Probable Causes of Alzheimer’s Disease

James Adams 1,*

1 Professor Emeritus 1; JimAdams91214@gmail.com
* Correspondence: JimAdams91214@gmail.com

Abstract: A three-part mechanism is proposed for the induction of Alzheimer’s disease: 1. Decreased blood lactic acid, 2. Increased blood ceramide, 3. Decreased blood folic acid. The age-related nature of these mechanisms comes from age associated decreased muscle mass, increased visceral fat and changes in diet. This mechanism also explains why many people do not develop Alzheimer’s disease. Simple changes in lifestyle and diet can prevent Alzheimer’s disease.

Keywords: lactic acid; ceramide; folate; nicotinamide; Alzheimer’s disease

1. Introduction

The failure of anti-amyloid β therapies in the treatment of Alzheimer’s disease [1, 2] has pointed out that the amyloid-tau theories of Alzheimer’s disease induction are wrong. As many Scientists have published for many years, amyloid β and tau are the results of the disease not the causes. Amyloid β and tau are misfolded proteins that accumulate in neurons and may be released into extracellular spaces when neurons die.

There are several risk factors for the development of Alzheimer’s disease including loss of muscle mass, high alcohol consumption, type 2 diabetes, high blood pressure, high blood cholesterol, heart disease, atrial fibrillation and other factors [3-5]. The variables that are common to all these risk factors are sedentary lifestyles and visceral fat obesity. As people age and become sedentary, visceral fat increases, muscle mass decreases and vascular damage increases. Cerebrovascular damage is prominent in the brains of Alzheimer’s disease patients [6]. Alcohol consumption increases visceral fat accumulation.

Several research articles have found that Alzheimer’s disease can be prevented by eating diets low in fat, high in fruits and vegetables, and by regular physical activity [7-9]. The health benefits of fruits, vegetables and exercise cannot be over emphasized in cultures where meat-eating and sedentary lifestyles are abundant.

2. Exercise/Lactic Acid

There is a muscle brain axis that is based on the fact that the brain must have substances that are secreted into the blood by muscles. This muscle brain axis is critical to brain health. Loss of muscle mass with aging is dangerous for the brain. Sarcopenia is a normal consequence of aging, even in athletes [10]. There is no question that frailty increases the risk of developing Alzheimer’s disease [11].

Lactic acid comes from muscle, especially exercising muscle [10]. Lactic acid is very important to the body, including the brain. Blood lactic acid levels can reach 32 mM in athletes. Lactic acid is an energy source for brain neurons, astrocytes and pericytes [12]. It is taken up across the blood brain barrier and into cells by anion channels and monocarboxylic acid transporters [13]. Due to sarcopenia and sedentary lifestyles, many people may not get enough lactic acid to supply essential energy to brain cells, especially cells of the blood brain barrier.
Hydroxycarboxylic acid receptor1 is the receptor that mediates lactic acid signaling and is abundant in cells of the blood brain barrier [13]. The receptor is found on both the luminal and abluminal surfaces of endothelial cells of the blood brain barrier. Autophagy and mitophagy can be inhibited by lactic acid [14]. Alzheimer’s disease appears to be associated with improperly functioning autophagy [15]. Physical exercise enhances brain levels of brain derived neurotrophic factor, vascular endothelial growth factor and lactic acid, all of which stimulate neurogenesis, even in the adult hippocampus [14, 16, 17]. Lactic acid improves brain health and neurogenesis, but may not stimulate memory retention [17].

