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GREEN COFFEE AS A NOVEL AGENT FOR ALZHEIMER'S DISEASE PREVENTION BY ATTENUATING DIABETES

Merina Varghese[1],
Lap Ho[1,2],
Jun Wang[1,2],
Wei Zhao[1,2],
Samara Levine[1],
Kenjiro Ono[3],
Salvatore Mannino[4],
Giulio Maria Pasinetti[1,2]*

[1]*Department of Neurology, Mount Sinai Icahn School of Medicine at Mount Sinai, New York, New York 10029*

[2]*Geriatric Research, Education and Clinical Center, James J. Peters Veterans Affairs Medical Center, Bronx, New York 10468*

[3]*Department of Neurology and Neurobiology and Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, 920-9640 Japan*

[4]*Geriatric Output Unit, Ospedale Alzano, Bergamo, Italy*

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Abstract

Diabetes type 2, caused mainly by insulin resistance, is growing in incidence worldwide. In addition to being a major public health concern, type 2 diabetes is also a risk factor for dementia, including Alzheimer's disease type dementia. Coffee consumption is reported to have protective effects in both diabetes and Alzheimer's disease. We review here the reported beneficial effects of coffee in both disease conditions and the previously identified active ingredients of coffee. Furthermore, we revisit our recent findings of improved glucose utilization in the periphery and in the brain in a mouse model of high-fat diet induced type 2 diabetes after treatment with a decaffeinated green coffee preparation. Overall, consumption of coffee appears to improve diabetes and reduce the risk of dementia, although future studies are required to further identify the active components and the type of coffee that is most effective in addressing these conditions.

Keywords

• Coffee • Alzheimer's disease • Diabetes • Diabetes type 2 • Brain • Energy metabolism

Introduction

Diabetes mellitus affected more than 371 million people globally in the year 2012 [1] and the incidence is rising every year. Approximately 90% of those affected are diagnosed with type 2 diabetes (T2DM), which is caused by insulin resistance, viz. defective insulin action or defects in insulin secretion [2,3]. Several studies have reported the association of T2DM with increased risk of dementia, including Alzheimer's disease (AD) type dementia, and a recent meta-analysis of 15 epidemiological studies confirmed this association [4]. AD is the most common type of dementia and by the year 2025, it is projected that 7.1 million elderly people will be affected by AD, in the United States alone [5]. Considering the high impact that these diseases have on public health, therapeutic or lifestyle interventions that are beneficial in both T2DM and AD would be invaluable.

Coffee is one of the most widely consumed beverages in the world. It is reported to have health benefits in many diseases, ranging from cancer to neurodegenerative disorders [6]. Here we review the previously identified effects of coffee in T2DM and in AD, together with our finding of improved peripheral and brain glucose utilization in a mouse model of diabetes following treatment with a decaffeinated green coffee extract.

Health benefits of coffee in diabetes

An inverse relationship between the amount of coffee consumed and the risk of developing T2DM was reported by two separate meta-analyses of population studies [7,8] and in a systematic review of 13 previous studies [9]. The consensus among studies from diverse populations was that more than 4 cups of coffee a day was the effective dose. There have also been a few reports that coffee has no effect on risk of T2DM [10,11].

Interestingly, a protective effect was also observed with decaffeinated coffee [12-14], suggesting that non-caffeine components are involved in the anti-diabetic actions of coffee. The potential use of decaffeinated coffee for diabetes prevention is also supported by studies showing that caffeine causes impaired glucose tolerance and decreased insulin sensitivity in people with T2DM [15].

The mechanisms by which the various components of coffee protect against T2DM have been examined using several experimental systems (Table 1). The beneficial effect of caffeine on T2DM is proposed to act through increased expression of the uncoupling protein in brown adipose tissue and muscle [16], leading to activation of resting metabolic rate [17]. Among the non-caffeine components, chlorogenic acid delays intestinal glucose absorption [18], inhibits hepatic glucose-6-phosphatase [19] and increases muscle glucose uptake via increased expression of glucose transporter 4 and peroxisomal proliferator-activated receptor γ [20]. Antioxidant activity is displayed by several coffee components. Specifically, kahweol and cafestol act by decreasing reactive oxygen species generation, prevention of DNA damage, and increased removal of superoxide radicals [21]; the major chlorogenic acid, 5-caffeoylquinic acid, reduces reactive oxygen species generation; and N-Methyl-2-methylpyridinium-iodide protects against DNA damage [22].

