UNIVERSITY OF TORONTO
Department of Nutritional Sciences
Mid-Term Examination 2010
November 11th, 2010

Advanced Nutrition
NFS 484H1 F/ 1484H1 F
Duration – 2 hours

General Instructions:

1. This is an open book examination; therefore students may use any aids that have been brought into the examination room.

2. The examination will be marked out of 50; however, it will constitute only 25% of your final grade.

3. Students must answer all questions in all parts of the examination.

4. All answers should be clearly written in the answer booklets provided. Please provide your answer on the right-hand side of the page only. It will be assumed that the left-hand side of the page is used for note making purposes only and material appearing on this side of the page will not be read or graded.

Introduction

Caffeine is a natural ingredient found in many plants, including coffee, tea, cocoa, kola, guarana and yerba mate. It is also used as a food additive in some carbonated drinks and as an ingredient in over the counter medication. In North America and Europe, up to 90% of adults regularly consume caffeine-containing beverages and foods making it the most widely consumed stimulant in the world. Current recommendations for adults are to consume less than 400 mg of caffeine per day. However, many individuals consume much higher concentrations of caffeine which has the potential to have an adverse effect on human health. According to scientific evidence, physiologic concentrations of caffeine can inhibit adenosine from binding to its receptors both in skeletal muscle and in the central nervous system. Competitive antagonism of adenosine receptors can increase synaptic activity and stimulates the release of neurotransmitters, particularly epinephrine. Epinephrine (or adrenaline) is the "flight or fight" hormone that binds to adrenergic receptors where it can alter pancreatic insulin secretion and/or influence tissue glucose uptake and metabolism.

STUDY 1 (Value 28/50)

Study Design

Study 1 used a hyperinsulinemic-euglycemic glucose clamp to determine whether acute caffeine intake can alter insulin sensitivity and/or glucose uptake in humans. Caffeine or placebo was administered intravenously to 12 healthy volunteers in a randomized double-blind crossover design, with all individuals receiving both caffeine and placebo. The infused caffeine created a blood caffeine level that would be experienced by an individual consuming 300-400 mg of caffeine per day (i.e. upper range of Health Canada's recommendation for caffeine intake). On the morning of each experiment, subjects arrived at the test location after an overnight fast (all subjects were caffeine naïve at the time of the experiment – so 'caffeine withdrawal or tolerance' does not need to be considered – assume this is the individual's first exposure to caffeine). The left artery was used for blood sampling, while the left vein was used for administering 20% glucose, insulin, and test substance (caffeine or placebo). The baseline variables were obtained at −20 min and then at 0 min a caffeine/placebo load was administered intravenously. The infusion of caffeine or placebo was continued for the remainder of the study period, aiming at a stable caffeine/placebo concentration. The hyperinsulinemic-euglycemic glucose clamp procedure was initiated following the caffeine/placebo load (at 0 min) and continued for 120 min. At −20, 0, 90, and 120 min, plasma levels of insulin, epinephrine, free fatty acids (FFAs), and cortisol were determined. Moreover, glucose uptake was reported in the leg of subjects at 120 min following placebo or caffeine treatment.

Questions

1. Describe the effect of caffeine on total glucose infusion rate and glucose uptake by the leg muscle. (Figure 1 and 2) (6/50 marks)

2. Using the data from figures 1 and 2 and drawing on your understanding of tissue glucose uptake and metabolism, explain how caffeine affects insulin sensitivity and glucose utilization under the hyperinsulinemic-euglycemic glucose clamp paradigm. (8/50 marks)

3. Describe the effect of caffeine on plasma epinephrine, FFA and cortisol (Figure 3). (6/50 marks)

4. Discuss the relevance of the three measured outcomes in figure 3 as they relate to the understanding of the mechanism associating caffeine and insulin sensitivity? [i.e. why were they measured and what does it tell you.] Be certain to draw from your understanding of how caffeine modulates insulin sensitivity (shown in figure 1 and 2). (8/50 marks)

