histologically characterized by parenchymal deposition of amyloid-β (Aβ) and intracellular neurofibrillary tangle formation due to hyperphosphorylation of tau protein (Cunnane et al., 2011). Since the discovery of the Aβ peptide in 1984, the amyloid hypothesis has largely been the paradigm in understanding AD and the basis for researching potential therapeutic treatments. The amyloid hypothesis posits that the formation of senile plaques, composed predominantly of the proteinaceous Aβ peptide, leads to synaptic toxicity and cognitive deficits in AD (Banwait et al., 2008). In recent years, however, the validity of this theory has come into question; for although the neurotoxicity of Aβ is supported by substantial genetic and biochemical data, Aβ-centered therapeutic trials aimed at limiting the production of amyloid or facilitating its removal have failed to prove clinically effective in slowing cognitive decline in AD patients (Pimplikar, 2009). These results suggest that perhaps, rather than being the primary cause of the disease, Aβ is a "downstream response to injury, with both beneficial and injurious properties" (McCaully & Grush 2017). With the entire premise of the current Alzheimer's paradigm under question, it seems that perhaps a new understanding of the role of Aβ is necessary.

Paradigm Shift

Dr. Bredesen and associates address the inconsistencies of the prevalent amyloid cascade theory and clinical outcomes with a new approach, radically different than its monotherapeutic precedents. They have advanced a model in which, "AD results from an imbalance in endogenous plasticity signaling, and in which the β-amyloid precursor protein (APP) is a mediator of such plasticity-related signaling," suggesting an etiology analogous to chronic illness such as osteoporosis and arthrosclerosis. Osteoporosis occurs when there is a chronic imbalance between osteoblastic and osteoclastic signaling and new bone formation is exceeded by old bone resorption. "By analogy, in Alzheimer's disease, there is a fundamental age-associated imbalance between the dynamically opposed physiological processes that mediate plasticity, i.e. between synaptoblastic and synaptoclastic activity" (Bredesen, 2014).

Aβ is a peptide produced by the proteolytic cleavage of its precursor protein, APP, mediated by γ-secretase and β-secretase 1 (Heneka et al., 2014). This integral membrane protein can be cleaved via two alternative pathways and in this way act as a molecular switch to mediate neuroplasticity. Amyloidogenic processing of APP leads to cleavage at the beta, gamma, and caspase sites to produce pro-AD peptides sAPPβ, Aβ, Jcasp, and

C31 - all of which have been shown to mediate neurite retraction and caspase activation. In contrast, the non-amyloidogenic processing of APP through cleavage at the alpha site results in the formation of sAPPα and αCTF, peptides which mediate neurite extension and inhibit Aβ production and caspase activation (Bredesen, 2014; Chen, 2017).

In studies using regular and transgenic mice, both genetic and pharmacologic methods were used to manipulate the APP derivative peptide balance and were found to cause predictable effects on learning and memory. This suggests that the APP cleavage pathway may be a potential target to inhibit AD pathophysiology. A number of agents that affect this pathway, including nitrin-1 and Aβ, have been identified, however, targeting any of these agents individually has had limited success. Additionally, other potential intervention targets, aside from Aβ oligomers, including inflammatory mediators, apolipoproteins, trophic factors and their receptors, and axoplasmic machinery have been identified. Although targeting any one of these pathways shows great promise in preclinical studies, it has not proven effective in human studies. This inconsistency seems to suggest that a "network-based therapeutics approach, rather than a single target-based approach, may be more effective for the treatment of cognitive decline due to Alzheimer's disease" (Bredesen, 2014). The complex, multifactorial nature of the disease may require interventions that target several risk factors and disease mechanisms simultaneously for optimum effect. Comprehensive combination therapies have been shown to greatly improve treatment of other chronic illnesses, such as HIV and cancer. In the case of HIV, the development of highly active antiretroviral therapy, a form of combination therapy, caused a significant decline in death rates for a disease that had been minimally treatable for decades (Brady et al., 2010).

