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FOOD INTAKE AND CAFFEINE DETERMINE AMYLOID BETA METABOLISM WITH RELEVANCE TO MITOPHAGY IN BRAIN AGING AND CHRONIC DISEASE

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ABSTRACT: *In the global world diabetes and mitochondrial disease is expected to cost the developing world in the next 30 years US \$400 million. In diabetes an absent peripheral sink amyloid beta clearance pathway is now relevant to amyloid beta induced mitochondrial apoptosis. The quality of food consumed has raised major concerns with increased levels of plasma bacterial lipopolysaccharides (LPS) that induces amyloid beta aggregation and mitochondrial apoptosis with programmed cell death linked to non alcoholic fatty liver disease (NAFLD) and many organ diseases. The amount, nature and time of day of fat consumption in diabetes has become important with relevance to caffeine metabolism, brain toxic amyloid beta oligomer formation and neuron apoptosis. To prevent programmed cell death dietary fat and caffeine consumption need to be revised to allow rapid hepatic caffeine and amyloid beta metabolism with the prevention of global mitophagy associated with diabetes, NAFLD and neurodegenerative diseases.*

Key Words: mitochondria, amyloid beta, diabetes, circadian rhythm, caffeine, fat diet

INTRODUCTION

Unhealthy diets, environmental influences and lifestyle changes lead to overnutrition with an excess of glucose, fats and proteins that enter the blood plasma and induce cell and nuclear alterations that lead to programmed cell death in many cells of various organs in individuals in the developing and developed world. Diseases such as gastrointestinal disorders, cardiovascular disease, non alcoholic liver disease (NAFLD), brain, thyroid, lung and diseases of the reproductive organs have increased in both the developing and developed world. Induction of various chronic diseases, Martins (2015) are associated with various cellular changes in the mitochondria (mitophagy), Vásquez-Trincado *et al* (2016), Duchen (2004), Bosch *et al* (2011), Nicholson (2014), Martins (2016), endoplasmic reticulum (ER)/golgi apparatus (ER stress/protein synthesis) and lysosomal disorders (lipid/protein metabolism). Insulin resistance without the hormone apelin, Martins (2015) leads to early global chronic disease progression and associated with inflammatory processes that alter nuclear, subcellular and cell membrane function that leads to cell transformation without reversible changes with accelerated cell aging associated with chronic diseases.

Healthy diets in the developed world have been encouraged to prevent mitochondrial apoptosis that may be induced by increased toxic amyloid beta oligomers, Manczak *et al* (2011), Chen and Yan (2006), Paganic and Eckert (2011), Chen and Yan (2007), Mossman *et al* (2014) that are associated with global chronic disease (**Figure 1**). Therapeutic diets in diabetes are urgently required to increase amyloid beta metabolism and prevent mitochondrial apoptosis that is a major defect in diabetes in individuals in the developed world. Healthy diets that contain unsaturated fat, fruit and fish (omega-3) are associated with the reversal of NAFLD with the prevention of accelerated brain ageing, Martins (2015), Martins (2014), Martins (2016). The amount, nature of fat consumed and time of day of fat consumption has become important with relevance to the brain regulation of peripheral hepatic amyloid beta metabolism, Martins (2015). In diabetes the circadian rhythm of brain amyloid beta metabolism is corrupted with mitochondrial apoptosis associated with NAFLD, Martins (2015), Martins (2014) in these patients. Interests in the time of day (morning, afternoon, evening) of fat consumption in diabetes has become important that may determine cellular toxic amyloid beta oligomer levels and mitochondrial senescence versus apoptosis.