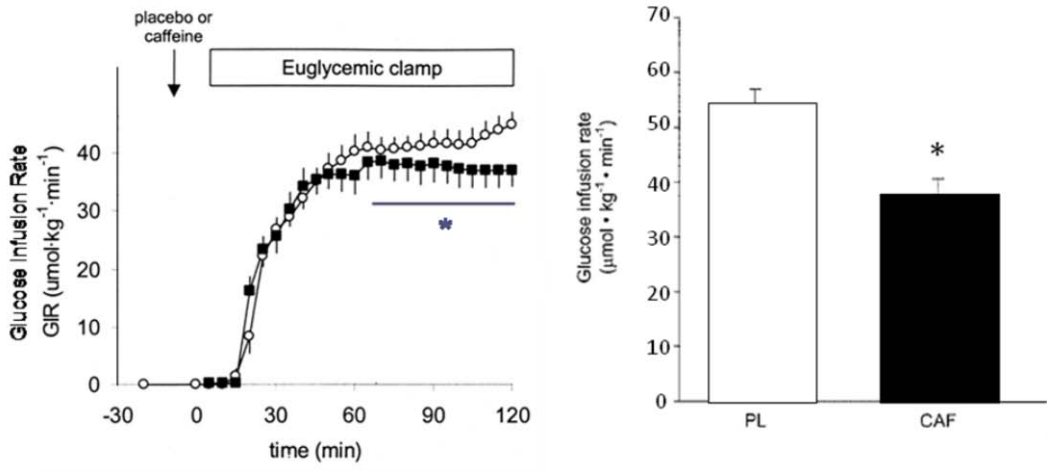

Figure 1. Glucose infusion rate following placebo and caffeine during the euglycemic-hyperinsulinemic clamp. The arrow denotes the start of caffeine or placebo infusions. Caffeine (■); placebo (○). * p<0.05 difference between treatments, across all time points under the bar. The histogram represents area under the curve for glucose infusion rate between 0 and 120 minutes. * p<0.05 vs. placebo.

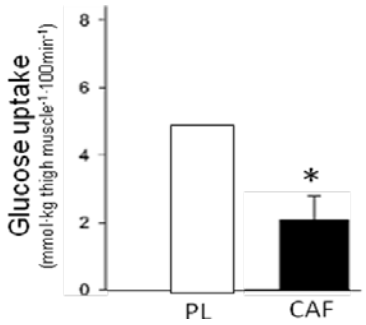

Figure 2. Total (area under the curve) glucose uptake by leg muscle following placebo and caffeine during the euglycemic-hyperinsulinemic clamp. Values are means ± SEM. CAF, caffeine; PL, placebo. * P<0.05 vs. placebo.

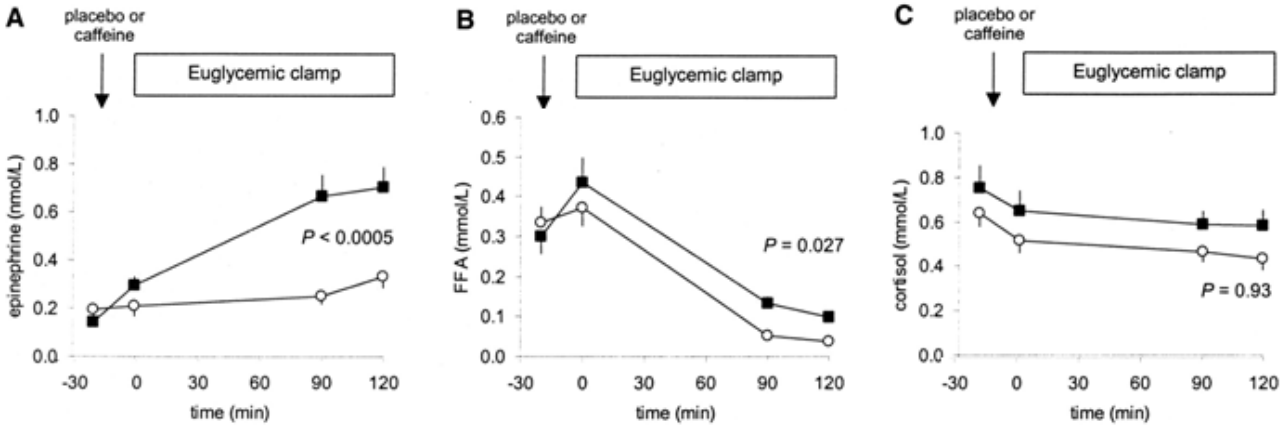

Figure 3. Response of plasma epinephrine (A), Free Fatty Acids (B) and cortisol (C) to caffeine (■) and placebo (○). Arrows denote start of caffeine or placebo infusion. P values are given for differences between caffeine and placebo studies over the entire 120 minutes.

STUDY 2 (Value 22/50)

Obesity is associated with impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM). Common to both IGT and T2DM are hyperinsulinemia and insulin resistance, which result from the impairment of insulin's action on insulin-sensitive tissues such as skeletal muscle. Insulin resistance can be characterized by elevated basal serum insulin concentrations, an elevated insulin response to glucose ingestion, and a decrease in glucose uptake in the peripheral tissues, especially skeletal muscle. Lifestyle interventions, such as reductions in energy and saturated fat intakes and increases in physical activity, have resulted in improvements in insulin and glucose control in obese persons. However, the influence of caffeine on glucose tolerance and insulin sensitivity has not been studied. Thus, this study was conducted to examine the acute effects of caffeine ingestion on glucose and insulin homeostasis in lean and obese subjects.