The Finger Study

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) assessed a multi-domain approach towards improvement of cognitive functioning and prevention of cognitive decline in the first extensive, long-term, methodologically rigorous trial to date. They conducted a two-year trial to confirm the associations of several modifiable factors, such as diet and physical inactivity, with Alzheimer's disease.

Participants were required to be between 60-77 years of age and have a minimum CAIDE (Cardiovascular Risk Factors, Aging, and Dementia) Score of 6 points. The Consortium to Establish a Registry for Alzheimer's disease Neuropsychological Battery Test was used for cognitive screening. Only participants who tested at or slightly lower than the mean level of cognitive performance, as compared to the normal population, were included in the study. Individuals with diagnosed or suspected dementia, and several other disorders or impairments were excluded.

Participants were randomly assigned to the intensive multi-domain intervention or regular health advice group (control group) using computer-generated allocation at each of six testing centers. The trial was double-blinded to the maximum possible extent, wherein allocation was not disclosed to either participants or outcome assessors. Participants were restricted from interacting with each other and advised not to discuss their experiences.

Procedures

All participants met the study nurse five times during the two year trial where they received advice on a healthy diet, and physical, cognitive, and social activities to manage risk factors and prevent cognitive impairment. The intervention group received four additional components, including a nutritional intervention, a physical exercise training program, cognitive training, and social activities.

Results

There was significant improvement for the primary outcome in the intervention group, which showed 25% greater improvement in the neuropsychological test battery (NTB) total score than the control group. The intervention group also showed higher improvements in executive function and processing speed than the control group, 83% and 150% respectively. There was no evidence, however, of significant change in memory for the intervention group (Ngandu et al., 2015).

A More Comprehensive Multi-Domain Approach to Treatment of Alzheimer's Disease

The ReCODE Protocol

The ReCODE Protocol outlines a more comprehensive therapeutic system that targets as many as 36 risk factors or disease mechanisms to prevent and reverse cognitive decline. While the individual effects of any one of these factors may not be significant, the protocol targets many factors simultaneously to create a synergistic effect capable of reversing the imbalance of synoblastic/synoclastic activity mediated by APP. Typically, the evaluation of patients with cognitive decline does not include testing for genetics, inflammation, infection, homocysteine, fasting insulin level, toxic exposure, blood brain barrier or body mass index, all of which are known risk factors for AD. Patients following the ReCODE Protocol undergo extensive lab and genome testing, referred to as a "cognoscopy," to identify genetic risk factors and suboptimal physiological, metabolic, and cognitive parameters. The results are used to generate a personalized ReCODE Report™ which designs an individualized protocol targeting the identified risk factors in order to synergistically achieve an optimum outcome (Bredesen, 2017).

Three Subtypes of Alzheimer's

To optimize treatment development, Bredesen et al. uses metabolic profiling to distinguish between three subtypes of

Alzheimer's disease, each with its own characteristic biomarkers. Although there may be overlap, each subtype requires remediation of specific suboptimal indicators.

Subtype 1: Inflammatory

Carriers of the apolipoprotein E4 (ApoE4) gene are at increased risk for developing AD, particularly the inflammatory subtype. Carriers homozygous for the ApoE4 allele often become symptomatic as early as late forties or fifties, single ApoE4 allele carriers in late fifties or sixties, while symptom onset for those without the gene is typically in the sixties to seventies. This subtype is associated with biomarkers of systemic inflammation such as increased hs-CRP, IL-6 and TNFα as well as a decreased albumin:globulin ratio. Symptomatically, this subtype is characterized by the loss of the ability to form new memories while retaining long-term memories and the ability to calculate, spell, and write. Brain atrophy of the hippocampus is evident early in the disease progression (Bredesen, 2017).

