NOTE TO USERS

This reproduction is the best copy available.

THE ROLE OF INSOLUBLE FIBER IN FOOD INTAKE REGULATION, APPETITE AND BLOOD GLUCOSE IN HEALTHY YOUNG ADULTS

by

Atyeh Hamedani

A thesis submitted in conformity with the requirements
for the degree of Masters of Science
Graduate Department of Nutritional Sciences
University of Toronto

Your file Votre référence
ISBN: 978-0-494-55770-9
Our file Notre référence
ISBN: 978-0-494-55770-9

THE ROLE OF INSOLUBLE FIBER IN FOOD INTAKE REGULATION, APPETITE AND BLOOD GLUCOSE IN HEALTHY YOUNG ADULTS

Atyeh Hamedani

Master of Science 2009

Graduate Department of Nutritional Sciences
University of Toronto

ABSTRACT

The effect of a breakfast cereal containing insoluble fiber on subjective appetite, food intake, and blood glucose was investigated. Young adult men and women were fed equal servings (60 g) of high and low fiber cereals in a repeated measures design. Blood glucose and subjective appetite were measured at regular intervals up to 255 min and ad libitum food intake at 180 min. Food intake was not affected by treatment, but cumulative food intake (from breakfast and lunch) was lower following the high fiber cereal. The high fiber compared with the low fiber cereal increased subjective satiety per kilocalorie of energy and resulted in lower blood glucose after consumption and immediately after lunch.

In conclusion, this study provides evidence in support of short-term effects of insoluble fiber consumption on food intake and glycemic control.

AKNOWLEDGEMENTS

I thank God who has guided me thus far.

My deepest appreciation goes to Dr. G. Harvey Anderson for having accepted me as his student. It is difficult not to overstate my gratitude for his expertise and guidance, but most of all, for his patience. Thank you for your vital encouragement and support.

My sincere thanks goes to my committee advisors, Drs. David Jenkins and Rena Mendelson and the members of my examination committee, Dr. Elena Comelli and Dr. Richard Bazinet. The administrative staff: Louisa, Emeliana, Lucile and Vijay deserve a special mention for their continued support during the past years.

I warmly thank all my lab-mates for their academic and emotional support, including Christina, Pedro, Ali, Becky, Szeto, Chris, Shlomi, Barkha, and Sandra. Bohdan, thanks for your time and positive energy. Tina, Maria and Shirin I am very grateful for your presence, love and encouragement; and Nick, thanks for your expertise and patience. My former colleague, Rania, helped embark me on this path and I am grateful for her guidance.

This study would not have been possible without generous financial support from the Bell Institute of Health and Nutrition, General Mills Inc. I am equally indebted to the 40 participants of my study who endured the finger-pricks and early morning sessions.

And most importantly, my deepest and heartfelt gratitude goes to my parents, Ali and Zahra. They bore me, raised me, taught me, and loved me. To them, and to my most precious sister, I dedicate this thesis.

TABLE OF CONTENTS

Abstract ii
Acknowledgements iii
Table of Contents iv
List of Tables and Figures vi
List of Abbreviations vii

CHAPTER 1. INTRODUCTION 1

CHAPTER 2. LITERATURE REVIEW
2.1. Introduction 2
2.2. Short-term Food Intake Regulation 2
2.2.1. Hunger, Satiation and Satiety 3
2.2.2. Preabsorptive Signals 3
(i) Gastric Distention 3
(ii) Gastric Emptying 4
(iii) Gastrointestinal Peptides 4
2.2.3. Post-absorptive Signals 6
(i) Glucose 6
(ii) Insulin 7
2.3. Macronutrients and Food Intake Regulation 7
2.3.1. Carbohydrate, Food Intake Regulation and Satiety 8
2.3.2. Fiber, Food Intake Regulation and Satiety 9
2.3.2.1. Intrinsic Effects of Insoluble Fiber on Satiety 10
2.3.2.2. Hormonal Effects of Insoluble Fiber on Satiety 11
2.3.2.3. Effect of Insoluble Fiber on Blood Glucose 12
2.4. Measurement of Short-term Satiety, Food Intake and Blood Glucose 14

CHAPTER 3. HYPOTHESES AND OBJECTIVES
3.1. Hypothesis 15
3.2. Objectives 15

CHAPTER 4. REDUCED ENERGY INTAKE AT BREAKFAST IS NOT COMPENSATED FOR AT LUNCH IF A HIGH INSOLUBLE FIBER CEREAL REPLACES A LOW FIBER CEREAL 16

4.1. Abstract 16
4.2. Introduction 17
4.3. Subjects and Methods
4.3.1. Subjects 18
4.3.2. Study Design and Treatments 19
4.3.3. Protocol 19
4.3.4. Statistical Analysis 21
4.4. Results
4.4.1. Energy and Water Intake 22

4.4.2. Average Appetite..... 22
4.4.3. Plasma Glucose..... 23
4.4.4. Satisfaction, Physical Comfort and Palatability..... 24
4.5. Discussion..... 25
4.6. Tables and Figures..... 29

CHAPTER 5. FUTURE DIRECTIONS AND CONCLUSION
5.1. Summary of Results..... 35
5.2. Future Directions..... 35
5.3. Conclusion..... 38

CHAPTER 6. REFERENCES..... 39

CHAPTER 7. APPENDICES
7.1. Screening Questionnaires and Consent Form..... 47
7.2. Study Day Questionnaires..... 58
7.3. Pizza Composition..... 65
7.4. Permission for Reproduction of Manuscript..... 66

LIST OF TABLES AND FIGURES

Table 4.1. Composition of treatments..... 28

Table 4.2. Energy intake, cumulative energy intake and water intake after breakfast cereals..... 29

Figure 4.1. Average appetite score, change from baseline, measured by visual analog scales after consumption of low fiber (LF) and high fiber cereal (HF) before and after consumption of the ad libitum meal. Meal intake occurred at 180 min after cereal consumption..... 30

Figure 4.2. Average appetite score, as change from baseline, per kcal of energy intake and net incremental area under the curve (AUC) after consumption of low fiber (LF) and high fiber cereal (HF)..... 31

Figure 4.3. Plasma glucose concentrations, change from baseline, after consumption of low fiber (LF) and high fiber cereal (HF) and after consumption of the ad libitum meal and net incremental area under the curve (AUC)..... 32

Figure 4.4. Subjective satisfaction with breakfast cereals after consumption of low fiber (LF) and high fiber cereal (HF) and after consumption of the ad libitum meal and pre-meal total area under the curve (AUC)..... 33

LIST OF ABBREVIATIONS

A

AUC	Area under the curve

B

BG	Blood glucose

C

CCK	Cholecystokinin
CNS	Central nervous system

F

FI	Food intake

G

GI	Glycemic index
GLP-1	Glucagon-like-peptide-1

H

HF	High fiber

K

Kcal	Kilocalorie

L

LF	Low fiber

P

PFC	Prospective food consumption
PG	Plasma glucose
PYY	Peptite YY

S

SA	Subjective appetite
SCFA	Short-chain fatty acid

V

VAS	Visual analogue scale(s)

CHAPTER 1

1. INTRODUCTION

Over the past 30 years, there has been a dramatic increase in overweight and obesity among Canadians. In 2004, approximately 6.8 million Canadian adults were overweight, and an additional 4.5 million were obese (StatisticsCanada 2005). Prevention is an important priority as obesity can lead to many chronic conditions, the most devastating of which may be type 2 diabetes. There is great interest among the health care sector and agri-food industry to find affordable, food-based solutions for obesity and type 2 diabetes.

Dietary fiber is of interest because high cereal fiber intake is associated with a decrease in energy intake and diabetes in young adults (Schulze, Schulz et al. 2007; Tucker and Thomas 2009). According to the Institute of Medicine, suggested definition of dietary fiber is as follows: "1. Dietary fiber consists of non-digestible carbohydrates and lignin that are intrinsic and intact in plants 2. Added fiber consists of isolated, non-digestible carbohydrates that have beneficial physiological effects in humans and 3. Total Fiber is the sum of Dietary Fiber and Added Fiber" (Institute of Medicine 2001). Dietary fibers can be broadly classified as soluble or insoluble and fermentable or non-fermentable. Regular consumption of insoluble dietary fiber has been shown to reduce the risk of type 2 diabetes in cohort studies (de Munter, Hu et al. 2007; Kaline, Bornstein et al. 2007). The mechanism by which insoluble fiber improves body weight and type 2 diabetes is unclear, but may include increased satiety and reduced short-term food intake (Samra and Anderson 2007). Thus, the focus of this research is the effect of insoluble fiber cereal on appetite, short-term food intake and blood glucose regulation in normal-weight young adults.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

Obesity is the most prevalent nutritional disease within affluent societies, exceeding by far the number of nutritional deficiency diseases. It is the outcome of a positive energy balance due to either increased energy intake or decreased energy expenditure or both. Consequently, much research is focused on understanding the factors involved in this energy imbalance, particularly the regulation of energy intake. Among the macronutrients, dietary fiber has been shown to suppress short-term food intake, but the mechanisms by which this occurs have not been fully defined.

Because the focus of this research centers on the effect of consuming low or high fiber breakfast cereals on short-term responses in subjective satiety and food intake, this literature review provides background on short-term regulation of food intake and on the physiologic interaction of dietary fiber with known intake regulating mechanisms. The literature review is comprised of three sections. The first section gives a brief summary on the regulation of food intake. In the second section the effect of macronutrients on food intake regulation is reviewed with a focus on carbohydrate and dietary fiber. The third section reviews methods that are used to measure short-term energy intake and subjective appetite.

2.2. Short-term Food Intake Regulation

Food intake is determined by many environmental and physiologic factors that interact and affect energy balance for the individual. Short-term food intake is generally defined as the amount of food consumed during single meals or within a day. Its regulation involves preabsorptive signals and post-absorptive signals that initiate meal termination and modulate the intake of subsequent meals. The regulation of short-term food intake is also affected by signals that work in the long-term such as leptin and adiponectin from adipose tissue and insulin, which is involved in both short-term and long-term regulation of food intake. The following provides a review of short-term regulation of food intake.

2.2.1. Hunger, Satiation and Satiety

Defining hunger, satiation and satiety is necessary in order to better understand the processes that stimulate and inhibit food consumption. Hunger is the biological drive that impels individuals to search for food (Smith and Ferguson 2008). Once hunger has been fulfilled, physiological processes are stimulated to inhibit further eating and this process is termed satiation. Following food consumption, satiety helps delay the onset of the next meal (Smith and Ferguson 2008). The regulation of food intake is a balance between hunger, an excitatory process that arises from energy needs, and satiety, an inhibitory process that initially arises from postingestive physiological processing.

2.2.2. Preabsorptive Signals

Short-term regulation of energy homeostasis is dependant on pre and post-absorptive signals. Preabsorptive signals arise from the presence of food within the gastrointestinal tract before it is absorbed through the intestinal lumen. Ingested food evokes preabsorptive signals by two primary effects on the gastrointestinal tract; first, by mechanical stimulation and therefore stimulation of the nerve endings which initiate a myriad of signals to central nervous system (CNS) through vagal and spinal sensory nerves (Karhunen, Juvonen et al. 2008). And second, via release of gastrointestinal peptides which provide both neurocrine and humoral signals to the CNS.

(i) Gastric Distention

In the immediate postprandial period, the presence of food within the stomach stimulates stretch, tension and volume neural sensors which send satiety signals to the brain via sensory nerves (Oesch, Ruegg et al. 2006; Cummings and Overduin 2007). Experiments involving cuffs that can reversibly close the pylorus demonstrate that gastric distention alone is sufficient to reach satiation (Smith 1998; Ritter 2004). Volume of the food, irrespective of energy content, decreases feeling of hunger (Rolls, Castellanos et al. 1998). Within the human body, however, postprandial gastric distention contributes to satiation when acting in concert with the rate of gastric emptying (Cummings and Overduin 2007).