* *E-mail: giulio.pasinetti@mssm.edu*

Table 1. Bioactive components of coffee and their modes of action in diabetes. A summary of the bioactive components of coffee reported to have beneficial effects in diabetes and their modes of action.

Active component	Mode of action	Reference (experimental system)
Caffeine	Activation of thermogenesis and metabolic rate Upregulates uncoupling protein 3 expression	Yoshioka *et al.*, 1990 (mice) Kogure *et al.*, 2002 (obese mice)
Chlorogenic acid	Delays glucose absorption in intestine Inhibits liver glucose-6-phosphatase Increases muscle glucose uptake	Welsch *et al.*, 1989 (*ex vivo* rat small intestine) Hemmerle *et al.*, 1997 (rat liver microsomes) Prabhakar and Doble 2009 (rat myoblast culture)
Chlorogenic acid (5-Caffeoylquinic acid)	Antioxidant action	Bakuradze *et al.*, 2010 (HT-29 cells)
Diterpenes (cafestol, kahweol)	Antioxidant action	Lee and Jeong 2007 (NIH3T3 cells treated with H_2O_2)
N-Methyl-2-methylpyridinium-iodide	Antioxidant action; prevention of DNA oxidation	Bakuradze *et al.*, 2010 (Caco-2A cells)

Benefits of coffee in Alzheimer's disease

Epidemiological studies showing that certain diets are associated with decreased risk of AD have led to increasing interest in the prevention of AD by dietary intervention [23]. Coffee is one of the dietary components linked to a reduced risk of developing AD [24-26]. Patients with mild cognitive impairment who had high levels of plasma caffeine had no progression to AD dementia over a 2-4 year study period, possibly via maintaining levels of the plasma cytokines granulocyte colony-stimulating factor, interleukins -10 and -6 [27]. In a mouse model of AD, coffee, but not caffeine alone, was protective for cognitive function, indicating that other components of coffee were contributing to the benefits [28]. Gelber *et al.* reported no association between coffee or caffeine intake and dementia, but found fewer pathological lesions in the brains of people with higher caffeine consumption [29].

Studies with models of AD have revealed some of the mechanisms by which the various components of coffee may improve brain function. In AD, the amyloid-β peptide is neurotoxic, forming oligomers and aggregating as amyloid plaques in the brain. Various mouse models of AD have been developed by over-expression of mutant forms of the amyloid-β precursor protein, which is enzymatically cleaved into the amyloid-β peptide, leading to cognitive deficits and the development of amyloid plaques in the brain. The J20 mouse model of AD expresses amyloid precursor protein with two familial AD mutations, the Swedish and Indiana mutations. After treatment with crude caffeine extract but not pure caffeine, these mice showed improved learning and memory function and reduced amyloid-β pathology in the brain compared to untreated mice [30]. Caffeine decreases amyloid-β levels in another AD transgenic mouse model expressing two genes linked to familial AD, the Swedish mutation of the amyloid precursor protein and mutated presenilin 1 (*PSEN1*) [31]. It also reduced amyloid pathology and cognitive deficits in mice expressing the amyloid precursor protein with the Swedish mutation [32], by decreasing expression of presenilin 1 and β-secretase, enzymes needed for amyloid-β generation [33]. Caffeine serves as an antagonist of the adenosine receptors A_1 and A_{2A} [34,35]; these neurotransmitter receptors show altered distribution in the AD brain [36] and are being investigated as potential drug targets for AD. In a *Caenorhabditis elegans* model of amyloid-β toxicity, coffee, but not caffeine, showed protection mediated through the nuclear respiratory factor homolog [37]. Nuclear respiratory factor is a transcription factor that regulates expression of genes related to mitochondrial metabolism [38]. Similar results were also found in a *Drosophila* model expressing amyloid-β and treated with decaffeinated coffee, with cafestol proposed as the active component [39]. Trigonelline, another coffee component, protected from the reduction in length of dendrites and axons in rat cortical neurons treated with amyloid-β, *in vitro* [40]. Chlorogenic acid improved cognitive function in mice treated with scopolamine, a muscarinic acetylcholine receptor antagonist, to induce AD-like memory loss; it was shown to reverse the increased acetylcholinesterase activity and higher levels of the lipid peroxidation marker, malondialdehyde, that are characteristic of the model [41]. Chlorogenic acid also showed antioxidant properties in PC12 neuroblastoma cells treated with hydrogen peroxide to induce oxidative stress [42].