Lactic acid inhibits transient receptor potential cation channels of the vanilloid type (TRPV1) [16]. Endocannabinoids are the normal agonists for TRPV1 receptors, and also inhibit these receptors after prolonged stimulation [18]. Lactic acid augments the inhibitory actions of endocannabinoids at TRPV1 channels. TRPV1 channel overstimulation increases calcium influx into cells and enhances oxygen radical production [19]. There are three aspects to lactic acid that are important to the blood brain barrier. It is an essential nutrient to pericytes, astrocytes and neurons. It can inhibit autophagy. It can also inhibit TRPV1 channels which might decrease damage to the blood brain barrier. Pericytes and endothelial cells of the blood brain barrier are regulated, in part, by TRPV1 channels [20, 21]. Damage to pericytes and the blood brain barrier are prominent features of Alzheimer’s disease [22]. Inadequate lactic acid causes pericytes to die. Inadequate inhibition of TRPV1 by low levels of lactic acid causes pericytes to die. Pericytes secrete pleiotrophin that is essential for neuronal survival [23].

Exercise stimulates oxygen radical production, even in the brain [24]. Oxygen radical production includes the generation of hydrogen peroxide which is an important signaling molecule. Hydrogen peroxide crosses membranes at peroxiporin channels and rapidly damages nuclear DNA which results in poly(ADP-ribose) polymerase activation [25]. This enzyme is responsible for increasing the activities of DNA repair enzymes and enzymes that protect against oxidative stress. The transcription of nuclear factor erythroid 2 related factor 2 increases which activates genes of the antioxidant response elements [26]. These gene sequences enhance the transcription of several enzymes involved in defense against oxidative stress. Exercise enhances the ability of the brain to protect itself against oxygen radical toxicity and enhances brain health.

Exercising muscles secrete myokines into the blood. These proteins have a number of beneficial functions in the brain and the blood brain barrier. Cathepsin B is a myokine that crosses the blood brain barrier and enhances the synthesis of brain derived neurotrophic factor in the brain [17, 27]. Fibroblast growth factor 21 is a myokine that crosses the blood brain barrier, has neuroprotective effects and enhances circadian rhythms [17]. Irisin is derived from exercising muscles, crosses the blood brain barrier, increases synaptic plasticity and memory [28].

3. Ceramide

Ceramide levels are high in the brains of Alzheimer’s disease patients [29]. The higher the ceramide levels, the greater the risk of exhibiting Alzheimer’s disease [30]. Ceramide is released into the blood by visceral fat adipocytes and is taken up into the brain [31-4]. Endothelial nitric oxide synthase is induced by ceramide, but is dysfunctional in the presence of high ceramide levels [31-4] with the production of oxygen radicals. This damages endothelial cells of the blood brain barrier and may allow the penetration of monocytes/macrophages and neutrophils into the brain. Ceramide induced oxidative stress increases NADPH oxidase activity on the outside of the plasma membranes of macrophages in the brain which produces hydrogen peroxide and increases damage to brain neurons [31-4]. Ceramide activates toll like receptor 4 which leads to nuclear factor kappa B activation and inflammatory responses [35]. Ceramide inhibits vascular endothelial cell induced angiogenesis which compromises repair of the blood brain barrier [36].
4. Endocannabinoids

Many people use marijuana, Cannabis sativa, to self-treat their dementia and Alzheimer’s disease. Several studies have not found evidence for efficacy of C. sativa for this use [37, 38]. A population-based study of late onset Alzheimer’s disease found that C. sativa decreases dementia related symptoms [39]. So far, there is no question that C. sativa is safe to use in Alzheimer’s disease.

There are no changes in anandamide or 2-arachidonoyl glycerol brain levels in the brains of Alzheimer’s disease patients compared to controls [40]. Cannabinoid receptor 1, CB1, expression does not appear to change due to Alzheimer’s disease [40]. Fatty acid amide hydrolase deactivates anandamide and is enhanced in the brains of Alzheimer’s disease patients [40]. This suggests that the synthesis of anandamide may be high in Alzheimer’s disease, but is kept in the normal range by enhanced fatty acid amide hydrolase. CB2 expression increases in the microglial cells of brains from Alzheimer’s disease patients [40]. CB2 expression and microglial activation are involved in the neuroinflammation that causes Alzheimer’s disease. This suggests that the use of a CB2 inhibitor, cannabidiol, may be useful to slow down the progression of Alzheimer’s disease. The low oral bioavailability of cannabidiol may limit its usefulness.