(ii) Gastric Emptying

The release of stomach contents into the small intestine is known as gastric emptying. Solid foods compared with liquids, and foods that are high in energy density, viscosity and volume empty more slowly (Kong and Singh 2008). In general, meals with similar energy content are emptied from the stomach at similar rates (Faas, Steingoetter et al. 2002). Foods with high energy density are associated with longer emptying times (Hadi NA 2002). Among the macronutrients, fat is emptied more slowly than carbohydrates and proteins, primarily because of its high caloric density (9 kcal/g vs.4 kcal/g in carbohydrate or protein) (Gentilcore, Chaikomin et al. 2006).

Although longer gastric emptying rates are associated with increased sensation of short-term satiety, gastric emptying is not the only factor that predicts satiety. Gastric emptying was not different after isovolumetric and equalcaloric preloads despite increased satiety after a guar gum drink compared to placebo (Lavin and Read 1995). This disconnect between gastric emptying and satiety may be attributed to signals arising from the small intestine since up to 40% of a meal empties into the intestine before meal termination (Cummings and Overduin 2007). Therefore, intestinal satiation signals commence almost simultaneously with both pregastric and gastric stimuli, making uncertain the independent role of gastric stimuli.

(iii) Gastrointestinal Peptides

The entry of food into the small intestine stimulates many short-term signals of intestinal satiation including a cadre of gut peptides that are secreted from enteroendocrine cells within the duodenum. These peptides diffuse through interstitial fluids to activate nearby nerve fibers and/or enter the bloodstream where they function to regulate satiation and food intake (Badman and Flier 2005). The most investigated of these gastrointestinal peptides are cholecystokinin (CCK), glucagon-like-peptide-1 (GLP-1), peptite YY (PYY) and ghrelin.

CCK is an anorectic hormone produced by I cells in the duodenal and jejunal mucosa, as well as in the brain and enteric nervous system (Rehfeld 2004). Intestinal CCK is most potently secreted in response to luminal lipids and proteins but also carbohydrates and is responsible for reducing meal size and duration (Rehfeld 2004;

Seimon, Feltrin et al. 2009). CCK-induced satiation results in part from inhibition of gastric emptying (Hayes, Moore et al. 2004) and by regulation of pancreatic secretions and gallbladder contractions (Chandra and Liddle 2007).

GLP-1 is another well investigated hormone that is implicated in satiation. It is produced primarily by L cells in the distal small intestine and colon (Brubaker and Anini 2003). Ingested fats and carbohydrates stimulate GLP-1 secretion by indirect, duodenally activated neurohumoral mechanisms, as well as by direct contact within the distal intestine (Brubaker and Anini 2003). GLP-1 decreases food intake in adults (Verdich, Flint et al. 2001) and peripheral injections elicit satiety among normal-weight (Gutzwiller, Goke et al. 1999), obese (Naslund, Barkeling et al. 1999) and diabetic (Toft-Nielsen, Madsbad et al. 1999) individuals. In addition to regulating satiety, GLP1 accentuates glucose-dependent insulin release, inhibits glucagon secretion and increases pancreatic β cell growth (Drucker 2006). The mechanisms underlying GLP1-induced anorexia are not fully known but involve vagal and possibly direct central pathways (Baggio, Huang et al. 2004).

PPY is generally accepted as an anorexigenic hormone, although the results seem controversial when replicated in rodents. Similar to GLP-1, PYY is produced mainly by distal-intestinal L cells (Degen, Oesch et al. 2005). It is secreted postprandially, with a macronutrient potency of lipids being greater than that of carbohydrates, which is greater than that of proteins. Like GLP1, PYY delays gastric emptying (Di Francesco, Zamboni et al. 2005). PYY is rapidly proteolyzed and cleaved into $PYY_{3-36,}$ which has been shown to induce satiety and reduce food intake in both rodents and humans (Batterham, Cowley et al. 2002; Batterham, Cohen et al. 2003).

The only known orexigenic hormone is ghrelin, produced by the stomach and proximal small intestine (Cummings, Foster-Schubert et al. 2005). One of the most important biological activities of ghrelin is the stimulation of food intake and long-term regulation of body weight. Short-term ghrelin application in humans directly stimulates gastric motility, acid secretion and appetite for several hours and reduces postprandial satiety (Wren, Seal et al. 2001). In contrast to satiation peptides, circulating levels of ghrelin surge before meals and fall within an hour of nutrient ingestion, particularly

carbohydrates. Pre-prandial ghrelin secretion seems to be a cephalic response, possibly stimulated by the sympathetic nervous system (Mundinger, Cummings et al. 2006).

2.2.3. Post-absorptive Signals

The digestion of food leads to the release and absorption of glucose, amino acids and fatty acids. Each of these can have direct effects on physiological mechanisms of intake regulation, or indirect effects through stimulation of hormones. Since the focus of this research is on the gastrointestinal effects of carbohydrate and fiber, only short-term post-absorptive signals associated with carbohydrate and fiber catabolism will be discussed; namely, glucose and insulin for their role in regulating short-term food intake and hunger.

(i) Glucose

Half a century ago, a possible role of blood glucose in signaling meal initiation was proposed by Mayer (Mayer 1955). The glucostatic theory postulates that a transient decline in blood glucose occurs before food-seeking behavior and initiation of a meal. When blood glucose is continuously monitored in healthy individuals, hunger ratings and meal requests are preceded by and correlated with a transient decline in glucose (Campfield, Smith et al. 1996). Consistent with this hypothesis, increasing blood glucose is associated with satiation (Anderson, Catherine et al. 2002).

The mechanism behind the glucostatic theory is attributed to hypothalamic, glucose-responsive and glucose-sensitive neurons whose firing rate is altered by changes either in plasma or local glucose (Penicaud, Leloup et al. 2002). Glucose-responsive neurons increase their activity when blood glucose increases while glucose-sensitive neurons decrease their activity under the same conditions. In this manner, they contribute to the regulation of short-term food intake and satiety (Penicaud, Leloup et al. 2002). However, hormones like insulin also affect glucose-responsive neurons (Schuit, Huypens et al. 2001; Williams, Bing et al. 2001). It has been shown that insulin receptors and insulin sensitive glucose transporters in the hypothalamus help regulate glucose homeostasis (Plum, Belgardt et al. 2006) and help reduce food intake and body weight (Plum, Schubert et al. 2005).

(ii) Insulin

Insulin is a hormone secreted by the β-cells of the endocrine pancreas, in direct proportion to glucose entry into the blood and its response is modulated by body fat content (Drazen and Woods 2003). Both the short-term response of insulin to glucose and its concentration in the blood reflecting body fat content contribute to the regulation of food intake (Anderson, Aziz et al. 2006).

Both animal and human studies provide evidence that insulin plays a role in the short-term regulation of food intake (Drazen and Woods 2003). When exogenous insulin was administered directly into the brain, animals reduced their food intake (Woods and Seeley 2001). Similarly, when insulin antibodies were administered in or near the hypothalamus, animals overate and gained weight (Woods, Lutz et al. 2006). Humans who received insulin intranasally (with a consequent increase of insulin in cerebrospinal fluid) also ate less food and lost body fat (Born, Lange et al. 2002; Hallschmid, Benedict et al. 2004). Moreover, intrameal hepatic portal infusion of insulin acutely reduced spontaneous meal size in rats, suggesting that insulin may play a role in satiation (Langhans, Grossmann et al. 2001).

The role of insulin in long-term regulation of food intake is supported by the observation that hyperinsulinemic men compensate better at a pizza meal 1 hr after a glucose load than healthy men (Samra, Wolever et al. 2007). Thus, it may be that hyperinsulinemia is the body's attempt to resist weight gain by reducing food intake. Moreover, insulin can enhance the hypothalamic sensitivity to peripheral CCK signals in times of excess energy intake, thus, reducing the trajectory of weight gain or promoting weight loss (Schwartz, Woods et al. 2000; Woods and D'Alessio 2008).

2.3. Macronutrients and Food Intake Regulation

Animals and humans consume food in order to maintain energy balance. Energy requirement is dynamically changing with the nutritional status of the organism and its surroundings. Although all food components provide energy, their effect on food intake can not be predicted simply from their energy content (Anderson, Aziz et al. 2006). Humans tend to over-consume when provided palatable energy dense foods or a high fat diet (Blundell and Stubbs 1999; Yeomans, Blundell et al. 2004), indicating that factors

other than energy content contribute to the regulation of food intake. Each macronutrient possesses unique physical and chemical properties that regulate pre- and post-absorptive satiation and satiety signals. Within the macronutrient hierarchy, protein has been shown to suppress food intake more than carbohydrate which in turn suppresses food intake more than fat (Anderson, Aziz et al. 2006). Much attention has been given to the role of fat, protein and carbohydrate on energy intake control but few studies have focused on the role of dietary fiber, which is primarily a component of carbohydrate containing foods. The following sections provide an overview of the role of carbohydrate and fiber and their interaction in short-term food intake regulation.

2.3.1. Carbohydrate, Food Intake Regulation and Satiety

Carbohydrates have typically been categorized and assessed based on their glycemic index (GI) or resultant increase in blood glucose. Although there is support for the notion that low-GI carbohydrate foods induce greater satiety than high-GI carbohydrates (Brand-Miller, McMillan-Price et al. 2008; Pal, Lim et al. 2008), it appears that both can suppress appetite and food intake depending on the time of measurement. High-GI carbohydrates, such as glucose drinks, have been reported to result in greater satiety and lower food intake in the 60 min after consumption (Anderson, Catherine et al. 2002). An inverse association between blood glucose and both subjective appetite and food intake at 1 h after consumption of isovolumetric preloads of carbohydrates has been reported (Anderson, Catherine et al. 2002). High-GI carbohydrates such as glucose, polycose and sucrose suppressed food intake more than low-GI carbohydrates namely, amylose, amylopectin and a fructose–glucose mixture. Similarly, lower food intake was reported at 80 min following isocaloric solutions with high- rather than low-glucose and fructose concentration (Akhavan and Anderson 2007). The early satiating effect of high-GI carbohydrates have also been observed in obese women (Burton-Freeman and Keim 2008).

Interaction of carbohydrates with receptors in the gastrointestinal tract plays a major role in their effect on satiety. Ingestion of carbohydrates stimulates the release of a number of gastrointestinal hormones, including GLP-1 (Aziz and Anderson 2002) and CCK (Bellissimo and Anderson 2003). GLP-1 in particular has been associated with

carbohydrate-induced satiety and it is released when glucose comes in contact with the intestinal L-cells (Bornet, Jardy-Gennetier et al. 2007). Prolonged contact of glucose with the L-cells is assumed to be one mechanism by which low-GI carbohydrates prolong satiety (Anderson and Woodend 2003).

Because many studies supporting an increase in satiety with low-GI foods are also characterized by high fiber content (Pasman, Blokdijk et al. 2003; Jimenez-Cruz, Gutierrez-Gonzalez et al. 2005), it is difficult to tease out the separate effects of low-GI carbohydrate-induced satiety *per se* and fibers.