Beneficial effects of decaffeinated green coffee

We have recently reported the effects of a decaffeinated green coffee preparation Svetol® in a diet induced model of diabetes in mice, with particular emphasis on its effects in the brain [43]. Svetol® (Naturex, Avignon, France) is an unroasted, decaffeinated green coffee extract containing 40-45% chlorogenic acids, of which 5-caffeoylquinic acid is the major component. The study was conducted in female C57B6SJL mice randomly assigned to four groups viz. normal diet, normal diet with Svetol®, high-fat diet and high-fat diet with Svetol®. The high-fat diet was based on that previously described to cause insulin resistance in mice [44] and Svetol was administered in the drinking water at a concentration of 80 mg/kg body weight. Treatments were for 5 months, starting when the mice were 3 months of age.

We found that Svetol reversed the impaired glucose tolerance induced by high fat diet (Figure 1A), without any effect on weight gain in the high fat diet groups (Figure 1B). The mice on the various treatments had comparable food intake (Figure 1C). Thus, Svetol showed beneficial effects on peripheral glucose regulation in our model of diabetes.

Since diabetes increases the risk to develop AD, we tested the effects of high-fat diet induced diabetes on glucose metabolism in brain mitochondria. We measured oxygen consumption rates using the Seahorse XF24 Extracellular Flux Analyzer and dissected

mitochondrial function at various steps in the electron transport chain by adding specific substrates or inhibitors during the recording period (Figure 2A). When comparing mitochondrial function in the brains of mice on control and high-fat diets, we found a decrease in mitochondrial oxygen consumption rates at the level of electron transport chain complex I in basal and adenosine diphosphate stimulated state 3 respiration (Figure 2B). Treatment with Svetol protected against this decline in mitochondrial respiration at complex I (Figure 2B). While there were no significant changes induced by high fat diet on complex II respiration, treatment with Svetol induced

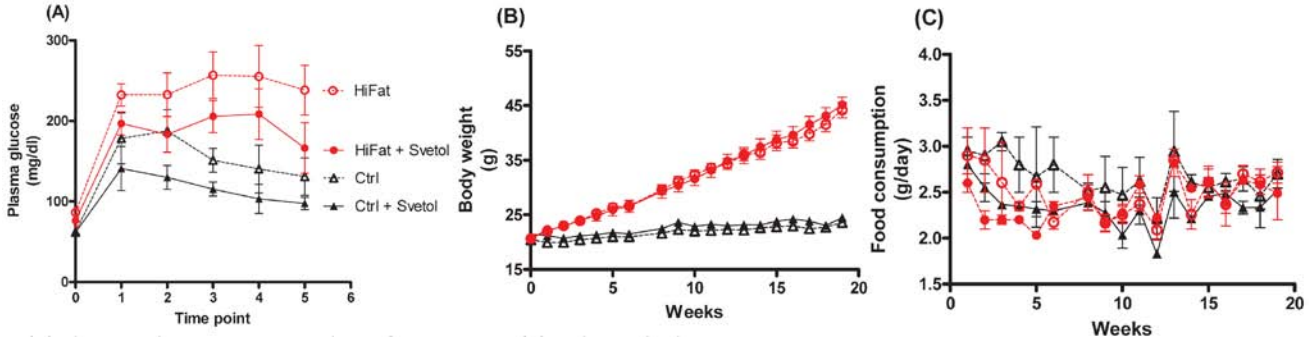

Figure 1. Decaffeinated green coffee ameliorates impaired glucose utilization, but not weight gain, in the high-fat diet induced mouse model of diabetes. (A) Glucose-tolerance test at week 14 of treatment. Normal (Ctrl) vs. high-fat (HiFat) diet, $P < 0.015$; Ctrl + Svetol vs. HiFat, $P < 0.001$; Ctrl + Svetol vs. HiFat + Svetol, $P < 0.005$ by ANOVA with repeated measures. (B) Body weight during treatment period. Ctrl vs. HiFat, $P < 0.0001$; Ctrl vs. HiFat + Svetol, $P < 0.0001$; ctrl + Svetol vs. HiFat, $P < 0.0001$; ctrl + Svetol vs. HiFat + Svetol, $P < 0.001$ by ANOVA with repeated measures. (C) Food intake over treatment period of 20 weeks. All data are expressed as mean ± SEM, n =5 for glucose tolerance test, n = 10 for body weight. Reproduced from Ho *et al.*, Nutr Neurosci., 2012, 15, 37-45, with permission of W. S. Maney & Son Ltd.