5. Adipokines

Visceral fat secretes inflammatory adipokines into the blood that cause type 2 diabetes, heart disease, arthritis and other problems [31]. Visfatin is a visceral fat derived inflammatory adipokine, as is monocyte chemoattractant protein-1. Visfatin works with xanthine oxidase and NADH oxidase to increase oxygen radical production in the lumens of capillaries which damages the blood brain barrier [31-4]. Monocyte chemoattractant protein-1 allows monocytes to adhere to damaged endothelial cells and cross the blood brain barrier to enhance brain inflammation.

Several inflammatory adipokines are elevated in the blood of patients with Alzheimer’s disease [2] including: dipeptidyl peptidase-4, IL-1β, IL-2, IL-6, IL-18, interferon-γ, C-reactive protein, CXC chemokine-10, epidermal growth factor, vascular cell adhesion protein1, tumor necrosis factor α and leptin. Dipeptidyl peptidase-4 enhances vascular aging and may increase blood brain barrier damage [41]. IL-1β and IL-6 induce hepcidin transcription [42] which causes iron overload in neurons during neuroinflammation possibly increasing neuronal death [43]. C-reactive protein elevation is predictive of death in frail patients [44]. C-reactive protein binds to lysophosphatidylcholine on damaged cells, including endothelial cells, and activates the complement system. It also induces NADPH oxidase on the luminal membranes of endothelial cells of the blood brain barrier, which enhances oxygen radical formation and damages the blood brain barrier [45]. Chemokines and vascular cell adhesion protein1 increase the adhesion and brain penetration of monocytes and neutrophils. Homocysteine is higher in the blood of patients with Alzheimer’s disease than controls [2]. Nitric oxide synthase dysfunction and oxygen radical production occur due to high blood homocysteine with consequent damage to the microvasculature [46]. This damages the blood brain barrier which allows essential compounds to leak out of the brain and harmful compounds and inflammatory cells to enter into the brain.

6. Diet

Dietary changes in aging have been noted in several studies [47-50]. These dietary changes probably explain why up to 40% of elderly people do not eat diets that contain adequate amounts of nicotinamide, which is a form of vitamin B3 [51]. Nicotinamide is neuroprotective [52]. Nicotinic acid intake has been shown to be inversely related to the
incidence of Alzheimer’s disease [53]. Nicotinic acid is converted into nicotinamide by nicotinamidase before it can be taken up into the brain [52]. However, increased blood high density lipoprotein by nicotinic acid may be beneficial to the blood brain barrier. The metabolite of nicotinamide, N-methylnicotinamide, protects the vasculature and decreases homocysteine levels [54]. Inadequate dietary intake of magnesium occurs in 60% of people due to inadequate intake of fruits and vegetables [55]. Chocolate is a good source of magnesium, with 41 mg of magnesium per 28 g of dark chocolate. Magnesium protects the vasculature against atherosclerotic changes [56].

N-3 polyunsaturated fat consumption, α linolenic acid C18:3N-3, eicosapentaenoic acid C20:5N-3, docosahexaenoic acid C22:6N-3, may benefit the brain but does not decrease the incidence or progression of Alzheimer’s disease [57]. A-Linolenic acid is from flax seed, chia seeds, soybean and canola oil. Eicosapentaenoic acid and docosahexaenoic acid are from fish and marine microalgae. Adequate daily intake of α linolenic acid in adults above 51 years old is 1.6 g per day for men and 1.1 g per day for women.

Low intake of folate, vitamin B9, increases the risk of developing Alzheimer’s disease and the severity of atrophy of the cerebral cortex [58]. This may relate to the ability of folate to decrease blood homocysteine levels [59]. Folate protects endothelial cells and may benefit the blood brain barrier. Folate is abundant in leafy green vegetables. The daily recommended intake of folate is 400 ug. Spinach, 30 g, contains 58.2 ug of folate. Fruit can also contain folate. One orange may contain 55 ug of folate. Vegetables are also good sources of folate, including asparagus, Brussels sprouts and broccoli. Blueberries are rich in folate, 24 ug per 340 g, and nicotinic acid 1.7 mg per 340 g. Strawberries are also good folate sources, 100 ug per 100 g of berries, and contain some nicotinic acid 0.5 mg per 100 g of berries. Recent studies have found diets that contain adequate leafy green vegetables and fruits slow age-related cognitive decline and may decrease the onset of Alzheimer’s disease [60, 61]. Of course, folate as well as flavonoids, betulinic acid and other natural compounds are beneficial in these diets [34].