2.3.2. Fiber, Food Intake Regulation and Satiety

Dietary fibers have specific chemical and physical properties and can be broadly classified as soluble or insoluble and fermentable or non-fermentable. Solubility depends on the extent to which the fiber dissolves in water or forms a gel (Slavin and Green 2007). Fermentability is related to whether the undigested fibers upon reaching the colon are fermented by anaerobic bacteria to yield short-chain fatty acids (SCFA) and gases (methane and hydrogen), which are absorbed and used as energy. Dietary fiber has been associated with improved body weight regulation perhaps because fiber increases satiety and decreases energy intake. A review of multiple studies on dietary fiber suggested that a 10% decrease in energy intake was associated with an additional 14 g of fiber per day (Howarth, Saltzman et al. 2001). That review primarily attributed the benefits of dietary fiber to the soluble, gel-forming component; however, more recent reports provide support for the role of insoluble fiber in short-term food intake.

Three recent studies have provided evidence for the short-term effects of high wheat/corn bran breakfast cereals on satiety and food intake. In healthy young men, a high fiber cereal containing 33 g of insoluble wheat and corn fiber reduced food intake 75 min following breakfast compared to an isocaloric low fiber cereal (Samra and Anderson 2007). The same insoluble fiber cereal (41 g) reduced ad libitum food intake at 60 min compared to a macronutrient-matched low fiber cereal (Freeland, Anderson et al. 2009). The desire for food was found to be reduced by insoluble resistant starch and corn bran muffins compared to a low fiber muffin over 180 min in healthy adults (Willis, Eldridge et al. 2009).

The mechanism by insoluble fiber reduces food intake is still under investigation. It is hypothesized that fiber suppresses energy intake and reduces body weight by inducing satiation and satiety (Slavin and Green 2007). Insoluble fiber may impact satiety as a result of its intrinsic physical properties, release of gut hormones, regulation of blood glucose and fermentation in the colon. The following sections will discuss these proposed mechanisms in detail.

2.3.2.1. Intrinsic Effects of Insoluble Fiber on Satiety

Several physiological effects of dietary fiber can be predicted to affect food intake and energy balance. Fiber-induced satiation begins as early on as mastication and continues into the stomach causing gastric distention and reducing gastric emptying.

Increased time and effort for mastication are generally the result of the textural and fibrous quality of high-fiber carbohydrate foods. Prolonged mastication promotes satiation by reducing eating rate, thereby providing greater time for metabolic feedback to curb intake (Burton-Freeman 2000). A direct neural effect of the mechanical action of chewing on central satiety centers has also been demonstrated in rodents (Sakata, Yoshimatsu et al. 2003).

Increased consumption of insoluble fiber contributes to maximize satiation through gastric distension. Dietary fibers cause gastric distention through bulking, which activates sensitive stretch mechanoreceptors that regulate satiety and food intake, irrespective of any chemical effects of food (Burton-Freeman 2000).

Fiber can increase satiation by adding weight and bulk to the food, and therefore, for a given weight or volume of food, it can displace the energy of other nutrients resulting in reduced energy density of the diet (Rolls and Bell 1999). This means that a similar weight of food containing fiber induces greater satiation while reducing energy intake, compared to a high fat food. Furthermore, the energy diluting effects of dietary fiber may reduce energy intake by lowering the overall palatability of the diet (Drewnowski 1998). Energy density and palatability have been shown to be positively correlated and this renders high fiber diets less appealing (Drewnowski 1998; Slavin and Green 2007).

Insoluble fiber can also enhance satiety by delaying gastric emptying and gastrointestinal transit (Howarth, Saltzman et al. 2001). Slower gastrointestinal transit prolongs contact time of macronutrients with the distal small bowel absorptive surfaces and may enhance the release of gut peptides with satiety properties as well as slow nutrient absorption, resulting in a metabolic profile that enhances satiety.

2.3.2.2. Hormonal Effects of Insoluble Fiber on Satiety

Although consumption of insoluble fiber has been associated with the release of gut hormones including CCK, PYY, GLP-1 and ghrelin, neither the mechanisms of their release nor the association between the blood hormone concentrations achieved by fiber ingestion and satiety is fully understood. Fiber content has been shown to elevate postprandial CCK, particularly as part of a low-fat diet, indicating that fiber delays fat absorption and increases intestinal exposure to fat, thereby intensifying its effect in satiety and increasing CCK concentrations (Burton-Freeman, Davis et al. 2002).

There is very limited data on the effect of insoluble fiber on PYY release and satiety, particularly in the short-term following fiber consumption. One study has reported a reduction in plasma PYY levels within the first hour of consuming wheat-fiber rich bread compared to isoenergetic and macronutrient matched white bread (Weickert, Spranger et al. 2006) but there was no effect on subjective ratings of satiety.

The short-term effects of insoluble fiber on GLP-1 and its association with satiety are also unclear. However, insoluble fiber has been shown to increase GLP-1 secretion in the long-term through fermentation of resistant starch that leads to SCFA production (Zhou, Martin et al. 2008). GLP-1 producing cells are abundant in the ileum and colon and SCFA acids upregulate the expression of the GLP-1 precursor, proglucagon mRNA (Zhou, Martin et al. 2008). In humans too, insoluble barley bread consumed the night before reduced total GLP-1 levels on day 2 following a standardized breakfast (Nilsson, Ostman et al. 2008).

Insoluble fiber also affects short-term ghrelin release, although again these acute changes appear not to affect satiety ratings (Weickert, Spranger et al. 2006). Post-prandial ghrelin was blunted after insoluble wheat fiber bread and this effect was independent of insulin and glucose release. The exact signals mediating meal-related

ghrelin suppression are not known (Weickert, Spranger et al. 2006). Clearly, support for a role for insoluble fiber in the regulation of gut hormone secretions is limited and further investigation is required to elucidate a role of insoluble fiber in gut hormone secretion and its association with satiety.

2.3.2.3. Effect of Insoluble Fiber on Blood Glucose

Insoluble fiber has recently been shown to have a direct action on blood glucose regulatory mechanisms. A breakfast cereal high in insoluble fiber from corn and wheat improved postprandial glucose response after the next meal independent of the glucose response associated with its consumption (Samra and Anderson 2007). Previous research has led to the conclusion that the enhanced glucose tolerance at a subsequent meal (known as the second meal effect) is due to the low GI of the treatment and the low rate of glucose absorption but the observations of Samra and Anderson suggest that the effect may also have resulted from insoluble fiber. Lower glycemic response at the second meal occurred when lentils and barley (both low GI foods) were fed as the first meal, but not after whole-meal bread, a high GI food. Lentils and barley are rich in soluble and fermentable fiber, whereas the whole meal bread is high in insoluble fiber (Jenkins, Wolever et al. 1982; Wolever, Jenkins et al. 1988).

The mechanism behind the beneficial effect of insoluble fiber on glucose tolerance at a second meal remains unknown. Enhanced release of SCFA (e.g. acetic, propionic, and butyric acids) during fermentation in the colon has been shown to increase proglucagon mRNA (Zhou, Martin et al. 2008) and secretion of incretin hormones including GLP-1 improve glucose metabolism and reduce postprandial glycemic responses (Lovshin and Drucker 2009). However, colonic fermentation does not begin until 4 to 6 hours after fiber consumption and can not explain the short-term benefits that are observed earlier than 4 hours. Data suggest that the short-term beneficial effect of insoluble fiber may actually be independent of colonic fermentation since low and high insoluble fiber cereals led to equal breath hydrogen production over 4 h (Freeland 2002).

A possible mechanism for the effect of insoluble fiber on post meal blood glucose may include indirect stimulation of vagal afferents that are involved in glucoregulation. The intestines have the ability to sense nutrients in a preabsorptive state and down

regulate hepatic glucose production upon nutrient exposure. It was recently shown that infusion of lipids into the upper intestine of rats led to an activation of neurocircuitry that connects the intestine to the brain and then to the liver with a consequent reduction in hepatic glucose production (Wang, Caspi et al. 2008). It was hypothesized that lipid administration induces CCK release which then binds to CCK-A receptors on gut vagal afferent neurons leading to reduction in hepatic glucose production via the CNS (Wang, Caspi et al. 2008). But, whether or not insoluble fiber may also act via similar indirect pathways has not been reported.

Insoluble fiber has also been implicated in improving short-term insulin sensitivity which may help regulate postprandial blood glucose. Insoluble oat fiber accelerated early phase insulin secretion and incretin gastric inhibitory polypeptide (GIP) response 30 min following consumption (Weickert, Mohlig et al. 2005). Release of insulin into the portal vein may be directly influencing hepatic glucose regulation in the short-term.

In summary insoluble fiber improves second meal glycemic control independent of the glucose response associated with its consumption. Suggested mechanisms for this short-term benefit may be through indirect stimulation of vagal afferents in the upper intestine and improved incretin release and insulin sensitivity. Insoluble fiber may reduce the risk for type 2 diabetes through long-term improvement in insulin sensitivity (Schulze, Schulz et al. 2007) but the protective effect of low fermentable, insoluble cereal fiber against diabetes remain poorly understood.

2.4. Measurement of Short-term Satiety, Food Intake and Blood Glucose

In order to assess the short-term (within a few hours) effect of macronutrients on satiety, food intake and blood glucose short-term studies are conducted.

The most widely used approach to assess short-term subjective satiety or motivation-to-eat are visual analogue scales (VAS), which record subjective sensations, such as hunger and fullness following a treatment. The original method developed by Hill and Blundell comprised of 6 questions, of which the most commonly used are: 'How strong is your desire to eat?' (very weak/very strong); 'How hungry do you feel?' (not at all hungry/as hungry as I've ever felt); 'How full do you feel?' (not at all full/as full as

I've ever felt); 'How much do you think you could eat?' (nothing at all/a large amount) (Hill and Blundell 1982) (Appendix 2).

A quantitative measure to assess satiety is made by feeding a caloric preload, or a meal. A common method of measuring post-ingestive satiety involves having participants consume either a calorie-free control treatment or a fixed amount of food or nutrient (the preload) followed by a meal a short time later (Samra and Anderson 2007). Treatment-induced satiety can be assessed by the caloric intake at the test meal after the preload compared to the control. The preload design has been used to assess the effects of different macronutrients on short-term food intake suppression, including carbohydrates (Anderson and Woodend 2003), protein (Anderson, Tecimer et al. 2004) and fat (Woodend and Anderson 2001). The satiating effects of the treatment are quantified by determining the degree by which the treatment suppressed food intake at the test meal (referred to as caloric compensation).

A primary mechanism by which macronutrients are thought to regulate satiety and food intake is through their effect on blood glucose (Anderson, Catherine et al. 2002). As a result, clinical studies use frequent or continuous monitoring of glucose concentrations following a preload or test meal. Testing has traditionally been performed using capillary blood samples taken by finger prick and read on a glucometer. Therefore, metabolic and behavior data, taken in conjunction with food intake measurements, help explain the effects of macronutrients on satiety and food intake.

CHAPTER 3
HYPOTHESES AND OBJECTIVES

3.1. Hypothesis

Insoluble fiber breakfast cereal, compared to a low fiber cereal, suppresses food intake, subjective appetite and blood glucose.

3.2. Objective

To investigate the effect of equal weight (as would approximate normal breakfast consumption) servings of high and low insoluble fiber breakfast cereals on pre- and post-meal glycemic response, satiety and food intake 3 h later and to compare the responses in men and women.

This chapter is a reproduction of the manuscript cited below with the exception that the references are integrated with those arising from the literature review. It has been reproduced here with permission from the American Society for Nutrition (Appendix 4).

Hamedani, A., T. Akhavan, R. A. Samra and G. H. Anderson (2009). "Reduced energy intake at breakfast is not compensated for at lunch if a high-insoluble-fiber cereal replaces a low-fiber cereal." Am J Clin Nutr 89(5): 1343-9.