The Inflammation Hypothesis

Inflammation has been implicated in AD mechanisms and is believed to play a critical role in the pathogenesis of the disease. When Aloysius Alzheimer studied the post-mortem brain of Aguste Deter in 1907, he found microglia, the primary cells of the innate immune system involved in the brain inflammation response, clustered around the amyloid plaques. Initially, the inflammation hypothesis was regarded as unlikely or even impossible due to the view of the brain as an "immune-privileged organ," allowing for inflammation only "through direct infection or after the breakdown of the blood brain barrier and subsequent infiltration of peripheral immune cells" (Heneka et al., 2014). However, extensive research over the last decade has confirmed the presence of neuroinflammation in AD and suggests that its presence may even begin in preclinical stages of the disease (McCaully & Grush 2017). PET imaging has shown evidence of significantly increased levels of neuroinflammation markers in brain areas affected by AD neuropathology while almost no neuroinflammation was found in individuals without dementia, despite high plaque burden (Krstic et al., 2012). Furthermore, several known risk factors for AD, such as a history of systemic infection, obesity, and reduced physical activity, are associated with some component of inflammation (Heneka et al., 2014). Increasing evidence suggests that neuroinflammation seems to correlate more directly with cognitive decline than plaque deposition alone.

Innate Immunity: Microglial Contribution to AD Pathogenesis

Innate immune cells, particularly microglia, have been implicated as mediators of neuroinflammation in AD and as contributors to its pathogenesis. Microglial cells are an essential part of the central nervous system and serve to protect the brain from injury and pathogenic invasion. In brain development, microglia assist in synapse formation and eliminate dysfunctional synaptic connections (Van Eldik et al., 2016). Rice, et. al. (cited in Spangenberg & Green, 2017) found that healthy adult mice, without a proliferation of microglia, showed 35% more synapse-bearing dendritic spines than mice with significant microglial proliferation, indicating that microglial participation in synaptic maintenance may continue even into adulthood through the dismantling of dendritic spines in the AD brain.

In the homeostatic adult brain microglia are in a "surveillance state," constantly surveying the brain parenchyma to detect abnormalities and supporting neuronal health and function by regulating synaptic plasticity and pruning unnecessary synapses. Upon detection of an insult, such as Aβ plaques, these immune cells are activated and assume an entirely different phenotype with both chemical and morphological changes, including the retraction of their processes. This phenotypic change may inhibit the ability of microglia to alter and adapt synapses and contribute to the impaired synaptic plasticity characterized by AD (Van Eldik et al., 2016). Once activated, microglia secrete pro-inflammatory cytokines, including TNFα, IL-6, and IL-1β to induce other cells to migrate to the injury site and mediate clearance of the invasive material through phagocytosis. In acute inflammatory events, the inflammatory response is resolved through regulatory proteins which induce microglia to secrete anti-inflammatory factors to promote tissue repair. The microglia then revert to their "surveillance state". However, in AD, microglia are unable to phagocytose Aβ, as evidenced by the presence of plaques surrounded by microglial cells in post-mortem AD brains (Spangenberg & Green, 2017). This leads to the sustained release of pro-inflammatory mediators which "has been shown to be involved in the suppression of axonal transport and adult neurogenesis" (Heneka et al., 2014).

Inflammatory dyshomeostasis drives microglia into a state of chronic activation in which they no longer function properly, resulting in aberrant synaptic pruning, neuronal loss, and accumulation of Aβ, eventually leading to cognitive dysfunction (Spangenberg & Green, 2017). Cytokines, for instance, have been linked to cytoskeletal and synaptic alteration through increased tau phosphorylation and decreased synaptophysin levels.