7. Discussion

It is probable that Alzheimer’s disease is caused by sedentary lifestyles, visceral fat accumulation, inadequate exercise and poor nutrition especially in terms of fruit and vegetable intake. All of this leads to damage to the blood brain barrier, neuronal death and inflammation of the brain that are hallmarks of Alzheimer’s disease.

Prevention of Alzheimer’s disease involves daily exercise, maintaining a lean body with little visceral fat, and eating fruits and vegetables daily. Healthcare professionals can do a great service to their patients by teaching them how to prevent Alzheimer’s disease: exercise daily, maintain a lean body, eat green leafy vegetables, other vegetables and fruit.

Funding: “This research received no external funding.”

Conflicts of Interest: “The author declares no conflict of interest.”

References

1. Lien, E.; Adams, J.; Lien, L.; Law, M. Alternative approaches to the search for Alzheimer’s disease treatments. J Multidiscipl Sci J 2018, 1, 2-7. doi.org/10.3390/j1010002.
2. Adams, J. Can peripheral inflammation cause Alzheimer’s disease? Biomed Res J 2019, 1, 1-3.
3. Kivipelto, M.; Helkala, E.; Laakso, M.; Hänninen, T.; Hallikainen, M.; Alhainen, K.; Soininen, H.; Tuomilehto, J.; Nissinen, A. Midlife vascular risk factors and Alzheimer’s disease in later life: longitudinal, population based study. BMJ 2001, 322, 1447-51. doi.org/10.1136/bmj.322.7300.1447.
4. Breteler, M. Vascular risk factors for Alzheimer’s disease: an epidemiological perspective. *Neurobiol Aging* 2000, 21, 153-60. doi.org/10.1016/S0197-4580(99)00110-4.

5. Burns, J.; Johnson, D.; Watts, A.; Svedrot, R.; Brooks, W. Reduced lean mass in early Alzheimer Disease and its association with brain atrophy. *Arch Neurol* 2010, 67, 428-33. doi.org/10.1001/archneur.2010.38.

6. Snowden, D.; Greiner, L.; Mortimer, J.; Riley, K.; Greiner, P.; Markesbery, W. Brain Infarction and the Clinical Expression of Alzheimer Disease The Nun Study. *JAMA* 1997, 277, 813-817. PMID: 9052711.

7. Lindsay, J.; Laurin, D.; Verreault, R.; Hébert, R.; Helliwell, B.; Hill, G.; McDowell, I. Risk factors for Alzheimer’s disease: a prospective analysis from the Canadian study of health and aging. *Am J Epidemiol* 2002, 156, 445-53. doi.org/10.1093/aje/kwf074.

8. Gu, Y.; Nieves, J.; Stern, Y.; Luchsinger, J.; Scarmeas, N. Food combination and Alzheimer Disease risk: A protective diet. *Arch Neurol* 2010, 67, 499-706. doi.org/10.1001/archneur.2010.84.

9. Scarmeas, N.; Stern, Y.; Mayeux, R.; Luchsinger, J. Mediterranean diet, Alzheimer Disease, and vascular mediation. *Arch Neurol* 2006, 63, 1709-17. doi.org/10.1001/archneur.63.12.noc60109.

10. Dhillon, R.; Hasni, S. Pathogenesis and Management of Sarcopenia. *Clin Geriatr Med* 2017, 33(1), 17-26. doi:10.1016/j.cger.2016.08.002.