CHAPTER 4

4. REDUCED ENERGY INTAKE AT BREAKFAST IS NOT COMPENSATED FOR AT LUNCH IF A HIGH INSOLUBLE FIBER CEREAL REPLACES A LOW FIBER CEREAL

4.1. Abstract

Background: In cohort studies, insoluble fiber has been associated with reduced risk of obesity and diabetes; however, compared to soluble fiber, its role in the regulation of short-term food intake (FI) and satiety has received little attention.

Objective: To compare the effects of a high insoluble fiber (HF) with a low fiber (LF) cereal on FI, subjective appetite (SA) and plasma glucose (PG) in healthy individuals.

Design: Males and females (n = 32) randomly consumed either 60 g of HF (26 g insoluble fiber, 120 kcal) or LF (1 g fiber, 217 kcal) breakfast cereal. Pre- and post-lunch SA and PG were measured regularly for 4 h and ad libitum FI at 3 h.

Results: Pre-lunch SA area under the curve (AUC) did not differ between the two cereals; but, when expressed as change in appetite/kcal of cereal, HF suppressed SA more than LF (-17.6 ± 1.8 *vs.* -10.0 ± 1.1 mm.min/kcal, respectively; $P < 0.01$). Lunchtime FI was not different between cereals, but cumulative energy intake (cereal + lunch) was lower after the HF than LF cereal (1330 ± 57 *vs.* 1422 ± 66 kcal, respectively; $P = 0.01$). Pre-lunch PG AUC ($P < 0.0001$) and immediate post-lunch PG ($P = 0.01$) were lower following HF.

Conclusions: A high insoluble fiber breakfast cereal contributes to a cumulative reduction in breakfast and lunch energy intake, possibly due to its high satiety value/kcal. A short-term benefit of the HF, compared to LF cereal, was lower PG before and immediately after lunch.

4.2. Introduction

Several reports support the importance of breakfast consumption in reducing risk of chronic disease and achieving healthy body weights (Albertson, Anderson et al. 2003; Timlin and Pereira 2007). Fiber-containing breakfast cereals are of particular interest because diets high in fiber have been associated with reduced weight gain (Howarth, Saltzman et al. 2001; Slavin 2005) and improved glycemic response (Chandalia, Garg et al. 2000; McIntosh and Miller 2001), thereby reducing the risk for obesity and type 2 diabetes. A pooled analysis of 18 studies reported that consumption of more than 14 g per day of dietary fiber for more than 2 days is associated with a 10% decrease in energy intake (Howarth, Saltzman et al. 2001).

The beneficial effects of dietary fiber have typically been attributed to its soluble, gel-forming components, which delay gastric emptying and reduce glycemic response to carbohydrate (Wood, Braaten et al. 1994; Brenelli, Campos et al. 1997; Dikeman and Fahey 2006). However, it is the consumption of insoluble cereal fiber and whole grains, rather than soluble fiber, that is consistently associated with reduced risk of type 2 diabetes in large cohort studies (de Munter, Hu et al. 2007; Kaline, Bornstein et al. 2007; Schulze, Schulz et al. 2007). Additionally, insoluble fiber has been associated with increased insulin sensitivity (McKeown, Meigs et al. 2002; Weickert, Mohlig et al. 2005; Weickert, Mohlig et al. 2006; Weickert and Pfeiffer 2008), reduced appetite (Slavin 2005) and modulation of hormonal (Weickert, Mohlig et al. 2005) and inflammatory responses (Ma, Griffith et al. 2006).

Yet, the underlying mechanisms for the protective effect of cereal fiber, particularly insoluble fiber, against diabetes remain poorly understood. It is generally assumed that the beneficial effects of insoluble fiber arise from chronic consumption and its subsequent fermentation in the colon (Thorburn, Muir et al. 1993; Weickert and Pfeiffer 2008). As a result, few studies have examined the short-term physiological effect of insoluble fiber in the small intestine.

Recently, we showed that isoenergetic servings of a high, compared with a low insoluble fiber breakfast cereal resulted in greater suppression of appetite and food intake at a lunch meal 75 min later and post-lunch glucose response (Samra and Anderson 2007). In these studies, serving sizes of LF and HF cereals were adjusted to provide equal

quantities of available carbohydrate and to be isoenergetic. The only difference between the two cereals was in the insoluble fiber component, composed of corn and wheat bran. We proposed that the beneficial effects of insoluble fiber were due to its physiological activity in the small intestine because an earlier report showed that breath hydrogen, a marker of colonic fermentation, was not significantly increased until 3 h after ingestion of a high insoluble fiber cereal (Levine, Tallman et al. 1989). Furthermore, in the latter study, when cereals were fed on an equal weight basis, a lower lunchtime food intake was found after cereals high in soluble and insoluble fiber (Levine, Tallman et al. 1989).

The aim of the present study was to extend these observations by comparing the effect of equal weight (as would approximate normal breakfast consumption), rather than isoenergetic servings, of high and low insoluble fiber breakfast cereals on glycemic response, satiety and food intake 3 h later and to compare the responses in men and women.

4.3. Subjects and Methods

4.3.1. Subjects

Healthy individuals aged 20-26 y with a body mass index of 20.5-24.5 kg/m^2 were recruited through advertisements posted across the University of Toronto campus. Those with diabetes, non-regular breakfast eaters, smokers, and those who were on a diet or taking medication were excluded. Those who scored ≥ 11 on a questionnaire on eating habits were identified as restrained eaters and were excluded (Appendix 1) (Herman CP 1980). Males ($n = 16$) and females ($n = 16$) from a range of ethnic backgrounds were recruited in order to extend the relevance of findings to the general population. To reduce potentially confounding factors on glucose metabolism and food intake, females were studied in the early phase of the menstrual cycle (Dalvit 1981; Diamond, Simonson et al. 1989). Those with irregular menstruation and/or taking oral contraceptive were excluded (Sheu, Hsu et al. 1994).

Every participant gave informed consent and all procedures were reviewed and approved by the Human Subjects Review Committee, Ethics Review Office of the University of Toronto (Appendix 1).

4.3.2. Study design and treatments

In a repeated-measures crossover design the treatments were randomly assigned to each subject. Equal serving sizes of two treatments were tested, including a high fiber (HF) cereal (60 g, 26 g insoluble fiber from a corn and wheat brand blend; Fiber One; General Mills Inc, Minneapolis, MN) and a low fiber (LF) cereal (60 g, 1.2 g soluble fiber, 0.3 g insoluble corn fiber; Kellogg's Corn Flakes, Kellogg Company, Battle Creek, MI). The low fiber cereal was crushed with a spoon in order to equalize its volume with that of the high fiber cereal. The cereals were served with 250 mL milk (1% milk; Sealtest, Markham, Canada) and 250 mL of water on the side, and they were prepared immediately before consumption. The treatments had equal weight and volume (Table 4.1).

4.3.3. Protocol

The present study protocol and procedures are similar to those reported in previous studies (Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Wolever, Campbell et al. 2004; Akhavan and Anderson 2007; Samra and Anderson 2007). Subjects chose a time between 8-11 a.m. at which to participate in the sessions, and arrived at the same time for the subsequent session. They arrived to the Department of Nutritional Sciences at the University of Toronto after an overnight fast (10-12 hrs). Water was allowed up to 1 hr before the start of each session. All participants were instructed to refrain from alcohol consumption and consume the same meal the night before each session, to adhere to their typical daily routine, including diet and exercise. On arrival, those participants whose answers on a questionnaire on sleep habits and stress factors indicated feelings of illness, atypical fatigue, or stress were asked to reschedule.

Upon arrival, a baseline blood sample was taken and subjects completed baseline visual analogue scale (VAS) questionnaires measuring their motivation-to-eat (Stubbs, Harbron et al. 1996; Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Samra and Anderson 2007; Samra, Wolever et al. 2007) and physical comfort (Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Samra and Anderson 2007) levels. Subjects with baseline plasma glucose > 5.6 mmol/L were rescheduled as this may have suggested recent food or drink consumption. Participants then proceeded to a taste panel

room where they consumed one of the 2 treatments (HF or LF cereal) within 10 minutes. They then returned to the study room and completed a VAS questionnaire assessing the palatability of and their satisfaction with the treatment (Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Samra, Wolever et al. 2007) as well as their motivation-to-eat and physical comfort. At 15, 30, 60, 180, 195, 210, 225, 240 and 255 min after consumption of the treatment and lunch meal (at 180 min), finger-prick blood samples were obtained using a Monojector Lancet Device (Sherwood Medical, St Louis, MO) and read on the Accu-Chek monitor (Accu-Chek Compact and Compact-Plus; Roche Diagnostics Canada, Laval, QC). Readings are reported as plasma glucose. Accuracy and variance of the monitors and test strips was monitored prior to and after each experimental session for each subject by comparison against a commercial human serum standard (6.3 mmol/L, Assayed Human Multi-Sera, Randox Laboratories Canada Ltd, Mississauga, Ontario). The motivation-to-eat VAS questionnaire was administered every 15 min during the first and last hour and every 30 min during the second and third hour. Physical comfort VAS questionnaires were also administered before and immediately after the treatment and test meal and at 60 and 225 min. Each page of the questionnaire was folded out of view after each rating. The subjects remained seated throughout the experimental sessions and were allowed to use the restroom.

At 180 min after start of the session and 170 min after cereal consumption, subjects returned to the taste panel room and were given a 500 mL of bottled spring water (Crystal Springs) and an ad-libitum pizza meal (McCain Foods Ltd. Florenceville, NB, Appendix 3) and were specifically instructed to eat until "comfortably full". Additional bottles of water were available upon request. Three varieties of small round (5-inch diameter, ≈200 kcal each) pizzas (Deluxe, Pepperoni, and 3 Cheese) were available. Participants ranked the pizzas according to their preference at screening and their same choices were provided at each session. Each tray contained two pizzas, of their first choice and one each of their second and third choice. Each pizza was divided into four quarters. All cooked pizza (8 min at 430° F, and cut in four) were weighed before serving. The pizzas were served to the subjects at 6-7 min intervals, and the previous tray removed and remaining pizza weighed, until they declined further trays (Akhavan and Anderson 2007). The energy consumed was calculated from the net weight of each

variety of pizza consumed.On termination of the lunch meal, the subjects rated its palatability and completed the post-lunch satisfaction and motivation-to-eat questionnaire. .

The motivation-to-eat, palatability and physical comfort questionnaires have previously been described by us in detail (Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Wolever, Campbell et al. 2004; Akhavan and Anderson 2007; Samra and Anderson 2007). An additional question regarding subjective satisfaction with cereals was added: How satisfied with your breakfast do you feel right now? ("not at all" to "very satisfied"). Each VAS consisted of a 100-mm line and subjects marked an "X" on the line to indicate their feelings at the given moment (Stubbs, Harbron et al. 1996). Scores were determined by measuring the distance (in mm) from the left starting point of the line to the intersection of the "X."

4.3.4. Statistical analysis

SAS version 9.1 (Statistical Analysis Systems, SAS Institute Inc., Carey, NC) was used to conduct the statistical analysis. Two-factor repeated measures ANOVA (via PROC MIXED) was used to test for the effect of treatment and time on plasma glucose concentration, average appetite score, subjective satisfaction and physical comfort questionnaires over 3 h (Samra and Anderson 2007). When an interaction was statistically significant, one-factor ANOVA (via PROC GLM) was followed by Tukey's post-hoc test to identify mean differences among treatments at each time of measurement. One-factor repeated measures ANOVA tested for the effect of treatment on lunch time FI and cumulative energy intakes, appetite, palatability, physical comfort and the corresponding net area under the curves (AUC). The net AUCs were determined by applying the trapezoid rule as previously reported (Woodend and Anderson 2001) and included areas over and under the baseline values.

