

Caffeine Consumption with Relevance to Type 3 Diabetes and Accelerated Brain Aging

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Editorial Article

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EDITORIAL

The main constituent of plaques in the brain of Alzheimer's disease (AD) individuals namely amyloid beta (A β)^[1] is a proteolytic product of a larger protein, the amyloid precursor protein (APP) protein. Carriers of the apo E4 allele are at greater risk of developing AD with increased deposition of amyloid beta plaques in Western countries. Apo E4 is also a major risk factor for cardiovascular disease linked to defective cholesterol metabolism^[2,3]. Protein and A β homeostasis is now crucial to the lifespan of organisms and is an important feature that determines the aging process in obesity, diabetes and neurodegenerative diseases^[4]. The scientific understanding of the maintenance of peripheral blood plasma A β metabolism has now become essential to prevent neurodegeneration and is now linked to Type 3 diabetes^[5,6]. The concentration of A β within the brain is determined by hepatic A β clearance and interest in the liver has increased markedly since in Western countries the incidence of non-alcoholic fatty liver disease (NAFLD) has reached approx. 20% of the developed world and by the year 2050 it may reach to approx. 40% of the global population^[7]. Induction of Type 3 diabetes disease progression now involves unhealthy diets that corrupts neuron calcium flux and the circadian rhythm of the neuron A β peptide^[8-13] connected to defective peripheral hepatic glucose and A β metabolism^[4] in individuals with NAFLD^[4]. The liver is of principal importance and the mechanisms for the clearance of A β by the liver involve lipoproteins (5%) and albumin (90%) which bind and sequester A β for clearance to the liver, preventing the toxic effects of A β to the heart and brain^[4]. Caffeine is hydrophobic and increased consumption can rapidly allow distribution to the liver and adipose tissue with rapid transport across the blood brain barrier to neurons^[14-17]. In adipose tissue caffeine has been shown to increase adinoplectin levels with relevance to anti-aging gene activation^[18-20] and the adipose tissue-liver crosstalk^[21]. Caffeine has become important to peripheral A β metabolism with suppression of plasma and brain A β in AD transgenic mice^[22,23] and beneficial effects involve prevention of bacterial lipopolysaccharides (LPS) induction of inflammation and A β aggregation^[24,25]. In the developing world increased plasma LPS levels may override caffeine effects with spontaneous A β aggregation^[26,27]. Caffeine consumption over many years' effects cerebrospinal fluid production (CSF) and increased caffeine binding to albumin may displace A β from CSF albumin and mediate toxic effects on A β oligomer generation relevant to the development of Type 3 diabetes and various neurological diseases^[28-31].

In global NAFLD epidemic caffeine metabolism is markedly reduced and metabolism of caffeine (4-6 hr) delayed (**Figure 1**) with increased transport of caffeine to the brain with effects on altered neuron calcium signalling relevant to the induction of Type 3 diabetes and circadian rhythm abnormalities^[14-16,32-36]. Caffeine is metabolized mostly by the P450 enzyme system in the body and specifically the CYP1A enzymes (CYP1A1, 1A2)^[37,38]. The metabolism by hepatic CYP1A enzymes of caffeine follows first-order kinetics and is the rate-limiting step of plasma clearance^[37,38]. Interest in the anti-aging gene Sirtuin 1 (Sirt 1) in neuron transcriptional responses has accelerated with relevance to Type 3 diabetes^[5,6] and the gene Sirt 1 is now connected to the development of NAFLD^[39,40] with its deacetylation of nuclear pregnane X receptor (PXR) relevant to drug metabolism^[39]. Sirt 1/PXR interactions are now important to the regulation of the CYP1A enzymes^[37,38] with rapid metabolism of caffeine in individuals without NAFLD. Caffeine consumption (coffee, coca cola, chocolate, tea, other sources) that was previously recommended to be approx. 200 mg

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per day and not to exceed to 500-600 mg per day need to be revised (**Figure 1**) in the current global NAFLD epidemic^[40]. Elevated caffeine concentrations can override Sirt 1 regulation of cell cycle control and prevention of Sirt 1 regulation of programmed cell death^[41-43]. Sirt 1 is a histone deacetylase that targets transcription factors such as p53 to adapt gene expression to A β metabolism, metabolic activity and insulin resistance^[40]. The effect on Sirt 1 modulation of programmed cell death by caffeine involves its p53 dependent induction of mitochondrial apoptosis^[44-46]. High calorie diets downregulate Sirt 1 with altered drug, cholesterol, A β and caffeine metabolism^[38-40]. Caffeine metabolism is now important to statin treatment of brain cholesterol levels with drug transport to the brain^[6] connected to hepatic caffeine metabolism and caffeine modulation of brain Sirt 1 activity in global populations. Sirt 1 activators (leucine, resveratrol, pyruvic acid) compared to the ingestion of Sirt 1 inhibitors (alcohol, palmitic acid, suramin, sirtinol, LPS) are now important to the global NAFLD epidemic with relevance to hepatic Sirt 1 regulation of drug, caffeine, glucose and A β metabolism.