11. Yoon, D.; Lee, J.; Shin, S.; Kim, Y.; Song, W. Physical Frailty and Amyloid-β Deposits in the Brains of Older Adults with Cognitive Frailty. *J Clin Med* 2018, 7, 169; doi:10.3390/jcm7020169.

12. Ma, K.; Ding, X.; Song, Q.; Han, Z.; Yao, H.; Ding, J.; Hu, G. Lactate enhances Arc/arg3.1 expression through hydroxycarboxylic acid receptor 1β-arrestin2 pathway in astrocytes. *Neuropharmacol* 2020, 171, 108084. doi:10.1016/j.neuropharm.2020.108084.

13. Morland, C.; Husa Lauritzen, K.; Puchades, M.; Holm-Hansen, S.; Andersson, K.; Gjedde, A.; Attramadal, H.; Storm-Mathisén, J.; Bergersen, T. The Lactate Receptor, G-Protein-Coupled Receptor 81/Hydroxycarboxylic Acid Receptor 1: Expression and Action in Brain. *J Neurosci Res* 2015, 93, 1045–1055. DOI: 10.1002/jnr.23593.

14. Zhu, Y.; Ji, J.; Yang, R.; Han, X.; Sun, X.; Ma, W.; Liu, N. Lactate accelerates calcification in VSMCs through suppression of BNIP3-mediated mitophagy. *Cell Signal* 2019, 58, 53-64. doi:10.1016/j.cellsig.2019.03.006.

15. Uddin, M.; Stachowiak, A.; Al Mamun, A.; Tzvetkov, N.; Takeda, S.; Alanov, A.; Bergantin, L.; Abdel-Daim, M.; Slankiewicz, M. Autophagy and Alzheimer’s Disease: From Molecular Mechanisms to Therapeutic Implications. *Front Aging Neurosci* 2018, 10:4. doi.org/10.3389/fnagi.2018.00004.

16. Lev-Vakhnish, Y.; Cadury, S.; Rotter-Maskowitz, A.; Feldman, N.; Roichman, A.; Illouz, T.; Varvak, A.; Nicola, R.; Madar, R.; Okun, E. L-Lactate Promotes Adult Hippocampal Neurogenesis. *Front Neurosci* 2019, 13, 403. doi:10.3389/fnins.2019.00403.

17. Di Liegro, C.; Schiera, G.; Proia, P.; Di Liegro, I. Physical Activity and Brain Health. *Genes* 2019, 10, 720. doi.org/10.3390/genes10090720.

18. de la Roche, J.; Walther, I.; Leonow, W.; Hage, A.; Eberhardt, M.; Fischer, M.; Reeh, P.; Sauer, S.; Leffler, A. Lactate is a potent inhibitor of the capsaicin receptor TRPV1. *Scientific Rep* 2016, 6, 36740. DOI: 10.1038/srep36740.

19. Medeiros, P.; Oliveira-Silva, M.; Negrini-Ferrari, S.; Medeiros, A.; Elias-Filho, D.; Cysne Coimbra, N.; de Freitas, R. CB 1-cannabinoid-, TRPV 1-vasilidol- and NMDA-glutamatergic-receptor-signalling systems interact in the prelombic cerebral cortex to control neurophatic pain symptoms. *Brain Res Bull* 2020, 165, 118-128. doi:10.1016/j.brainresbull.2020.09.013.

20. Negri, S.; Faris, P.; Berra-Romani, R.; Roche, J.; Moccia, F. Endothelial Transient Receptor Potential Channels and Vascular Remodeling: Extracellular Ca 2+ Entry for Angiogenesis, Arteriogenesis and Vasculogenesis. *Front Physiol* 2020, 10, 1618. doi:10.3389/fphys.2019.01618.

21. Harigharan, A.; Weir, N.; Robertson, C.; He, L.; Betsholtz, C.; Longden, T. The Ion Channel and GPCR Toolkit of Brain Capillary Pericytes. *Front Cell Neurosci* 2020, 14, doi.org/10.3389/fncel.2020.61324.