Two-factor repeated measures ANOVA was also used to test the effect of treatment and sex on FI and all AUC's. Because no treatment-by-sex interactions were found, all analyses were completed by pooling the results for both sexes. Student's paired *t* test was used to compare changes in plasma glucose between pre- and post-lunch periods.

A composite score of the four motivation-to-eat and the five physical comfort VAS questions was calculated as described previously by us (Woodend and Anderson 2001; Anderson, Catherine et al. 2002; Wolever, Campbell et al. 2004; Akhavan and Anderson 2007; Samra and Anderson 2007). The average appetite and physical comfort scores were reflective of the individual scores respectively and were used here as a summary of subjective appetite and physical comfort for analyses.

Correlation analysis was conducted with the use of Pearson's correlation coefficients. All values are presented as mean ± SEM and a P-value < 0.05 was considered to indicate statistical significance.

4.4. Results

4.4.1. Energy and water intake

Treatment did not affect the amount of food consumed at lunchtime, 180 min after the cereals were provided ($P = 0.9$). However, cumulative energy intake (from breakfast and lunch) differed by cereal ($P = 0.01$) and sex ($P < 0.0001$) with no treatment-by-sex interaction ($P = 0.8$). The HF cereal led to a lower cumulative energy intake compared to the LF cereal (Table 4.2). Within each group, males had a higher cumulative intake than females (females, LF: 1191 ± 65 , HF: 1109 ± 60; males, LF: 1654 ± 80, HF: 1551 ± 58 kcal). The amount of water consumed with the test meal was not affected by treatment ($P = 0.3$).

4.4.2. Average appetite

Average appetite, reported as the change from baseline, did not differ between treatments in the pre- (0 – 180 min) and post-lunch (180 – 255 min) periods (Figure 4.1). Average appetite increased with time ($P < 0.0001$), but no time-by-treatment interaction was observed. The average appetite AUC was not different between treatments. Pre-lunch average appetite differed between the sexes ($P < 0.0001$) without treatment or treatment-by-sex interaction. Pre-lunch average appetite was lower in females than males following both cereals (females, LF: -5046 ± 899, HF: -4874 ± 628; males, LF: -1400 ±

384, HF: -1648 ± 503 mm, $P < 0.0001$). Post-lunch average appetite was not affected by sex ($P = 0.1$).

When the 4 questions in the average appetite composite score were analyzed individually, there were no differences between the cereals on ratings of "desire to eat", "hunger" or "prospective food consumption". However, individuals felt "fuller" immediately following the HF compared to the LF cereal (HF, 70.0 ± 3.3; LF, 64.3 ± 3.6 mm; $P = 0.008$). Furthermore, there was an effect of sex on the individual pre-meal AUC scores following both treatments, with males scoring higher on "huger," "desire to eat," and "prospective food consumption," and lower on "fullness," compared to females ($P < 0.01$). There were no treatment-by-sex interactions ($P > 0.4$).

When expressed as change in appetite per kcal of cereal, an effect of treatment was observed (Figure 4.2). In the pre-lunch period, change in appetite per kcal of breakfast cereal (HF, 220; LF, 317 kcal) was affected by both treatment and time with a time-by-treatment interaction ($P < 0.0001$). There were no effects of sex ($P = 0.6$) or treatment-by-sex interaction. Suppression of appetite AUC, on the basis of energy intake, was higher following HF than LF cereal (HF, -17.6 ± 1.8; LF, -10.0 ± 1.1 mm.min/kcal; $P < 0.0001$).

In the post-lunch period, change in appetite was expressed per kcal of cumulative energy intake, from breakfast and lunch (Figure 4.2). Post meal appetite suppression was affected by time and treatment ($P < 0.001$) with no effect of sex ($P = 0.4$) or interactions with time ($P = 0.9$) and sex ($P = 0.2$). Suppression of appetite AUC was not different between the treatments ($P = 0.7$).

4.4.3. Plasma glucose

Plasma glucose concentration was reported as change from baseline. In the prelunch period, plasma glucose was affected by treatment, time ($P < 0.0001$), and time-by-treatment interaction ($P < 0.01$). There was no effect of sex ($P < 0.2$) or treatment-by-sex interaction ($P < 0.2$) in this period. At 15, 30, and 60 min plasma glucose concentrations were lower after the HF than LF breakfast cereal (Figure 4.3). Plasma glucose AUC to 60 min was lowest after the HF cereal ($P < 0.0001$). Pre-meal plasma glucose was only measured from the first 16 subjects.

In the post-lunch period, plasma glucose concentrations were affected by time ($P < 0.001$) and a treatment-by-time interaction was observed ($P = 0.02$). There was no influence of treatment ($P = 0.5$), sex ($P = 0.8$) or treatment-by-sex interaction ($P = 0.4$) on the post-meal plasma glucose. However, plasma glucose concentration immediately after the ad libitum meal at 195 min was lower after the HF cereal ($P = 0.006$). This effect was not related to the pre-lunch plasma glucose AUC ($r = 0.35$, $P = 0.2$) (Figure 4.3). Furthermore, there was a direct association between the change from baseline plasma glucose at 195 min with mean lunch intake (LF, $r = 0.6$, $P = 0.0004$; HF, $r = 0.4$, $P = 0.01$) and time attributed to lunch consumption (LF, $r = 0.5$, $P = 0.002$; HF, $r = 0.6$, $P = 0.0008$).

At 225 min, 45 min following lunch, plasma glucose was higher after the HF compared with the LF cereal ($P = 0.048$). Plasma glucose AUC from 180-255 min was not different after both treatments ($P = 0.3$) and was not associated with the amount of lunch consumed. Plasma glucose concentrations after, compared to before the ad libitum meal increased after both HF and LF cereals (Student's paired t test, $P < 0.0001$).

4.4.4. Satisfaction, physical comfort and palatability

Over the study period (0-255 min), subjective ratings of satisfaction with breakfast cereals changed with time ($P < 0.0001$) without main effects of treatment ($P = 0.1$), sex ($P = 0.8$) or interactions between treatment with time or sex ($P = 0.5$) (Figure 4.4). Pre-meal (15 – 180 min) satisfaction with cereals differed by treatment ($P = 0.03$) and time ($P < 0.0001$) without an interaction ($P = 0.6$). Net AUC did not differ between the treatments; however, the total AUC was higher following HF cereal ($P = 0.049$).

Physical comfort ratings changed with time ($P = 0.002$) but no treatment ($P = 0.3$), sex ($P = 0.6$) or treatment interaction with time ($P = 0.4$) or sex ($P = 0.07$) were observed (data not shown). Subjective ratings of palatability differed between treatments ($P = 0.046$). Immediately following cereal consumption, HF was rated as more "tasty" than the LF cereal (HF, 69.5 ± 3.2 mm; LF, 60.9 ± 3.5 mm; $P = 0.046$). There were no effects of sex or treatment-by-sex interaction on ratings of cereal palatability.

4.5. Discussion

This study provides additional evidence in support of the putative health benefits associated with insoluble fiber at least, in part, as a result of its short-term effects after consumption. The high insoluble fiber compared to the low fiber cereal, resulted in higher subjective satiety per kcal, lower cumulative energy intake (from breakfast and lunch) and pre- and immediate post-meal plasma glucose concentrations.

In a previous study, we found increased satiety and lower ad libitum food intake after consumption of the same HF cereal compared with LF cereal at 75 min (Samra and Anderson 2007). This immediate effect was attributed to the insoluble fiber because the cereals were equalized for available carbohydrates and energy content. In the present study, the cumulative sum of kilocalories consumed at breakfast and lunch was lower after the high insoluble fiber cereal because equal weight servings of the HF and LF cereals led to similar food intake at lunchtime despite the lower energy content of the HF cereal (Tables 4.1 and 4.2). This observation may be explained by the rankings of subjective appetite after the two cereals.

The lack of energy compensation at lunch for the lower energy value of the HF cereal may be attributed to its high satiety value per kcal. Immediately prior to eating lunch, subjective appetite scores were similar for both cereals. Because appetite scores prior to lunch consumption is predictive of amounts eaten by adults (Samra and Anderson 2007), this may further explain the lack of caloric compensation. Similarly, in a comparison of isoenergetic breakfasts of either a high insoluble fiber breakfast cereal or bacon and eggs, subjects delayed eating again by 178 and 122 min, respectively, reflecting the reported fullness ratings for the two breakfasts. This response may however be due to the lower energy density of the breakfast cereal, but also due to physiological action of insoluble fiber in the small intestine (Holt, Delargy et al. 1999). However, although insoluble fiber has been shown to affect the secretion of several gut hormones that are satiety factors, these hormonal changes have not been linked to acute feelings of satiety (Weickert and Pfeiffer 2008).

High fiber cereal led to lower pre- and post-lunch glycemic response but this was not a factor in determining later food intake. In the pre-lunch period, plasma glucose response was lower after consumption of HF cereal, which can be directly attributed to its

lower available carbohydrate content (Table 4.1). As previously reported, the consumption of these same cereals with equal available carbohydrates, elicited similar pre-lunch plasma glucose response (Samra and Anderson 2007), consistent with previous evidence that insoluble fiber does not modify the absorption rate of available carbohydrate (Schenk, Davidson et al. 2003; Weickert, Mohlig et al. 2005). Although overall post-meal plasma glucose did not differ between cereals, HF cereal improved glucose handling immediately after lunch, which may be attributed to increased insulin sensitivity (Weickert, Mohlig et al. 2005). Insoluble fiber accelerates early phase insulin secretion and GIP response 30 min following consumption (Weickert, Mohlig et al. 2005) and may, via a delayed effect, reduce glucose response at a later meal. The increased plasma glucose in the later postprandial period following HF cereal is difficult to interpret. Future studies that measure hormones controlling plasma glucose (such as insulin and glucagon-like-peptide-1) may help elucidate this mechanism.

A direct effect of insoluble fiber on plasma glucose, independent of glucose absorption, is also suggested by the observation that increased insoluble fiber intake for three days improved whole-body glucose disposal in overweight and obese individuals, without observable effects on blood lipids, serum ghrelin, or serum adiponectin (Weickert, Mohlig et al. 2006). A possible mechanism for this effect of insoluble fiber on plasma glucose may be through stimulation of upper intestinal neurons, which activate neural input via the vagus nerve to the hypothalamus which in turn provides neural output via the hindbrain to reduce glucose production in the liver. It has been shown recently that upper intestinal lipids trigger a gut-brain-liver neural axis that inhibits hepatic glucose production, thereby reducing serum glucose in normal, but not insulin resistant rats (Wang, Caspi et al. 2008).

Although the second meal effect of indigestible carbohydrates has also been attributed to colonic fermentation (Brighenti, Benini et al. 2006), this observation may also be due to their effect in the small intestine. Breath hydrogen excretion, a measure of colonic fermentation, increases above baseline values only after 4 (Nilsson, Ostman et al. 2008) to 6 hrs (Brighenti, Benini et al. 2006) following consumption of indigestible carbohydrates, while the second meal effect of HF cereal in this study was observed at 195 min (~3 hr). Furthermore, it is uncertain if presumed improvement in glucose uptake

observed on the second day after consumption of insoluble fiber is due to colonic fermentation. While improved postprandial insulin sensitivity was attributed to higher SCFA concentrations in the portal vein, resulting from colonic fermentation of resistant starch consumed the day before (Robertson, Currie et al. 2003), improved glucose handling after 24 h intake of purified insoluble wheat or oat fiber was found to be independent of the rate of colonic fermentation (Weickert, Mohlig et al. 2005).