Experimental Correlation Between Innate Immune Activation and Neurodegenerative Disease

Numerous animal studies have linked immune responses to neurodegeneration. In one study, the NLRP3 gene, an important component of the neuroinflammatory pathway, was removed from APP/PS1 mice. This gene knockout resulted in reduced inflammation, enhanced Aβ clearance, as well as improved synaptic plasticity and cognitive function (Heneka et al., 2013). In another experimental study, inflammation caused by systemic

immune challenges alone was revealed to trigger Alzheimer-like neuropathology in mice. Mice exposed to systemic immune stimulation prenatally and then again later in adulthood were predisposed to develop sporadic-like AD during aging. They displayed chronic microglial activation, increased Aβ deposition, and working memory impairment (Krstic et al., 2012). In another study, neutralizing increased levels of the inflammatory cytokine, IL-1β, was found to reduce Aβ and p-tau in triple-transgenic AD mice (Ferreira et al., 2014).

A recent study found a correlation between increased proliferation of microglial cells in human AD and disease severity. To establish the influence of inflammation over the onset and progression of AD they targeted the colony-stimulating factor 1 receptor (CSF1R), a receptor protein that regulates the activation and proliferation of microglial cells. A tyrosine kinase inhibitor was administered to APP/PS1 to induce prolonged inhibition of CSF1R. This inhibition resulted in decreased microglial proliferation and improved performance in memory related tasks. These results support the "link of the inflammatory response generated by microglia...with the observed synaptic and behavioural deficits" (Olmos-Alonso, et. al. 2016).

In their review of innate immune activation in neurodegenerative disease, Heneka et al. conclude that neuroinflammation is likely not only a consequence but also an early cause of the pathology (Heneka et al., 2014).

Key Measures of Inflammation

C-reactive protein (CRP) is produced by the liver in response to inflammation. ReCODE protocol advises testing for hs-CRP (high sensitivity) as the standard CRP test cannot always distinguish optimal levels, below 0.9 mg/dl, from mildly abnormal levels. The albumin to globulin ratio is a complementary measure of inflammation and should be at least 1.8. Fatty acids omega-6 and omega-3 are pro and anti-inflammatory respectively. Their ratio should be between 0.5 and 2.9. Levels of cytokines such as IL-6 and TNFα are also important indicators of inflammation. Concentration of IL-6 should be less than 3.0 pg/ml and that of TNFα should be less than 6.0 pg/ml. (Bredesen, 2017)

Reducing Inflammation

The ReCODE protocol recommends a three-pronged approach to reducing inflammation. Treating inflammation is of no use if the trigger is still present, so first, it is critical to remove the sources of inflammation by preventing exposure to "inflammagens". There could be several sources, including chronic infection, viruses, a diet high in simple carbohydrates, leaky gut, and even poor oral hygiene. The second step is to resolve the inflammation through specialized pro-resolving mediator (SPM) supplements. SPMs are small cell signaling molecules such as resolvins, and maresins that have been identified during active inflammation resolution in the body and mediate the return to tissue homeostasis (Serhan et al., 2011). Chronic inflammation indicates the inability to return to homeostatic condition and SPM supplements can provide the missing resolution agonists. The third step is to inhibit new inflammation through ingestion of anti-inflammatories such as omega-3 and curcumin (Bredesen, 2017).

Subtype 2: Non Inflammatory or Atrophic

Homozygous and heterozygous carriers of the ApoE4 allele are at increased risk for this subtype as well, though symptoms typically begin about a decade later than the inflammatory subtype. Symptoms are similar to those in inflammatory Alzheimer's, with an impaired ability to form new memories but retained ability to write and calculate. Inflammation is not present and some of its biomarkers may actually be suboptimal. Rather, this subtype is associated with reduced overall support of synaptic plasticity marked by an atrophic profile, including insulin resistance, hypovitaminosis D, hyperhomocysteinemia, and reductions in hormonal support from molecules such as estradiol, progesterone, and testosterone (Bredesen, 2017). While the extent to which each of these risk factors contributes to AD pathology is still being studied, scientists have proposed theoretical mechanisms to support the contribution of many of these mediators, including homocysteine and insulin, to its pathogenesis.