In the developed world the amount of healthy fat consumed is between 44 and 78 gms/day in man <http://IdealyHowManyGramsofFatShouldYouConsumeDaily>, (2016) and the amount is similar to the calculations in mice (4.5 % diet/20-35 gms/day) for rapid hepatic fat and amyloid beta metabolism, Martins (2014). The healthy fat diet maintains the brain circadian rhythm (12 light/12h dark cycle) that is important to hepatic amyloid beta metabolism and peripheral cell mitochondrial function. When excess fat is consumed hepatic caffeine metabolism, Martins (2016) is delayed with detrimental effects on the brain circadian circuitry of peripheral amyloid beta metabolism, Martins (2015), Martins (2016). Caffeine can mediate its beneficial effects by the sympathetic nervous system, Acheson (2004) and excess transport with age may completely inactivate the apelinergic pathway with relevance to the autonomic nervous system, Martins (2015). The effects of delayed caffeine metabolism is associated with mitochondrial apoptosis, Lu *et al* (2008), He *et al* (2001), Dubrez *et al* (2001) and may be relevant to global mitochondrial disease (**Figure 1**) and amyloid beta induced mitochondrial apoptosis, Manczak *et al* (2011), Chen and Yan (2006), Paganic and Eckert (2011), Chen and Yan (2007), Mossman *et al* (2014).

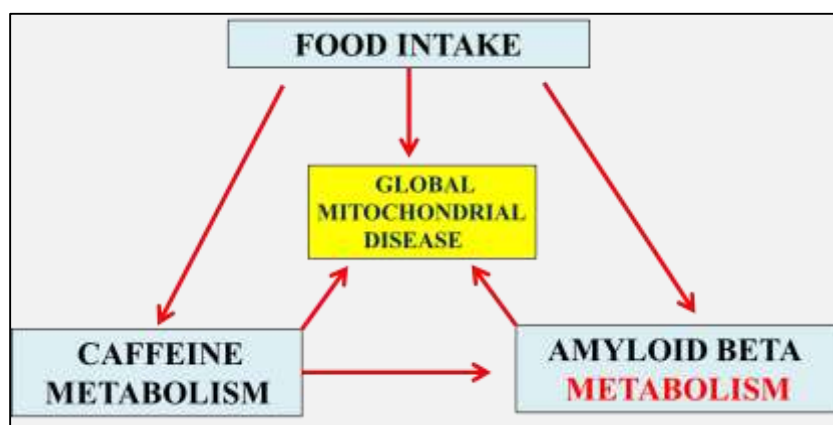


Figure 1. Healthy diets in the developed and developing world that maintain the brain circadian rhythm (12 light/12h dark cycle) have become important to hepatic amyloid beta metabolism. Ingestion of excess fat delay caffeine metabolism with relevance to toxic amyloid beta oligomer metabolism with relevance to corruption of cell mitochondrial function. Hepatic caffeine metabolism

is delayed by excess fat consumption with increased transport to the brain and interference with the circadian rhythm and amyloid beta metabolism.

Diabetes is expected to double in the next 30 years with an expected cost of US\$376 million. In the developing world 4 out of 5 people have diabetes, www.idf.org/diabetes-burden-shifting-developing-countries (2010), www.who.int/mediacentre/releases/ WHO | Diabetes cases could double in developing countries in next 30 (2003) with mitochondrial apoptosis and the major cellular alteration linked to many organ diseases, Martins 2015. Major concerns with relevance to food quality, Martins (2016) and the developing world have accelerated with the increased levels of bacterial lipopolysaccharides (LPS) in the plasma of developing world individuals, Martins (2016), Martins (2015). LPS induces amyloid beta aggregation, Martins (2015) with relevance to mitochondrial apoptosis and irreversible cellular changes with programmed cell death. In the developing world the LPS induced NAFLD delay hepatic xenobiotic and caffeine metabolism with relevance to accelerated peripheral tissue and brain mitochondrial apoptosis, Martins (2013). LPS induced NAFLD corrupt essential metabolizing cytochrome p450 enzymes that metabolize hepatic drug, xenobiotic and caffeine from the blood plasma and LPS may accelerate excess caffeine/drug transport to the brain with the aging process.