The effect of insoluble fiber breakfast cereal on satiety, food intake and plasma glucose and the association among these measures in men and women has not been compared. A sample size sufficient for this comparison was obtained because satiety hormones in response to fat and fiber have been found to differ between men and women (Burton-Freeman, Davis et al. 2002) and in addition to the effect of the menstrual cycle, women are more sensitive to energy deficits created by increased energy expenditure (Hagobian, Sharoff et al. 2009) and women, but not men, who eat breakfast are less likely to become overweight or obese (Song, Chun et al. 2005). In the current study, compared with men, women had a greater reduction in subjective appetite after breakfast and a lower food intake at lunch. However, the treatment effects were similar as no interactions between sex and treatment were found. Women's lower energy consumption, compared to men, is in line with their reports of stronger suppression of subjective appetite.

Although the high insoluble fiber breakfast cereal resulted in lower cumulative energy intake when breakfast and food intake 3 h later were combined, the effect on daily energy balance remains uncertain. It has been proposed that a daily energy deficit of 100 kcal per day goes unnoticed by the intake regulatory system and would be a significant factor in the prevention of weight gain or reduction of obesity (Hill, Wyatt et al. 2003). Thus, these results are encouraging and point to a requirement to examine the effect of chronic consumption of a high insoluble fiber breakfast cereal compared with a LF cereal.

In conclusion, consumption of insoluble fiber, in the form of a breakfast cereal, leads to short-term responses in both men and women that may contribute to the putative health benefits associated with fiber consumption. Associated with its high satiety value per kcal, compensation for the reduced energy content of the high insoluble fiber cereal did not occur at the lunch meal, resulting in a cumulative reduction in breakfast and lunch

energy intake. Furthermore, a high insoluble fiber cereal, compared to the LF cereal, led to lower glycemic response before and immediately after lunch.

4.6. Tables and Figures

Table 4.1. Composition of Treatments[1]

	Treatments	
Ingredients	**HF**	**LF**
Water (mL)	250	250
1% Milk (mL)	250	250
Nutrients		
Energy (kcal)	120	217
Dietary fiber (g)	28	1.5
Soluble fiber (g)	2	1.2
Insoluble fiber (g)	26	0.3
Total carbohydrates (g)	50	52
Sugars (g)	0	6
Protein (g)	4	4
Fat (g)	2	0
Weight (g)	60	60
Total volume (mL)	290	290

[1] HF, high fiber cereal, Fiber One; LF, low fiber cereal, Corn Flakes

Table 4.2. Energy intake, cumulative energy intake and water intake after breakfast cereals[1]

Breakfast Cereals	Energy Intake at Breakfast[2] (kcal)	Energy Intake at Test Meal[3] (kcal)	Cumulative Energy Intake[4] (kcal)	Water Intake at Test Meal (g)
Low Fiber	317	1105.4 ± 65.6	1422.4 ± 65.6[a]	308.5 ± 25.7
High Fiber	220	1109.9 ± 57.1	1329.9 ± 57.1[b]	295.8 ± 28.0
P		0.9	0.01	0.3

[1] All values are mean ± SEM; $n = 32$; $P < 0.05$ (paired t-test). Means in the same column with different superscript letters are significantly different.

[2] Total energy from low fiber cereal = 100 kcal from milk + 217 kcal from cereal; Total energy from high fiber cereal = 100 kcal from milk + 120 kcal from cereal

[3] Energy (kcal) consumed in a test meal 180 min after treatments

[4] Energy from cereals (kcal) + energy from test meal (kcal); Females LF: 1191 ± 65, HF: 1109 ± 60; males, LF: 1654 ± 80, HF: 1551 ± 58 ($P < 0.0001$)

Figure 4.1.

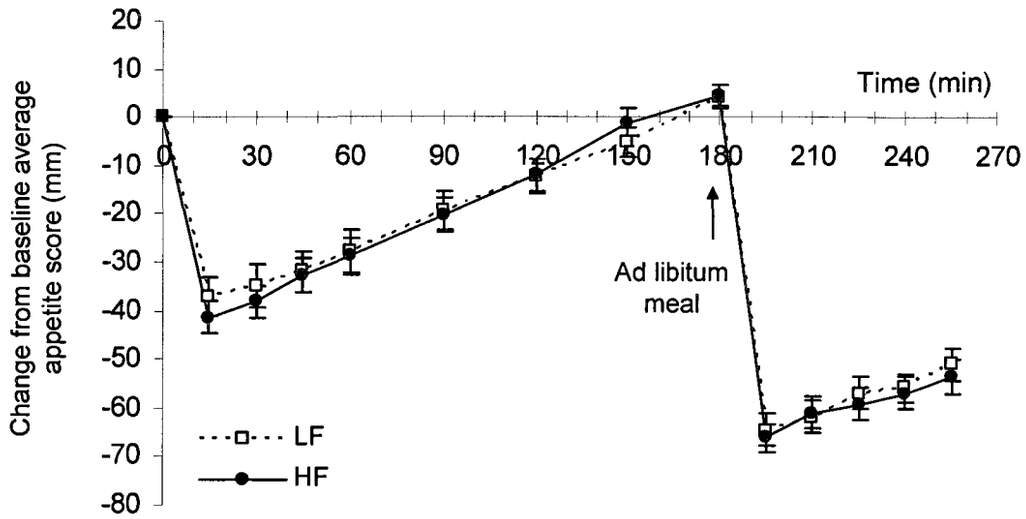

Figure 4.1. Average appetite score, change from baseline, measured by visual analog scales after consumption of low fiber (LF) and high fiber cereal (HF) before and after consumption of the ad libitum meal. Meal intake occurred at 180 min after cereal consumption. All values are mean ± SEM; $n = 32$ (2-factor ANOVA)

Pre-meal period (0-180 min): Main effect of time ($P < 0.0001$) with no main effect of treatment ($P = 0.8$) or treatment x time interaction ($P = 0.6$). Fasting absolute appetite score at 0 min for LF = 70.8 ± 2.1 and HF = 71.7 ± 1.8 mm ($P = 0.7$)

Post-meal period (180-255 min): Main effect of time ($P < 0.0001$) with no main effect of treatment ($P = 0.9$) or treatment x time interaction ($P = 0.9$). Pre-lunch absolute appetite score at 180 min for LF = 75.1 ± 2.5 and HF = 76.2 ± 2.7 mm ($P = 0.4$)

Figure 4.2.

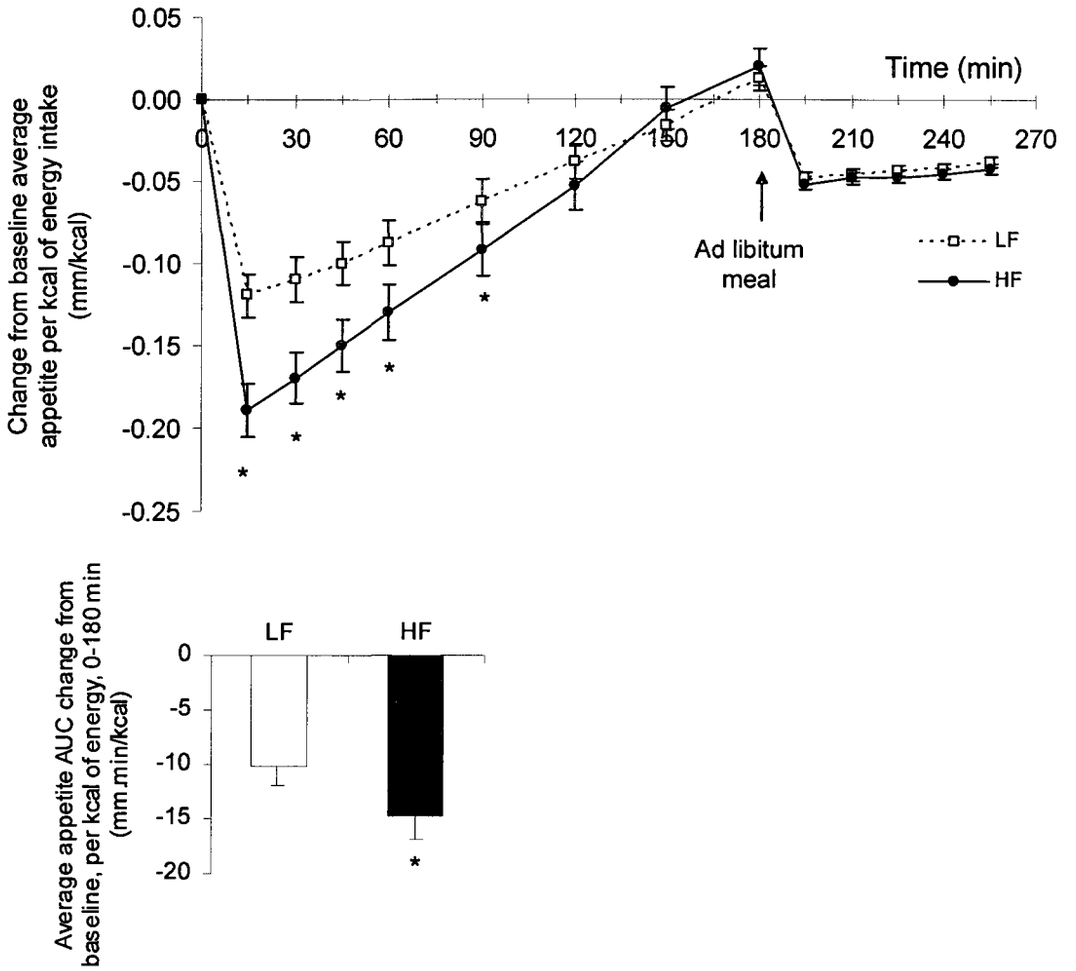

Figure 4.2. Average appetite score, as change from baseline, per kcal of energy intake and net incremental area under the curve (AUC) after consumption of low fiber (LF) and high fiber cereal (HF). All values are mean ± SEM; $n = 32$, $^*P < 0.05$ (2-factor ANOVA, Tukey's post hoc test)

Pre-meal period (0-180 min): Appetite change from baseline is expressed per kcal of energy from cereals (HF = 220, LF = 317 kcal). Main effect of time, treatment and time x treatment interaction ($P < 0.0001$).

Post-meal period (180-255 min): Average appetite change from baseline is expressed per kcal of cumulative (cereal + lunch) energy intake. Main effect of time ($P < 0.001$) and treatment ($P < 0.001$) with no interaction ($P = 0.9$).

Figure 4.3.

