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

The main constituent of plaques in the brain of Alzheimer’s disease (AD) individuals namely amyloid beta (Aβ) [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 Aβ 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 Aβ metabolism has now become essential to prevent neurodegeneration and is now linked to Type 3 diabetes [5,6]. The concentration of Aβ within the brain is determined by hepatic Aβ 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 Aβ peptide [8-13] connected to defective peripheral hepatic glucose and Aβ metabolism [4] in individuals with NAFLD [4]. The liver is of principal importance and the mechanisms for the clearance of Aβ by the liver involve lipoproteins (5%) and albumin (90%) which bind and sequester Aβ for clearance to the liver, preventing the toxic effects of Aβ 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 [14-16]. In adipose tissue caffeine has been shown to increase adinopectin levels with relevance to anti-aging gene activation [18-20] and the adipose tissue-liver crosstalk [21]. Caffeine has become important to peripheral Aβ metabolism with suppression of plasma and brain Aβ in AD transgenic mice [22,23] and beneficial effects involve prevention of bacterial lipopolysaccharides (LPS) induction of inflammation and Aβ aggregation [24,25]. In the developing world increased plasma LPS levels may override caffeine effects with spontaneous Aβ aggregation [26,27]. Caffeine consumption over many years’ effects cerebrospinal fluid production (CSF) and increased caffeine binding to albumin may displace Aβ from CSF albumin and mediate toxic effects on Aβ 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, cola, chocolate, tea, other sources) that was previously recommended to be approx. 200 mg.
per day and not to exceed to 500-600 mg per day need to be revised (Figure 1) in the current global NAFLD epidemic\cite{40}. Elevated caffeine concentrations can override Sirt 1 regulation of cell cycle control and prevention of Sirt 1 regulation of programmed cell death\cite{41-43}. Sirt 1 is a histone deacetylase that targets transcription factors such as p53 to adapt gene expression to Aβ metabolism, metabolic activity and insulin resistance\cite{40}. The effect on Sirt 1 modulation of programmed cell death by caffeine involves its p53 dependent induction of mitochondrial apoptosis\cite{44-46}. High calorie diets downregulate Sirt 1 with altered drug, cholesterol, Aβ and caffeine metabolism\cite{38-40}. Caffeine metabolism is now important to statin treatment of brain cholesterol levels with drug transport to the brain\cite{5} 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 Aβ metabolism.

The major side effects of caffeine overconsumption (Figure 1) leads to magnesium and calcium deficiency\cite{47} with relevance to insulin resistance and corruption of the peripheral sink Aβ clearance pathways\cite{48}. Magnesium is a Sirt 1 activator with caffeine responsible for low brain magnesium levels and induction of Type 3 diabetes\cite{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 Aβ metabolism\cite{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\cite{27} of the circadian rhythm with relevance to glucose, caffeine, Aβ and cholesterol metabolism. Concerns for recent in vivo and in vitro scientific reports with relevance to caffeine effects on delayed circadian rhythm\cite{36} interferes with Sirt 1 modulation of circadian rhythm circuitry\cite{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 Aβ clearance in the periphery and to maintain the effects of drugs such as statins to reduce toxic Aβ formation not only in Type 3 diabetes but to various neurological diseases. Anti-aging gene Sirt 1 is responsible for brain Aβ 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 Aβ regulation in Type 3 diabetes.
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