Study Design

Eight lean and obese subjects ingested a placebo and 5 mg of caffeine/kg body weight (~350-400 mg caffeine). One hour post treatment, a 75 g oral glucose load was administered and blood levels were measured at 0, 15, 30, 60, 90 and 120 min.

Questions

5. Describe the effect of caffeine on serum insulin levels during the glucose tolerance test in lean and obese subjects (Figure 4) {**Briefly** describe the top graph visually, then draw on the bottom graph for statistical outcomes}. (value 4/50 marks)

6. Discuss the independent and combined roles of the pancreas and muscle in altering type 2 diabetes (T2DM) risk in individuals associated with caffeine intake – be certain to discuss how the two different experimental approaches allow you to address this question, especially as it relates to different tissue responses to caffeine intake. Make certain to comment about the risk of developing T2DM in both lean and obese subjects and whether this risk differs depending upon the obesity status (lean vs. obese) of the individual. (value 10/50 marks)

7. Studies have shown that in pregnancy, there is a pronounced physiological decrease in peripheral insulin sensitivity that worsens as pregnancy proceeds and places women at risk of developing gestational diabetes (GD; diabetes that develops during pregnancy). Moreover, during pregnancy, the rate of caffeine metabolism slows, resulting in more prolonged increases in blood levels following caffeine consumption. Based on all the information provided, what recommendations for caffeine intake would you give to pregnant women? Would these recommendations differ for women planning to conceive? Why or why not? Defend you answer by drawing on data in studies 1 and 2. (value 8/50 marks)

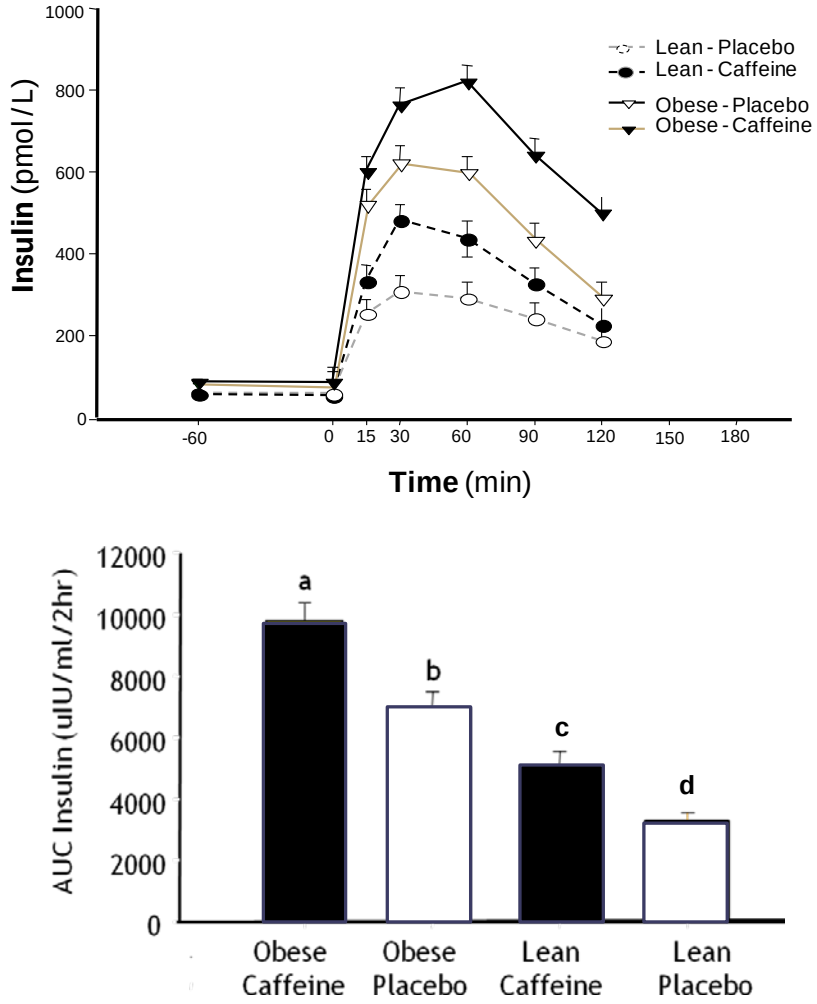

Figure 4. Serum insulin concentrations during a 75 g oral glucose tolerance test in male subjects: either lean or obese. Bars in histogram with different superscripts are significantly different ($p<0.05$).