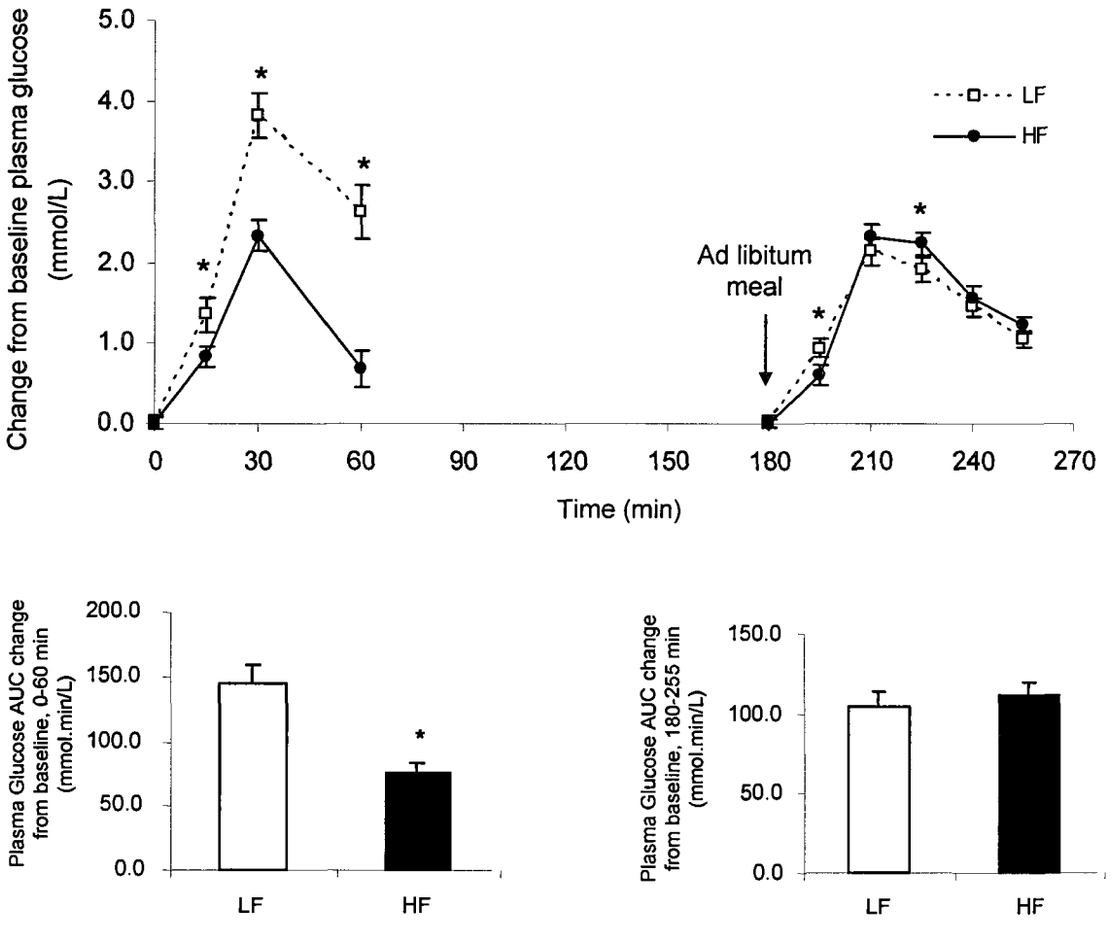

Figure 4.3. Plasma glucose concentrations, change from baseline, after consumption of low fiber (LF) and high fiber cereal (HF) and after consumption of the ad libitum meal and net incremental area under the curve (AUC). Data are presented as mean ± SEM; $n = 16$ for pre-meal and $n = 32$ for post-meal, $*P < 0.05$ (2-factor ANOVA, Tukey's post hoc test)

Pre-meal period (0-60 min): Main effect of treatment and time both ($P < 0.0001$) with treatment x time interaction ($P = 0.01$), fasting absolute plasma glucose concentration at 0 min for LF = 5.0 ± 0.1 and HF = 4.9 ± 0.1 mmol/L ($P = 0.5$).

Post-meal period (180-255 min): Main effect of time ($P < 0.0001$), treatment x time interaction ($P = 0.02$) with no effect of treatment ($P = 0.5$), pre-lunch absolute plasma glucose concentration at 180 min for LF = 4.8 ± 0.1 and HF = 4.8 ± 0.1 mmol/L ($P = 0.7$).

Figure 4.4.

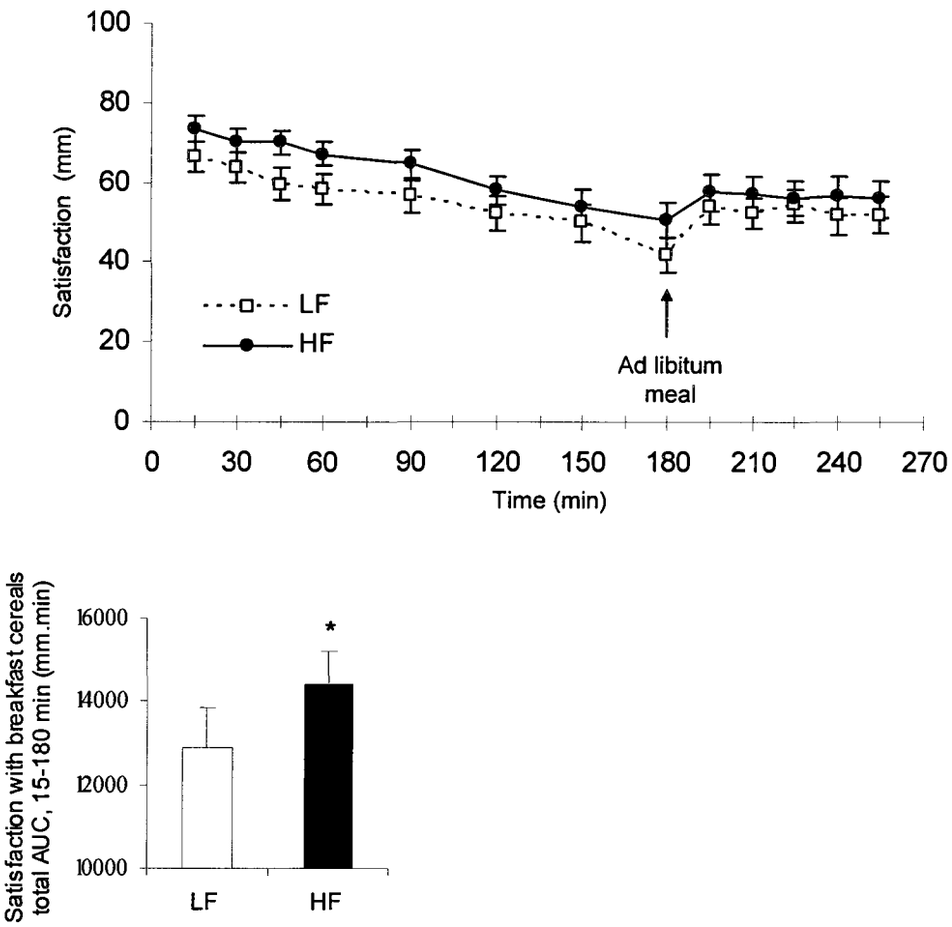

Figure 4.4. Subjective satisfaction with breakfast cereals after consumption of low fiber (LF) and high fiber cereal (HF) and pre-meal total area under the curve (AUC). All values are mean ± SEM; $n = 32$, $^*P < 0.05$ (2-factor ANOVA, Tukey's post hoc test)

Pre-meal (15-180 min): Main effect of treatment ($P = 0.03$) and time ($P < 0.0001$) with no interaction ($P = 0.6$).

Overall (15-255 min): Main effect of time ($P < 0.0001$) with no treatment ($P = 0.1$) or interaction ($P = 0.5$).

CHAPTER 5

5.1. SUMMARY OF RESULTS

In summary, equal weight servings of a high insoluble breakfast cereal compared to a low fiber cereal led to similar ad libitum food intake at lunch but lower cumulative food intake (from breakfast and lunch). Subjective appetite was similar between the cereals. When expressed per calories of the cereals, high fiber cereal suppressed subject appetite. Blood glucose response was reduced following breakfast and immediately after lunch after the high fiber cereal.

5.2. FUTURE DIRECTIONS

This study adds to the evidence that insoluble fiber provides health benefits through its physiological actions in the small intestine. However, further understanding of the short-term effects of insoluble fiber and its mechanism of action require further investigation as reflected by the following seven questions.

1. Given the importance of food matrix on physiological response, are the results of this research due to composition of the breakfast cereal?

The food matrix and/or processing of dietary fiber can alter its resulting health benefits. It was shown that oat beta-glucan added to a drink was more effective in reducing LDL cholesterol than was the same preparation administered in bread and cookies (Kerckhoffs, Hornstra et al. 2003) indicating that beta-glucan in solid form may have changed bile acid reabsorption or viscosity within the intestine, rendering it less effective.

It is uncertain whether the short-term beneficial effects of the insoluble wheat/corn blend observed in this study are contingent on the fiber being processed into cereal form or an inherent property of the fiber. To address this question, purified corn/wheat insoluble fiber (the same preparation as the cereal) in liquid form and/or as part of a solid meal can be compared to the intact breakfast cereal to determine whether the second meal glycemic response would disappear or become more pronounced when the food matrix is altered.

2. Will obese and insulin resistant subjects fail to compensate for the energy deficit in the high insoluble fiber cereal?

Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce an insulin response from fat, muscle and liver cells. Therefore, it leads to impaired glucose uptake with continuous endogenous or hepatic glucose production and increased production of NEFA from the adipose tissue (Chan, Tong et al. 2002). Insulin resistance is preceded by hyperinsulinemia and this condition has been associated with improved short-term food intake compensation 1 h after a glucose load (Samra, Wolever et al. 2007). It was suggested that improved caloric compensation in hyperinsulinemia could be attributed to increased levels of insulin and its interaction with gut hormones such as ghrelin and GLP-1.

If high levels of insulin can promote satiety it follows that insulin resistance may reduce or inhibit short-term compensation. It remains unknown whether similar short-term compensation would occur following the administration of insoluble fiber in an insulin resistant population. A study showed that the GLP-1 and GIP responses to a mixed meal were impaired and related to the degree of insulin resistance in men (Rask, Olsson et al. 2001). Similar postprandial attenuations in incretin response were observed in obese subjects (Verdich, Toubro et al. 2001).

In healthy subjects, insoluble oat fiber has been shown to accelerate short-term insulin and GIP response at 30 min (Weickert, Mohlig et al. 2005). It is unclear if insoluble fiber would help or fail to enhance insulin and incretin release in an insulin resistant state, which may directly influence compensation for the energy deficit in the fiber cereal. In order to address this question, purified insoluble corn and wheat fibers can be administered to insulin resistant individuals in a drink and solid form and incretin hormones along with glucose, insulin and glucagon can be monitored before and after an ad libitum second meal, along with caloric compensation.

3. What are the mechanisms involved in the short-term effect of insoluble fiber on food intake, appetite and blood glucose?

The measurement of satiety hormones following the consumption of insoluble fiber is needed, since the involvement of appetite hormones on the satiating effect of insoluble

fiber is unclear. Measurement of plasma incretin hormones or hormones of the enteroinsular axis e.g. GLP-1 and GIP after consumption of purified insoluble fiber is needed. Incretin release has been measured following insoluble fiber (Weickert, Mohlig et al. 2005) but whether or not it enhances satiety is unknown.

4. Is the effect of insoluble fiber on second meal glycemic regulation related to stimulation of upper intestinal neurons?

To clarify the mechanisms involved in the second meal effect of insoluble fiber the following approaches can be addressed. Purified insoluble fiber can be infused into the upper intestinal portion of normal and insulin resistant rats and through the use of ion channel blockers and vagotomy an existence of an intestine to brain to liver neurocircuitry can be elucidated (Wang, Caspi et al. 2008).

Since intestinal hormones are produced following fiber digestion, CCK and GLP-1 receptor blockers can also be used to distinguish between the direct stimulation of vagal afferents by fiber components vs. indirect stimulation by intestinal hormones.

5. Is the effect of insoluble fiber on second meal glycemic regulation also present in insulin resistant populations?

Insoluble oat fiber increases insulin sensitivity by inducing improved insulin action and not by reducing hepatic insulin clearance in overweight and obese women (Weickert, Mohlig et al. 2006). It is unclear if a similar enhanced insulin action would be evident in type 2 diabetes where tissues are insulin resistant. Using a euglycemic-hyperinsulinemic clamp, the effect of purified corn, wheat and resistant starch insoluble fibers on insulin sensitivity can be measured.

6. Does daily consumption of insoluble fiber lead to weight loss?

Because individuals did not compensate for the lower energy content of the high fiber cereal at lunch time, they consumed approximately 100 kcal less energy by mid-day. If this daily deficit of 100 kcal goes unnoticed by the intake regulatory system (Hill, Wyatt et al. 2003) then long term consumption may lead to reduction of weight gain and

obesity. Therefore, an immediate follow up study would be to determine if the energy deficit is compensated for later in the day after lunch.