22. Sweeney, M.; Zhao, Z.; Montagne, A.; Nelson, A.; Zlokovic, B. Blood-Brain Barrier: From Physiology to Disease and Back. *Physiol Rev* 2019, 99(1), 21-78. doi:10.1152/physrev.00050.2017.

23. Nikolakopoulou, A.; Montagne, A.; Kisler, K.; Dai, Z.; Wang, Y.; Huusko, M.; Sagare, A.; Lazic, D.; Sweeney, M.; Kong, P.; Wang, M.; Owens, N.; Lawson, E.; Xie, X.; Zhao, Z.; Zlokovic, B. Pericyte loss leads to circulating failure and piliotoxin depletion causing neuron loss. *Nat Neurosci* 2019, 22(7), 1089–1089. doi:10.1038/s41593-019-0434-z.

24. Quan, H.; Kollai, E.; Suzuki, K.; Aguiar, A.; Pinho, R.; Boldogh, I.; Berkes, I.; Radak, Z. Exercise, redox system and neurodegenerative diseases. *Biochim Biophys Acta Mol Basis Dis* 2020, 1866(10): 165778. doi:10.1016/j.bbadis.2020.165778.

25. Adams, J.; Mukherjee, S.; Klaidman, L.; Morales, M.; Williams, L.; Inouye, G.; Cummings, V. Ischemic and metabolic stress induced apoptosis. In *Free Radicals in Brain Pathophysiology*; Poli, G., Cadenas, E., Packer, L., Eds.; Marcel Dekker, New York, USA, 2000; pp. 55-76.

26. Wu, T.; Wang, X.; Tian, W.; Jaramillo, M.; Lau, A.; Zhang, D. Poly(ADP-ribose) polymerase-1 modulates Nr2f2-dependent transcription. *Free Radic Biol Med* 2014, 67, 69–80. doi:10.1016/j.freeradbiomed.2013.10.806.

27. Klarrlund Pedersen, B. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol* 2019, 15(7): 383-392. doi:10.1038/s41574-019-0174-x.
Prado, M.; Abisambra, J.; Tovar-Moll, F.; Mattos, P.; Arancio, O.; Ferreira, S.; De Felice, F. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer’s models. Nat Med 2019, 25(1), 165-175. doi: 10.1038/s41591-018-0275-4.

29. Yuyama, K.; Mitsutake, S.; Igarishi, Y. Pathological roles of ceramide and its metabolites in metabolic syndrome and Alzheimer’s disease. Biochim Biophys Acta 2014, 1841(5), 793-8. doi: 10.1016/j.bbabip.2013.08.002.

30. Mielke, M.; Haughey, N.; Han, D.; An, Y.; Ratnam Bandaru, V.; Lyketsos, C.; Ferrucci, L.; Resnick, S. The Association Between Plasma Ceramides and Sphingomyelins and Risk of Alzheimer’s Disease Differ by Sex and APOE in the Baltimore Longitudinal Study of Aging. J Alzheimers Dis 2017, 60(3), 819-828. doi: 10.3233/JAD-160925.

31. Adams, J.; Parker, K. Extracellular and Intracellular Signaling.; Royal Society of Chemistry: London, Great Britain, 2011; pp. 1-9, 175-187. doi.org/10.1039/9781849734344-00001.

32. Adams, JD. Alzheimer’s Disease, Ceramide, Visfatin and NAD. CNS Neurol Drug Disc Target 2008, 7(6): 492-8. PMID: 19128206

33. Adams, JD. DNA, Nuclear Cell Signaling and Neurodegeneration. In Extracellular and intracellular signaling; Adams, J.; Parker, K. Eds.; Royal Society of Chemistry: London, Great Britain, 2011; pp. 175-187.

34. Adams, J. The Treatment of Brain Inflammation in Alzheimer’s Disease: Can Traditional Medicines Help? Front Clin Drug Res Alzheimer Dis 2017, 6, 1-19.