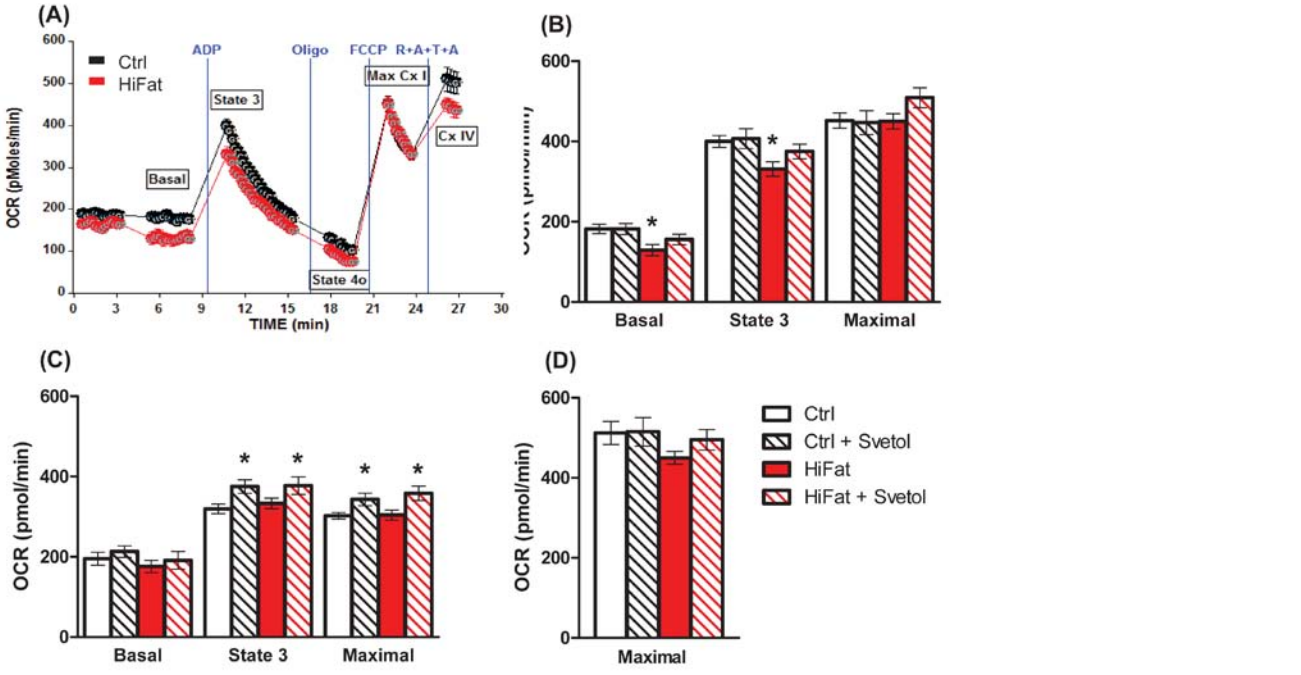

Figure 2. Decaffeinated green coffee improves brain mitochondrial function in a mouse model of diabetes. Mitochondria were prepared from the brain of mice on normal (Ctrl) or high-fat (HiFat) diet, with or without Svetol treatment. (A) The experiment was designed to measure basal oxygen consumption rate, 5 mM adenosine diphosphate (ADP)-stimulated state 3 respiration, state 4_o respiration in presence of 2 µM oligomycin (Oligo) and maximal respiration induced by 4 µM p-trifluoromethoxy carbonyl cyanide phenyl hydrazone (FCCP). (B) Respiration in presence of complex I substrates (10 mM pyruvate and malate). (C) Respiration with complex II substrate, 10 mM succinate. (D) Respiration at complex IV (Cx IV, assayed in presence of 2 µM rotenone and 4 µM antimycin A to inhibit complexes I and III respectively, with 50 mM ascorbate + 0.5 mM tetramethyl-phenylenediamine as artificial electron donors for complex IV; R+A+T+A in Figure 2A). Data are expressed as mean ± SEM, n = 5. * $P < 0.05$ compared to Ctrl and # $P < 0.05$ compared to HiFat by two-tailed t-test. Reproduced from Ho *et al.*, Nutr. Neurosci., 2012, 15, 37-45, with permission of W. S. Maney & Son Ltd.

an increase in state 3 and maximal respiration in both the normal and high-fat diet groups compared to the respective non-treated groups (Figure 2C). Maximal complex I (Figure 2B), basal complex II (Figure 2C) and maximal complex IV (Figure 2D) respiration were not significantly affected by any of the treatments. Thus, Svetol promotes mitochondrial metabolism in the brain and alleviates the deficits induced in brain mitochondria by the diabetic condition.