The major side effects of caffeine overconsumption (**Figure 1**) leads to magnesium and calcium deficiency^[47] with relevance to insulin resistance and corruption of the peripheral sink A β clearance pathways^[48]. Magnesium is a Sirt 1 activator with caffeine responsible for low brain magnesium levels and induction of Type 3 diabetes^[5,6,43]. Levels of plasma magnesium need to be carefully evaluated to determine the success of caffeine in the maintenance of glucose homeostasis and A β metabolism^[49-54]. Sirt 1 is responsible for neuron synaptic plasticity with Sirt 1 repression relevant to reduced synaptic plasticity and reduced effects of caffeine on adenosine A(2A) receptor with relevance to synaptotoxicity and memory dysfunction. Unhealthy diets should be avoided to activate Sirt 1 regulation^[27] of the circadian rhythm with relevance to glucose, caffeine, A β and cholesterol metabolism. Concerns for recent in vivo and in vitro scientific reports with relevance to caffeine effects on delayed circadian rhythm^[36] interferes with Sirt 1 modulation of circadian rhythm circuitry^[35] with relevance to brain glucose and amyloid beta regulation and induction of Type 3 diabetes.

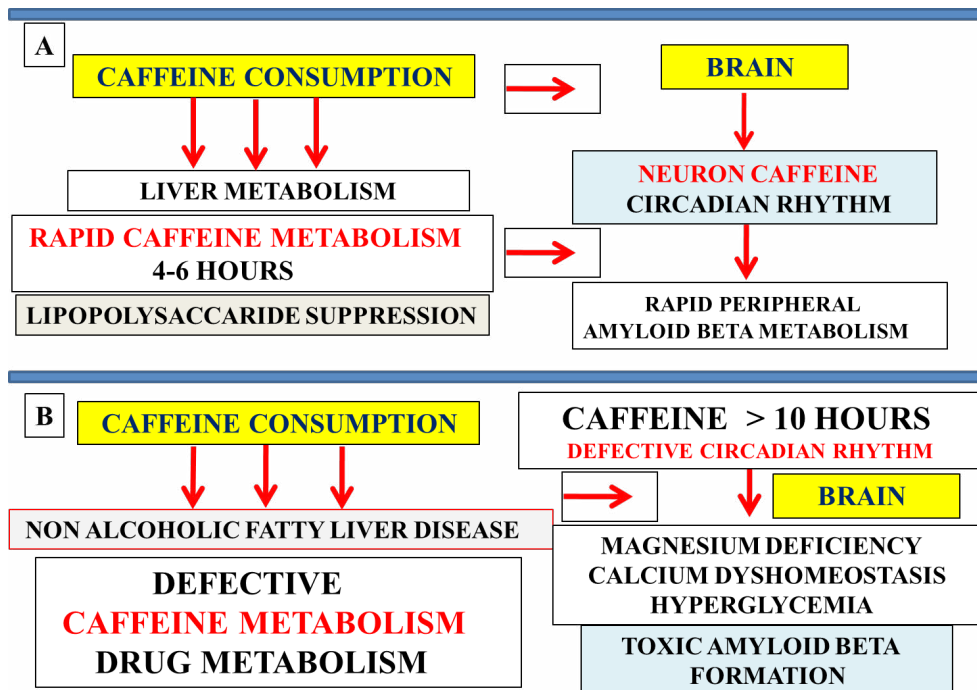


Figure 1. In panel A hepatic caffeine metabolism is rapid with a half-life between 4-6 hrs. Caffeine reduce LPS inflammatory effect with reduced LPS transport to the brain that allows efficient circadian rhythm circuitry with rapid brain amyloid beta transport to the liver. In panel B the global NAFLD epidemic indicates that caffeine consumption should be carefully modified to reduce excessive caffeine transport to the brain that induces Type 3 diabetes by interference with magnesium/Sirt 1 activation responsible for neuron proliferation and normal brain glucose and amyloid beta metabolism.