In the developing world understanding the molecular cause of rapid disease progression involves the nucleus (anti-aging genes), Martins (2016) and the post-translational modification of proteins such as amyloid beta that involves LPS, Martins (2015). LPS downregulates nuclear genes (anti-aging genes), Martins (2016) with relevance to brain circadian regulation of amyloid beta in diabetic individuals in the developing world (**Figure 2**). Caffeine has been used to increase amyloid beta metabolism, Martins (2016) but increased LPS induce NAFLD relevant to mitochondrial dysfunction and increased caffeine levels may not be able to reverse LPS effects with increased glucose dyshomeostasis and mitochondrial apoptosis. LPS levels are determined by LPS binding protein (LBP), apo B, apo E, apo AI and phospholipid transfer protein (PLTP) levels, Martins (2016) Martins (2015) with relevance of these proteins in binding to LPS and to LPS neutralization, Martins 2016, Martins (2015). The effects of increased caffeine intake are associated with hypercholesterolemia (high LDL levels) and low high density lipoprotein levels and effects of beneficial on LPS suppression may be reversed by toxic caffeine effects by caffeine overconsumption, Du *et al* (2005), Williams *et al* (1985), Dragicevic (2012) that leads to programmed cell death that involves mitochondrial apoptosis instead of mitochondrial biogenesis, Ding (2012), Vaughan *et al* (2012), Riedel *et al* (2012) in various tissues.

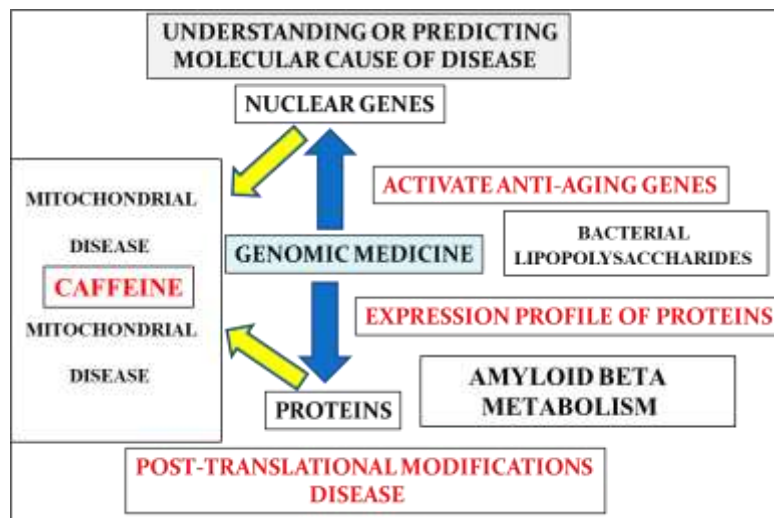


Figure 2. In the developing world the understanding of the cause of the diabetic epidemic has become of major concern to various communities. Inactivation of nuclear anti-aging genes by increased LPS levels in the blood plasma is associated with post-translational modifications of proteins (apo E, apo AI) with increased amyloid beta toxic oligomers associated with mitochondrial apoptosis. LPS induces NAFLD with relevance to defective caffeine metabolism in individuals from the developing world with increased risk for increased caffeine transport to the brain with neurodegeneration (Type 3 diabetes).

CONCLUSION

In the developed and developing world the diabetic epidemic indicates that global mitophagy may be the cause of accelerated organ disease with caffeine and fat intake relevant to accelerated mitochondrial apoptosis in these chronic diseases. In the developed world the amount of fat consumed and the time of the day for consumption has now become critical to maintain hepatic amyloid beta metabolism and promote mitochondrial biogenesis. In the developed world caffeine consumption and fat intake needs to be carefully controlled to allow rapid hepatic caffeine metabolism without excessive caffeine transport to the brain that may induce neuron mitochondrial apoptosis and promote neurodegeneration. In the developing world plasma LPS levels have increased with the induction of NAFLD and neurodegeneration. The hepatic metabolism of fat is delayed in these individuals and the amount/nature of fat need to be carefully controlled to facilitate rapid caffeine metabolism to prevent caffeine induced mitochondrial apoptosis. Protein diet formulas are required to increase essential plasma proteins such as apo E, apo AI, LBP and PLTP that interact with LPS and prevent free LPS reactions that interfere with nuclear genes. In the absence of the nuclear anti-aging genes the defective nuclear-mitochondria interaction in cells of developing world individuals allow LPS to induce amyloid beta oligomer formation with the prevention of the caffeine beneficial properties but the promotion of toxic amyloid beta formation and mitochondrial apoptosis.

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