Homocysteine

Epidemiological studies have associated increased levels of homocysteine (HC) with Alzheimer's disease progression (Morris, 2003). According to one study, homocysteine contributes to AD pathology through an Aβ-fibrinogen interaction. This interaction induces the oligomerization of fibrin and the formation of abnormal fibrin clots which are resistant to fibrinolysis. Accumulation of fibrin clots leads to inflammation and disruption of the blood brain barrier. In their study, AD patients with high levels of homocysteine showed increased Aβ plaques and fibrinogen levels in the brains. Similarly, researchers induced hyperhomocysteinemia in an AD mouse model by administering a high methionine diet for several months. These mice displayed severe Aβ plaque deposition along with learning and memory impairments (Chung et al., 2016). Homocysteine is a marker of both inflammation and suboptimal nutritional support. Sufficient amounts of vitamins B6, B12, and B9 (folate) are required to maintain an optimal level, below 6 mM/L (Bredesen, 2017).

Insulin Resistance

Insulin resistance is another significant risk factor for AD. Insulin is degraded by a protein known as insulin degrading enzyme. This enzyme has also been linked to the decomposition of Aβ plaques. High levels of insulin require insulin degrading enzyme to be constantly breaking down excess insulin, thus limiting its opportunity to decompose Aβ plaques. High levels of glucose

also lead to the production of advanced glycation end products. These molecules trigger inflammation when they bind to their receptors, cause the formation of free radicals, and damage blood vessels, thus reducing nutritional support to the brain. Fasting insulin level should be 4.5 mIU/ml or below and fasting glucose level should be between 70-90 mg/dL (Bredesen, 2017).

Subtype 3: Cortical or Toxic

Subtype 3 is characterized by biomarkers of toxicity and typically occurs in carriers of the ApoE3 rather than the ApoE4 allele. Symptom onset is often earlier, in the late forties to early sixties, and following a period of great stress, sleep loss, anesthesia, or menopause. Cortical Alzheimer's is completely different than the other two types; it is not predominantly amnestic in the early stages and presents itself instead with cortical deficits such as dyscalculia and aphasia. In addition to short-term memory loss, long-term memory loss, including procedural memory, is also affected (Bredesen, 2017). In these cases, PET imaging often indicates more general cerebral atrophy compared to the more restricted temporoparietal reduction typically seen in patients with subtypes 1 and 2 (Bredesen et al., 2016).

Current research seems to suggest a possible link between mercury toxicity and AD. In vitro studies have found that mercury increases secretion of Aβ, causes structural changes in mitochondria which induce a response from the innate immune system. Mercury also interferes with membrane structures leading to the aggregation of neurofibrillary fibers and degeneration of neuronal axons (Walach et al., 2015).

Exposure to other biotoxins such as arsenic has also been shown to affect neurological function. Arsenic exposure most commonly comes from groundwater, a phenomenon particularly prevalent in western United States where certain areas are estimated to have over 300 times the permitted EPA level of arsenic in the drinking water. Gong et al. proposed the Arsenic Exposure Hypothesis for AD based on premises of existing hypotheses for the disease. They find correlations between arsenic toxicity and several typical pathological markers of the disease. These include the following: over transcription of APP, brain inflammatory response, and the generation of free radicals which cause oxidative stress and neuronal death (Gong et al., 2010).

Although much of the literature on arsenic toxicity details its cognitive effects on children, recent studies have correlated it with altered adult cognition as well. The FRONTIER Project is an ongoing study being conducted on residents living in West Texas, an area that contains significant levels of arsenic in the groundwater. Participants with long-term chronic exposure to arsenic scored lower on tests for global cognition, processing speeds and immediate memory (Tyler & Allan, 2014).

It has been suggested that Toxic Alzheimer's is a phenotypic manifestation of chronic inflammatory response syndrome (CIRS), commonly caused by exposure to biotoxins such as molds or tick-borne pathogens. Cognitive decline in both patients with CIRS and Type 3 Alzheimer's is not limited to amnestic symptoms; it includes executive dysfunction often concomitant with hypozincemia, dysfunction of the hypothalamic-pituitary-adrenal axis, and psychiatric effects such as depression. In the case studies of patients displaying type 3 symptoms, all of them had a history of significant toxic exposure (Bredesen, 2016). Patients with the toxic subtype of Alzheimer's also often present significantly high levels of copper and low levels of zinc which can cause increased sensitivity to toxins such as mercury and mold. A copper:zinc ratio of 1.4 or higher has been associated with dementia.