CONCLUSION

Major interests in caffeine consumption has increased with the alarming increase in the global NAFLD epidemic relevant to increased transport of caffeine to the brain with the induction of Type 3 diabetes. Specific nutritional diets are essential to maintain hepatic caffeine metabolism to facilitate rapid A β clearance in the periphery and to maintain the effects of drugs such as statins to reduce toxic A β formation not only in Type 3 diabetes but to various neurological diseases. Anti-aging gene Sirt 1 is responsible for brain A β and caffeine metabolism and inactivation of Sirt 1 by unhealthy diets is now relevant to Type 3 diabetes and premature brain aging. In the current global NAFLD epidemic caffeine consumption should be carefully controlled to maintain its role as a Sirt 1 modulator with relevance to caffeine regulation of neuron calcium signaling important to circadian glucose and A β regulation in Type 3 diabetes.

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REFERENCES

1. Masters CL, et al. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci.* 1985;82:4245-4249.
2. Smith MA. Diet and oxidative stress: a novel synthesis of epidemiological data on Alzheimer's disease. *J Alzheimers Dis.* 1999;1:203-206.
3. Petot GJ, et al. Interactions of apolipoprotein E genotype and dietary fat intake of healthy older persons during mid-adult life. *Metabolism.* 2003;52:279-81.
4. Martins IJ, et al. Interactions Between Apo E and Amyloid Beta and their Relationship to Nutriproteomics and Neurodegeneration. *Current Proteomics.* 2014;11:173-183.
5. Martins IJ. Type 3 diabetes with links to NAFLD and Other Chronic Diseases in the Western World. *Int J Diab.* 2016;1:1-5.
6. Martins IJ. Diet and Nutrition reverse Type 3 Diabetes and Accelerated Aging linked to Global chronic diseases. *J Diab Res Ther.* 2016;2:1-6.
7. Loomba R and Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol.* 2013;10:686-90.
8. Kwak Y, et al. A calcium flux is required for circadian rhythm generation in mammalian pacemaker neurons. *J Neurosci.* 2005;17:7682-7686.
9. Ikeda M. Calcium dynamics and circadian rhythms in suprachiasmatic nucleus neurons *Neuroscientist.* 2004;10:315-24.
10. Brini M, et al. Neuronal calcium signaling: function and dysfunction. *Cell Mol Life Sci.* 2014;71:2787-2814.
11. Lucey BP and Bateman RJ. Amyloid- β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis. *Neurobiol Aging.* 2014;35:29-34.
12. Chang HC and Guarente L. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. 2013;153:1448-1460.
13. Musiek ES, et al. Sleep, circadian rhythms, and the pathogenesis of Alzheimer Disease. *Exp Mol Med.* 2015;47:148.
14. Nehlig A, et al. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Res Rev.* 1992;17:139-70.
15. Kaster MP, et al. Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress. *Proc Natl Acad Sci.* 2015;112:7833-7838.
16. Costenla AR. Caffeine, adenosine receptors, and synaptic plasticity. *J Alzheimers Dis.* 2010;20:25-34.
17. Cognato GP, et al. Caffeine and an adenosine A(2A) receptor antagonist prevent memory impairment and synaptotoxicity in adult rats triggered by a convulsive episode in early life. *J Neurochem.* 2010;112:453-62.
18. Yamashita K, et al. Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study. *Nutr Diabetes.* 2010;2:33.
19. Bhaktha G, et al. Relationship of Caffeine with Adiponectin and Blood Sugar Levels in Subjects with and without Diabetes. *J Clin Diagn Res.* 2015;9:BC01-BC03.
20. Martins IJ. The Role of Clinical Proteomics, Lipidomics, and Genomics in the Diagnosis of Alzheimer's Disease. *Proteomes.* 2016;4:1-19.
21. Martins IJ. Unhealthy Nutrigenomic Diets Accelerate NAFLD and Adiposity in Global communities. *J Mol Genet Med.* 2015;9:1-12.
22. Cao C, et al. Caffeine suppresses amyloid-beta levels in plasma and brain of Alzheimer's disease transgenic mice. *J Alzheimers Dis.* 2009;17:681-697.
23. Arendash GW, et al. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. *J Alzheimers Dis.* 2009;17:661-80.
24. Brothers HM, et al. Caffeine attenuates lipopolysaccharide-induced neuroinflammation.,” *Lett.* 2010;480:97-100.