35. Holland, W.; Bikman, B.; Wang, L.; Yuguang, G.; Sargent, K.; Bulchand, S.; Knotts, T.; Shui, G.; Clegg, D.; Wenk, M.; Pagliassotti, M.; Scherer, P.; Summers, S. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice. J Clin Invest 2011, 121 (5), 1888–1897. doi:10.1172/JCI43378.

36. Mehra, V.; Jackson, E.; Zhang, X.; Jiang, X.; Dobrucki, L.; Yu, J.; Bernatchez, P.; Sinusas, A.; Shulman, G.; Sessa, W.; Yarovinsky, T.; Bender, J. Ceramide-activated phosphatase mediates fatty acid-induced endothelial VEGF resistance and impaired angiogenesis. Am J Pathol 2014, 184 (5), 1562–1576. doi:10.1016/j.ajpath.2014.01.009.

37. Lim, K.; See, Y.; Lee, J. A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. Clin Psychopharmacol Neurosci 2017, 15(4), 301-312. doi.org/10.9758/cpn.2017.15.4.301.

38. Peprah, K.; McCormack, S. Medical Cannabis for the Treatment of Dementia: A Review of Clinical Effectiveness and Guidelines.; Canadian Agency for Drugs and Technologies in Health: Ottowa, Canada, 2019.

39. Ahmed, A.; van der Marek, M.; van den Elsen, G.; Olde Rikkert, M. Cannabinoids in late-onset Alzheimer’s disease. Clin Pharmacol Ther 2015, 97. doi.org/10.1002/cpt.117.

40. Bonnet, A.; Marchalant, Y. Potential Therapeutic Contributions of the Endocannabinoid System towards Aging and Alzheimer’s Disease. Aging Dis 2015, 6, 400-5. doi.org/10.14366/AD.2015.0617.

41. Xin, M.; Jin, X.; Cui, X.; Jin, C.; Piao, L.; Wan, Y.; Xu, S.; Zhang, S.; Yue, X.; Wang, H.; Nan, Y.; Cheng, X. Dipeptidyl peptidase-4 inhibition prevents vascular aging in mice under chronic stress: Modulation of oxidative stress and inflammation. Chem Biol Interact 2019, 314, 108842. doi:10.1016/j.cbi.2019.108842.

42. Kanamori, Y.; Murakami, M.; Sugiyama, M.; Hashimoto, O.; Matsu, T.; Funaba, M. Hecpicidin and IL-1β. Vitam Horm 2019, 110, 143-156. doi:10.1016/bsh.vh.2019.01.007.

43. Vela, D. The Dual Role of Hecpicidin in Brain Iron Load and Inflammation. Front Neurosci 2018, 12. doi.org/10.3389/fnins.2018.00740.

44. Yao, S.; Zheng, P.; Wan, Y.; Dong, W.; Miao, G.; Wang, H.; Yang, J. Adding high-sensitivity C-reactive protein to frailty assessment to predict mortality and cardiovascular events in elderly inpatients with cardiovascular disease. Exp Gerontol 2021, 111235. doi:10.1016/j.exger.2021.111235.

45. Kuhlmann, C.; Librizzi, L.; Closhen, D.; Pflanzner, T.; Lessmann, V.; Pietrzik, C.; de Curtis, M.; Luhmann, H. Mechanisms of C-reactive protein-induced blood–brain barrier disruption. Stroke 2009, 40, 1458-66.

46. Koller, A.; Szenasi, A.; Dornayi, G.; Kovacs, N.; Lelbach, A.; Kovacs, I. Coronary Microvascular and Cardiac Dysfunction Due to Homocysteine Pathometabolism; A Complex Therapeutic Design. Curr Pharm Des 2018, 24(25), 2911-2920. doi: 10.2174/1381612824666180625125450.

47. Freitas, H.; Isaac, A.; Malcher-Lopes, R.; Diaz, B.; Trevenzoli, I.; De Melo Reis, R. Polysaturated fatty acids and endocannabinoids in health and disease. Nutritional Neurosci 2017, 21, 695-714. DOI: 10.1080/1028415X.2017.1347373.