ReCODE recommends treating metal toxicity in one of several ways including chelation, or a gentler method called Detox Qube which helps optimize the natural detoxification process of the body to eliminate potentially toxic metals such as mercury and arsenic. Treatment for toxicity from other toxins such as mold are more complicated and exposure specific and thus should be treated by a physician experienced in biotoxin-associated illness (Bredesen, 2017).

Additional Factors Addressed by ReCODE

The primary characteristic of the ReCODE protocol is its attempt to simultaneously address as many potential disease mechanisms as possible, including diet, exercise, and cognitive training, among others.

Ketogenic Diet: A Neuroprotective Mechanism

The protocol recommends that patients adhere to a ketogenic diet which has been associated with neuroprotective benefits. Ketogenic diets have been linked to several neuronal and synapse supporting mechanisms. Studies have associated a ketogenic diet with antioxidant effects, increased cerebral ATP indicating metabolic effects, and decreased expression of pro-apoptotic factors clusterin and caspase-3, implicating anti-apoptotic mechanisms as well. Additionally, it has been found that the presence of β-HB increases the synthesis of BDNF, a trophic factor which mediates neuroprotection and is associated with cognitive improvement (Bredesen, 2017). Growing evidence of brain glucose hypometabolism in AD brains may provide a mechanism to explain this correlation; namely that the abundance of ketone bodies (KB) made available by a ketogenic diet may compensate for the decreased glucose uptake in the brain by acting as a fuel replacement, allowing the brain to work more efficiently.

Ketone Bodies and Brain Glucose Hypometabolism

The adult brain uses close to 23% of the body's total energy requirement, despite representing only about 2% of total body weight, with glucose used as the predominant form of fuel. It is well documented that glucose metabolism is significantly deteriorated in patients with AD. PET imaging has even shown significant

hypometabolism in subjects with risk factors for AD prior to the manifestation of any symptoms of cognitive decline. A recent review of several independent studies conducted on various groups at risk for AD shows evidence of increased presymptomatic brain glucose hypometabolism, ranging from 12-20% as compared to the control, in all at-risk groups (Cunnane et al., 2016).

For instance, subjects who were homozygous for the E4 allele with a family history of AD, both risk factors for developing AD, were screened for glucose hypometabolism against a control group. Despite no difference in cognitive test results, the experimental group displayed decreased glucose metabolism in the same brain regions identified in AD subjects, specifically in the posterior cingulate and prefrontal, parietal, and temporal cortices (Reiman et al., 2004). This indicates the possibility that PET scans measuring the cerebral metabolic rate of glucose (CMRg) can even be used to predict the onset of the disease.

Given the necessity of the brain for a constant energy supply, Cunnane et al. has proposed that glucose hypometabolism in the brain causes chronic, gradual brain energy starvation and may be part of the disease etiology of AD. Thus, it seems reasonable for potential therapeutic strategies to be aimed at correcting the underlying problem of deteriorating brain fuel supply, specifically by studying the body's normal method of coping with decreased glucose availability which occurs during fasting, malnutrition, or strenuous exercise. When glucose supply is severely compromised, the brain uses ketone bodies, specifically β-hydroxybutyrate and acetoacetate, as the main reserve fuel (Owen et al., 1967).