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25. Kang CH, et al. Caffeine suppresses lipopolysaccharide-stimulated BV2 microglial cells by suppressing Akt-mediated NF- κ B activation and ERK phosphorylation. *Food Chem Toxicol.* 2012;50:4270-4276.
26. Martins IJ. Bacterial Lipopolysaccharides Change Membrane Fluidity with Relevance to Phospholipid and Amyloid Beta Dynamics in Alzheimer's Disease. *J Microb Biochem Technol.* 2016;8:322-324.
27. Martins IJ. Unhealthy Diets Determine Benign or Toxic Amyloid Beta States and Promote Brain Amyloid Beta Aggregation. *Austin J Clin Neurol.* 2015;2:1060-1066.
28. Han ME, et al. Regulation of cerebrospinal fluid production by caffeine consumption. *BMC Neurosci.* 2009;10:110.
29. Islam MM, et al. Caffeine and sulfadiazine interact differently with human serum albumin: A combined fluorescence and molecular docking study. *Spectrochim Acta A Mol Biomol Spectrosc.* 2016;152:23-33.
30. Wu Q, et al. Study of caffeine binding to human serum albumin using optical spectroscopic methods. *Sci. China Ser. B-Chem.* 2005;52:2205.
31. Martins IJ. Food quality induces a miscible disease with relevance to Alzheimer's disease and Neurological diseases. *J Food Research.* 2016;5:45-52.
32. Nikolettou V and Tavernarakis N. Calcium homeostasis in aging neurons. *Front Genet.* 2012;3:200.
33. Verkhratsky A and Toescu EC. Calcium and neuronal ageing. *Trends Neurosci.* 1998;21:2-7.
34. Kramer RH, et al. Effects of caffeine on intracellular calcium, calcium current and calcium-dependent potassium current in anterior pituitary GH3 cells. *Pflugers Arch.* 1994;426:12-20.
35. Masri S and Sassone-Corsi P. Sirtuins and the circadian clock: bridging chromatin and metabolism. *Sci Signal.* 2016;7:6.
36. Burke TM, et al. Effects of caffeine on the human circadian clock in vivo and in vitro. *Sci Transl Med.* 2015;7:305.
37. Wolf KK, et al. Role of the nuclear receptor pregnane X receptor in acetaminophen hepatotoxicity. *Drug Metab Dispos.* 2005;33:1827-1836.
38. Begas E, et al. In vivo evaluation of CYP1A2, CYP2A6, NAT-2 and xanthine oxidase activities in a Greek population sample by the RP-HPLC monitoring of caffeine metabolic ratios. *Biomed Chromatogr.* 2007;21:190-200.
39. Martins IJ. Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries. *J Mol Genet Med.* 2013;S1:1-8.
40. Martins IJ. Induction of NAFLD with Increased Risk of Obesity and Chronic Diseases in Developed Countries. *Open Journal of Endocrine and Metabolic Diseases.* 2014;4:90-110.
41. Tiwari KK, et al. Differential concentration-specific effects of caffeine on cell viability, oxidative stress, and cell cycle in pulmonary oxygen toxicity in vitro. *Biochem Biophys Res Commun.* 2014;450:1345-50.
42. Bode AM and Dong Z. The enigmatic effects of caffeine in cell cycle and cancer. *Cancer Lett.* 2007;247:26-39.
43. Fernández MJ, et al. Apoptosis induced by different doses of caffeine on Chinese hamster ovary cells. *J Appl Toxicol.* 2003;23:221-4.
44. Saiki S, et al. Caffeine induces apoptosis by enhancement of autophagy via PI3K/Akt/mTOR/p70S6K inhibition. *Autophagy.* 2011;7:176-87.
45. He Z, et al. Induction of apoptosis by caffeine is mediated by the p53, Bax, and caspase 3 pathways. *Cancer Res.* 2003;63:4396-401.
46. Martins IJ. Appetite Control with Relevance to Mitochondrial Biogenesis and Activation of Post- Prandial Lipid Metabolism in Obesity Linked Diabetes. *Ann Obes Disord.* 2016;1:1-4.
47. Kynast-Gales SA and Massey LK. Effect of caffeine on circadian excretion of urinary calcium and magnesium. *J Am Coll Nutr.* 1994;13:467-72.
48. Martins IJ. Magnesium Therapy Prevents Senescence with the Reversal of Diabetes and Alzheimer's Disease. *Health.* 2016;vol.8: 694-710.
49. Mergenthaler P, et al. Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci.* 2013;36:587-597.
50. Lane JD, et al. Caffeine impairs glucose metabolism in type 2 diabetes. *Diabetes Care.* 2004;27:2047-2048.
51. Biaggioni I and Davis SN. Caffeine: a cause of insulin resistance? *Diabetes Care.* 2002;25:399-400.

Research & Reviews: Neuroscience

52. Battram DS, et al. The effect of caffeine on glucose kinetics in humans--influence of adrenaline. *J Physiol.* 2005;569:347-355.
53. Tunnicliffe JM and Shearer J. Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. *Appl Physiol Nutr Metab.* 2008;33:1290-300.
54. Sato N and Morishita R. Plasma $\alpha\beta$: a possible missing link between Alzheimer disease and diabetes. *Diabetes.* 2013;62:1005-1006.