48. Jafari Nasabian, P.; Inglis, J.; Reilly, W.; Kelly, O.; Ilch, J. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. J Endocrinol 2017, 234, R37-R51.

49. Spencer, S.; Korosi, A.; Layé, S.; Shukitt-Hale, B.; Barrientos, R. Food for thought: how nutrition impacts cognition and Emotion. npj Sci Food 2017, 1,7. doi.org/10.1038/s41538-017-0008-y.

50. Dyall, S. Interplay between n-3 and n-6 Long-Chain Polysaturated Fatty Acids and the Endocannabinoid System in Brain Protection and Repair. Lipids 2017, 52, 885–900. DOI 10.1007/s11745-017-4292-8.

51. Bianchetti, A.; Rozzini, R.; Carabellese, C.; Zanetti, O.; Trabucchi, M. Nutritional Intake, Socioeconomic Conditions, and Health Status in a Large Elderly Population. J Am Geriatr Soc 1990, 38, 521.

52. Adams, J.; Klaidean, K.; Morales, M.; Schiavoni, B.; Hsu, J.; Mukherjee, S. Nicotinamide and neuroprotection. In Chemicals and Neurodegenerative Disease; Bondy, S. Ed; Prominent Press: Scottsdale, USA, 1999; pp. 229-61.

53. Fricker, R.; Green, E.; Jenkins, S.; Griffin, S. The influence of nicotinamide on health and disease in the central nervous system. Int J Tryptophan Res 2018, 11, 1–11.
54. Nejabati, H.; Mihanfar, A.; Pezeshkian, M.; Fattahi, A.; latifi, Z.; Safaie, N.; Valiloo, M.; Jodati, A.; Nouri, M. N1-methylnicotinamide (MNAM) as a guardian of cardiovascular system. *J Cell Physiol* **2018**, *233*, 6386–6394. DOI: 10.1002/jcp.26636.

55. de Baaij, J.; Hoenderop, J.; Bindels, R. Magnesium in Man: Implications for Health and Disease. *Physiol Rev* **2015**, *95*(1), 1-46. doi: 10.1152/physrev.00012.2014.

56. Sakaguchi, Y.; Hamano, T.; Obi, Y.; Monden, C.; Oka, T.; Yamaguchi, S.; Matsui, I.; Hashimoto, N.; Matsumoto, A.; Shimada, K.; Takabatake, Y.; Takahashi, A.; Kaimori, J.; Moriyama, T.; Yamamoto, R.; Horio, M.; Yamamoto, K.; Sugimoto, K.; Rakugi, H.; Isaka, Y. A Randomized Trial of Magnesium Oxide and Oral Carbon Adsorbent for Coronary Artery Calcification in Predialysis CKD. *J Am Soc Nephrol* **2019**, *30*(6), 1073-1085; DOI: https://doi.org/10.1681/ASN.2018111150.

57. Alexander, Y.; Van Elswyk, D. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. *PLoS One* **2015**, *10*, e0120391.

58. Snowdon, D.; Tully, C.; Smith, C.; Perez Riley, K.; Markesbery, M. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the Nun Study. *Am J Clin Nutr* **2000**, *71*, 993–8.

59. Ubbink, J.; Vermaak, W.; van der Merwe, A.; Becker, P. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr* **1993**, *57*, 47–53.

60. McGrattan, A.; McGuinness, B.; McKinley, M.; Kee, F.; Passmore, P.; Woodside, J.; McEvoy, C. Diet and Inflammation in Cognitive Ageing and Alzheimer’s Disease. *Curr Nutr Rep* **2019**, *8*, 53–65. doi.org/10.1007/s13668-019-0271-4.

61. Morris, M.; Tangney, C.; Wang, Y.; Sacks, F.; Barnes, L.; Bennett, D.; Aggarwal, N. MIND diet slows cognitive decline with aging. *Alzheimers Dement* **2015**, *11*(9), 1015–1022. doi:10.1016/j.jalz.2015.04.011.