Ketone vs Glucose Metabolism and Uptake

A study comparing brain glucose and ketone uptake was conducted to determine whether hypometabolism in the brain is generalized to include both glucose and ketone metabolism or a condition specific to glucose. Results showed that global brain FDG (glucose analogue used in PET imaging) uptake was 14% lower in early AD patients than the control group while no significant difference in C-Ac (acetoacetate analogue) uptake was found. Thus, it seems possible that providing more KB to offset the deficit in energy caused by glucose hypometabolism in aging brains may decrease neuronal shrinkage and lower the risk of developing AD. Indeed, clinical studies suggest that nutritional treatments to increase plasma KB concentration may be effective against cognitive decline in early stages of AD (Cunnane et al., 2016).

This theory has been tested in a cell culture model of AD with positive results. Hippocampal cells of embryonic rats exposed to Aβ42 demonstrated a 50% decrease in cell number. When these cells were simultaneously exposed to β-HB, cell survival doubled, indicating the potentially protective nature of β-HB from amyloid toxicity (Henderson, 2008). The effectiveness of ketone body treatment in human AD subjects has also been tested in clinical trial. In this study, subjects with mild to moderate probable AD consumed a beverage containing emulsified medium-chain triglycerides (MCTs) to induce elevated serum KB levels. Due to its shorter chain length, MCTs generate the rapid production of ketone bodies, unlike longer fatty acid chains. After 90 minutes, neurophyscological testing showed a significant correlation between increased serum β-HB concentration and memory improvement, specifically for subjects without the ApoE4 allele (Reger et. al, 2004).

The Ketoflex 12/3 Diet

Due to significant evidence indicating the positive effects of a ketogenic state on cognitive function, the ReCODE Protocol posits the need for a ketogenic nutritional plan, referred to as the "Ketoflex 12/3" diet. The typical western diet is high in carbohydrates which inhibit ketogenesis and the utilization of KB. A ketogenic diet promotes the release of free fatty acids to be synthesized into KB, a process which is normally inhibited by insulin signaling in the presence of carbohydrates.

The Keto in Ketoflex 12/3 refers to the induced state of ketosis through a high-fat, low carbohydrate, plant-based diet. Consumption of MCTs has also been shown to help induce mild-ketosis and is recommended as well. These include coconut oil and palm kernel oil, of which approximately 10% consist of these medium chain fatty acids, or MCT oil which is a concentrated form of the fraction of medium chain fatty acids in coconut oil (Cunnane et al., 2016).

The flex in the Ketoflex 12/3 diet reflects the flexibility and variety of food choices. The diet is mainly plant-based with consumption of protein limited to just a few ounces a day. The consumption of too much protein causes some of it to be converted to carbohydrates. In his book, The End of Alzheimer's, Dr. Bredesen outlines some specifics regarding food choices. These include the following: choosing mainly foods with a glycemic index lower than 35, as these foods do not require significant insulin release; eating detoxifying plants such as cilantro, cruciferous vegetables, kale, maca, and avocados to help eliminate toxins such as heavy metals and Bisphenol A; and getting probiotics and prebiotics either in pill form or from fermented foods such as kimchi and sauerkraut, to help optimize bacteria in the gut. He also recommends reducing cooking times and temperatures to reduce the production of advanced glycation end products which create inflammation, and optimizing nutrition with supplements such as reservatol, nicotinamide riboside, citricoline, ubiquinol and polyquinoline quinine (Bredesen, 2017).

The 12/3 refers to the fasting times; namely a 12 hour fasting period between the last meal at night and the first meal of the next morning, and a 3 hour minimum between dinner and bedtime. As previously discussed, fasting is a highly effective way to induce ketosis.