In order to identify genes that may mediate the effects of high-fat diet and the protection by Svetol in the brain, we used an Agilent whole-genome microarray platform to identify genes differentially expressed in the high-fat diet group and restored to control levels by Svetol treatment. We identified 604 genes that are differentially regulated in the high-fat diet induced diabetic mice and reverted to control levels by treatment with Svetol. Among the differentially regulated genes, several were identified that are involved in pathways related to energy metabolism (listed in Table 2).

In conclusion, as summarized in Figure 3, our study indicates that decaffeinated green coffee presents a promising new intervention in T2DM. While our observations of improved energy metabolism in the brain of diet-induced diabetic mice are encouraging, further studies will be required to establish whether the

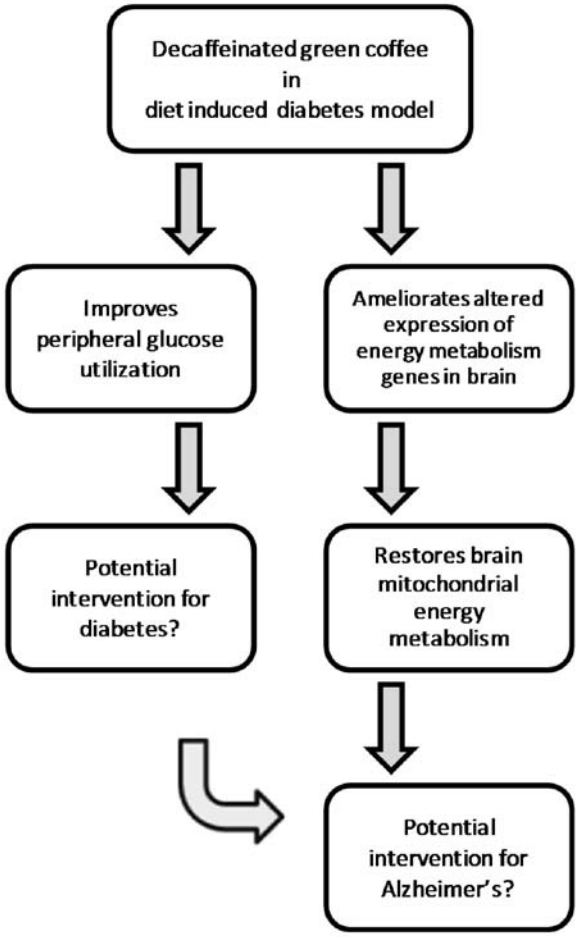

Figure 3. Summary of the effects of green decaffeinated coffee in a diet induced diabetes model.

Table 2. Metabolism related genes that were differentially expressed in the study. (Reproduced from Ho *et al.* Nutr. Neurosci., 2012,15, 37-45, with permission of W. S. Maney & Son Ltd).

Function	Gene name	Gene description
Glucose metabolism	*G6pd2*	Glucose-6-phosphate dehydrogenase 2
	Ogg1	8-Oxoguanine DNA-glycosylase 1
	Gfod1	Glucose-fructose oxidoreductase domain containing 1
	Glp1r	Glucagon-like peptide 1 receptor
	Dera	2-Deoxyribose-5-phosphate aldolase homolog (C. elegans)
	Fpgt	Fructose-1-phosphate guanylyltransferase
Insulin signaling	*Calm3*	Calmodulin 3
	Araf	v-Raf murine sarcoma 3611 viral oncogene homolog
	Pik3cd	Phosphatidylinositol 3-kinase catalytic delta polypeptide
	Tnf	Tumor necrosis factor
Mitochondrial/oxidative phosphorylation	*Tfb2m*	Transcription factor B2, mitochondrial
	Adh4	Alcohol dehydrogenase 4 (class II), pi polypeptide
	Cox7c	Cytochrome c oxidase, subunit VIIc
	Ndufa8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex,8
	Cbr1	Carbonyl reductase 1
	Blvrb	Biliverdin reductase B (flavin reductase (NADPH))
	Cryzl1	Crystallin, zeta (quinonereductase)-like1
	Dbt	Dihydrolipoamide branched chain transacylase E2
Lipid metabolism	*Pla2g3*	Phospholipase A2, group III
	Plce1	Phospholipase C, epsilon 1

beneficial effects of decaffeinated coffee can be extended to neurodegenerative disorders, including AD. Taken together with the previous reports of beneficial effects of coffee on T2DM and AD, our findings indicate that non-caffeine components of coffee have important effects on glucose metabolism and call for further investigation of these bioactive components of coffee as therapeutic interventions.

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