Stress Management

There are several mechanisms that may account for the association of chronic unresolved stress with cognitive decline. Stress activates the HPA axis to stimulate the release of stress related hormones, such as cortisol, from the adrenal glands. Increased levels of cortisol can lead to neuronal damage, particularly in the hippocampus, thus contributing to cognitive and memory decline. Stress also increases several risk factors for AD including blood glucose levels and hyperstimulation of neurons. Stress is most closely linked with Type 3 Alzheimer's, where onset of cognitive decline often coincides with a stressor. Therefore, a program for stress reduction is included in the ReCODE protocol, including meditation and yoga to lower cortisol levels and prevent hippocampal atrophy (Bredesen, 2017)

Sleep Optimization

There are several neural mechanisms through which sleep affects cognition. Sleep is associated with reduced amyloid plaque formation and induces autophagy in the brain, recycling dysfunctional components and improving cellular health. Production of growth hormone increases during sleep allowing for cell repair and production of supportive brain cells. More hours of sleep allow for a longer period of fasting which helps improve insulin sensitivity. ReCODE recommends at least 8 hours of sleep and the use of melatonin if falling asleep is difficult (Bredesen, 2017).

Physical Activity

Exercise has been linked to many benefits related to cognition. Among them are: reduced insulin resistance, increased ketosis, stress reduction, improved sleep, and increased size of the hippocampus which is a key region in memory and shows atrophy in AD. For optimal cognition benefits, ReCODE recommends combining aerobic exercise with weight training 5 days a week for 45 - 60 minutes per day (Bredesen, 2017).

Table 1. Summary of patients treated with the therapeutic system described

Patient	History, evaluation	Diagnosis	Status
67F 3/3	2yr memory ⇓; FH+	aMCI	Normal x 2.5 yrs; working
69M 4/3	12yr memory ⇓; FDG-PET+, NPsych+	Early AD	"Clearly improved;" working
70M 4/3	4yr memory ⇓; NPsych+, failed MemTrax	AD	Improved; MemTrax passed
75M 3/3	1yr memory ⇓	SCI	Improved; working
75F C677T	1yr memory ⇓	aMCI/early AD	Improved
55F 3/3	4yr memory ⇓	aMCI/early AD	Normal; working
72M 3/3	7yr memory ⇓	aMCI	Improved; working
55M 4/3	2yr memory ⇓	SCI	Normal; working
63F 4/3	FH dementia, mild memory ⇓	SCI	Normal, negative amyloid PET; working
60F 4/3	4yr rapid decline; MoCA 6, amyloid PET+	Late AD	Decline

F, female; M, male; 3/3, ApoE 3/3; 4/3, ApoE 4/3; C677T, the C677T mutation in methylene tetrahydrofolate reductase (MTHFR); FH, family history; aMCI, amnestic mild cognitive impairment; SCI, subjective cognitive impairment; FDG-PET+, fluorodeoxyglucose positron emission tomography interpreted as typical of Alzheimer's disease; amyloid PET+, amyloid PET scan read as abnormal, indicative of amyloid accumulation; NPsych+, quantitative neuropsychology tests showing abnormalities typical of AD; MoCA, Montreal Cognitive Assessment; MemTrax, an iPhone application that quantitates memory.

Cognitive Training

Although the effects of brain exercises are controversial, cognitive training was one of the additional intervention elements given to the intervention group of the FINGER study which suggest a positive correlation between brain exercises and cognition (Ngandu et al., 2015).

Patient Case Studies

The results of the multi-domain therapeutic system utilized by Bredesen et al. on 10 patients is summarized in the table below. As indicated, patients either reverted to their normal mental status prior to exhibiting symptoms of cognitive impairment, or showed improvement in cognition. One patient with advanced AD, however, showed decline. These results suggest that memory loss in cases of Subjective Cognitive Impairment (SCI), Mild Cognitive Impairment (MCI), and early AD may be reversed and show sustained improvement using the therapeutic program described by the ReCODE protocol (Bredesen, 2017).

Conclusion

Although preliminary results of this study seem promising, unlike the FINGER study, the results are only anecdotal and fail to include predefined criteria for success, any indication as to how patients were selected for inclusion, or clear descriptions of the exact protocol followed for each patient. Additionally, the protocol addresses many biomarkers that have been implicated in AD without proving whether they are etiologically or epiphenomenally linked. There is also no control group for comparison. Thus a more extensive, controlled clinical trial is required to determine the broad range effectiveness of the ReCODE protocol on cognitive impairment.

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