7. Does insoluble fiber have different effects on the short-term food intake and satiety signals in men and women?

Previous research suggests that women's appetite and energy intake is subject to hormonal fluctuations (Davidsen, Vistisen et al. 2007) and they are more sensitive to energy deficits created by increased energy expenditure (Hagobian, Sharoff et al. 2009). Compared to men, it may be that women have unique energy regulatory mechanisms that might be particular to different macronutrient. In one study, the addition of fiber to a low-fat diet elevated postprandial CCK which was associated with reduced satiety in women but not in men (Burton-Freeman, Davis et al. 2002).

Women participants in this research reduced their subjective appetite following insoluble fiber while no change was observed in male participants. They also reduced their food intake in accordance to their higher satiety ratings. It is uncertain if insoluble fiber can prolong post-absorptive satiety signals in women and/or women have greater sensitivity to changes in post-absorptive signals. Further research is required to determine if women and men differ in metabolism of insoluble fiber, particularly in terms of gut hormone release.

5.3. CONCLUSION

In conclusion, consumption of insoluble fiber, in the form of a breakfast cereal, leads to short-term responses in both men and women that may contribute to the putative health benefits associated with fiber consumption. Associated with its high satiety value per kcal, compensation for the reduced energy content of the high insoluble fiber cereal did not occur at the lunch meal, resulting in a cumulative reduction in breakfast and lunch energy intake. Furthermore, a high insoluble fiber cereal, compared to the LF cereal, led to lower glycemic response before and immediately after lunch.

CHAPTER 6

REFERENCES

Akhavan, T. and G. H. Anderson (2007). "Effects of glucose-to-fructose ratios in solutions on subjective satiety, food intake, and satiety hormones in young men." Am J Clin Nutr **86**(5): 1354-63.

Albertson, A. M., G. H. Anderson, S. J. Crockett and M. T. Goebel (2003). "Ready-to-eat cereal consumption: its relationship with BMI and nutrient intake of children aged 4 to 12 years." J Am Diet Assoc **103**(12): 1613-9.

Anderson, G. H., A. Aziz and R. Abou Samra (2006). "Physiology of food intake regulation: interaction with dietary components." Nestle Nutr Workshop Ser Pediatr Program **58**: 133-43; discussion 143-5.

Anderson, G. H., N. L. Catherine, D. M. Woodend and T. M. Wolever (2002). "Inverse association between the effect of carbohydrates on blood glucose and subsequent short-term food intake in young men." Am J Clin Nutr **76**(5): 1023-30.

Anderson, G. H., S. N. Tecimer, D. Shah and T. A. Zafar (2004). "Protein source, quantity, and time of consumption determine the effect of proteins on short-term food intake in young men." J Nutr **134**(11): 3011-5.

Anderson, G. H. and D. Woodend (2003). "Effect of glycemic carbohydrates on short-term satiety and food intake." Nutr Rev **61**(5 Pt 2): S17-26.

Aziz, A. and G. H. Anderson (2002). "Exendin-4, a GLP-1 receptor agonist, modulates the effect of macronutrients on food intake by rats." J Nutr **132**(5): 990-5.

Badman, M. K. and J. S. Flier (2005). "The gut and energy balance: visceral allies in the obesity wars." Science **307**(5717): 1909-14.

Baggio, L. L., Q. Huang, T. J. Brown and D. J. Drucker (2004). "Oxyntomodulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure." Gastroenterology **127**(2): 546-58.

Batterham, R. L., M. A. Cohen, S. M. Ellis, et al. (2003). "Inhibition of food intake in obese subjects by peptide YY3-36." N Engl J Med **349**(10): 941-8.

Batterham, R. L., M. A. Cowley, C. J. Small, et al. (2002). "Gut hormone PYY(3-36) physiologically inhibits food intake." Nature **418**(6898): 650-4.

Bellissimo, N. and G. H. Anderson (2003). "Cholecystokinin-A receptors are involved in food intake suppression in rats after intake of all fats and carbohydrates tested." J Nutr **133**(7): 2319-25.

Blundell, J. E. and R. J. Stubbs (1999). "High and low carbohydrate and fat intakes: limits imposed by appetite and palatability and their implications for energy balance." Eur J Clin Nutr **53 Suppl 1**: S148-65.

Born, J., T. Lange, W. Kern, G. P. McGregor, U. Bickel and H. L. Fehm (2002). "Sniffing neuropeptides: a transnasal approach to the human brain." Nat Neurosci **5**(6): 514-6.

Bornet, F. R., A. E. Jardy-Gennetier, N. Jacquet and J. Stowell (2007). "Glycaemic response to foods: impact on satiety and long-term weight regulation." Appetite **49**(3): 535-53.

Brand-Miller, J., J. McMillan-Price, K. Steinbeck and I. Caterson (2008). "Carbohydrates--the good, the bad and the whole grain." Asia Pac J Clin Nutr **17 Suppl 1**: 16-9.

Brenelli, S. L., S. D. Campos and M. J. Saad (1997). "Viscosity of gums in vitro and their ability to reduce postprandial hyperglycemia in normal subjects." Braz J Med Biol Res **30**(12): 1437-40.

Brighenti, F., L. Benini, D. Del Rio, et al. (2006). "Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect." Am J Clin Nutr **83**(4): 817-22.

Brubaker, P. L. and Y. Anini (2003). "Direct and indirect mechanisms regulating secretion of glucagon-like peptide-1 and glucagon-like peptide-2." Can J Physiol Pharmacol **81**(11): 1005-12.

Burton-Freeman, B. (2000). "Dietary fiber and energy regulation." J Nutr **130**(2S Suppl): 272S-275S.

Burton-Freeman, B., P. A. Davis and B. O. Schneeman (2002). "Plasma cholecystokinin is associated with subjective measures of satiety in women." Am J Clin Nutr **76**(3): 659-67.

Burton-Freeman, B. M. and N. L. Keim (2008). "Glycemic index, cholecystokinin, satiety and disinhibition: is there an unappreciated paradox for overweight women?" Int J Obes (Lond) **32**(11): 1647-54.

Campfield, L. A., F. J. Smith, M. Rosenbaum and J. Hirsch (1996). "Human eating: evidence for a physiological basis using a modified paradigm." Neurosci Biobehav Rev **20**(1): 133-7.

Chan, J. C., P. C. Tong and J. A. Critchley (2002). "The insulin resistance syndrome: mechanisms of clustering of cardiovascular risk." Semin Vasc Med **2**(1): 45-57.

Chandalia, M., A. Garg, D. Lutjohann, K. von Bergmann, S. M. Grundy and L. J. Brinkley (2000). "Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus." N Engl J Med **342**(19): 1392-8.

Chandra, R. and R. A. Liddle (2007). "Cholecystokinin." Curr Opin Endocrinol Diabetes Obes **14**(1): 63-7.

Cummings, D. E., K. E. Foster-Schubert and J. Overduin (2005). "Ghrelin and energy balance: focus on current controversies." Curr Drug Targets **6**(2): 153-69.

Cummings, D. E. and J. Overduin (2007). "Gastrointestinal regulation of food intake." J Clin Invest **117**(1): 13-23.

Dalvit, S. P. (1981). "The effect of the menstrual cycle on patterns of food intake." Am J Clin Nutr **34**(9): 1811-5.

Davidsen, L., B. Vistisen and A. Astrup (2007). "Impact of the menstrual cycle on determinants of energy balance: a putative role in weight loss attempts." Int J Obes (Lond) **31**(12): 1777-85.

de Munter, J. S., F. B. Hu, D. Spiegelman, M. Franz and R. M. van Dam (2007). "Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review." PLoS Med **4**(8): 1385-1395.

Degen, L., S. Oesch, M. Casanova, et al. (2005). "Effect of peptide YY3-36 on food intake in humans." Gastroenterology **129**(5): 1430-6.

Di Francesco, V., M. Zamboni, A. Dioli, et al. (2005). "Delayed postprandial gastric emptying and impaired gallbladder contraction together with elevated

cholecystokinin and peptide YY serum levels sustain satiety and inhibit hunger in healthy elderly persons." J Gerontol A Biol Sci Med Sci **60**(12): 1581-5.
Diamond, M. P., D. C. Simonson and R. A. DeFronzo (1989). "Menstrual cyclicity has a profound effect on glucose homeostasis." Fertil Steril **52**(2): 204-8.
Dikeman, C. L. and G. C. Fahey (2006). "Viscosity as related to dietary fiber: a review." Crit Rev Food Sci Nutr **46**(8): 649-63.
Drazen, D. L. and S. C. Woods (2003). "Peripheral signals in the control of satiety and hunger." Curr Opin Clin Nutr Metab Care **6**(6): 621-9.
Drewnowski, A. (1998). "Energy density, palatability, and satiety: implications for weight control." Nutr Rev **56**(12): 347-53.
Drucker, D. J. (2006). "The biology of incretin hormones." Cell Metab **3**(3): 153-65.
Faas, H., A. Steingoetter, C. Feinle, et al. (2002). "Effects of meal consistency and ingested fluid volume on the intragastric distribution of a drug model in humans--a magnetic resonance imaging study." Aliment Pharmacol Ther **16**(2): 217-24.
Freeland, K. R. (2002). The acute effect of cereal fibre on food intake. Nutritional Sciences. Toronto, University of Toronto. **Masters of Science:** 142.
Freeland, K. R., G. H. Anderson and T. M. Wolever (2009). "Acute effects of dietary fibre and glycaemic carbohydrate on appetite and food intake in healthy males." Appetite **52**(1): 58-64.
Gentilcore, D., R. Chaikomin, K. L. Jones, et al. (2006). "Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes." J Clin Endocrinol Metab **91**(6): 2062-7.
Gutzwiller, J. P., B. Goke, J. Drewe, et al. (1999). "Glucagon-like peptide-1: a potent regulator of food intake in humans." Gut **44**(1): 81-6.
Hadi NA, G. A., Morton R, Horton P, Spyrou NM. (2002). "Variations in gastric emptying times of three stomach regions for simple and complex meals using scintigraphy." IEEE Trans Nucl Sci **49**: 2328-31.
Hagobian, T. A., C. G. Sharoff, B. R. Stephens, et al. (2009). "Effects of exercise on energy-regulating hormones and appetite in men and women." Am J Physiol Regul Integr Comp Physiol **296**(2): R233-42.
Hallschmid, M., C. Benedict, J. Born, H. L. Fehm and W. Kern (2004). "Manipulating central nervous mechanisms of food intake and body weight regulation by intranasal administration of neuropeptides in man." Physiol Behav **83**(1): 55-64.
Hayes, M. R., R. L. Moore, S. M. Shah and M. Covasa (2004). "5-HT3 receptors participate in CCK-induced suppression of food intake by delaying gastric emptying." Am J Physiol Regul Integr Comp Physiol **287**(4): R817-23.
Herman CP, P. J. (1980). Restrained eating. Obesity S. A. Philadelphia, Saunders: 208-225.
Hill, A. J. and J. E. Blundell (1982). "Nutrients and behaviour: research strategies for the investigation of taste characteristics, food preferences, hunger sensations and eating patterns in man." J Psychiatr Res **17**(2): 203-12.
Hill, J. O., H. R. Wyatt, G. W. Reed and J. C. Peters (2003). "Obesity and the environment: where do we go from here?" Science **299**(5608): 853-5.
Holt, S. H., H. J. Delargy, C. L. Lawton and J. E. Blundell (1999). "The effects of high-carbohydrate vs high-fat breakfasts on feelings of fullness and alertness, and subsequent food intake." Int J Food Sci Nutr **50**(1): 13-28.

Howarth, N. C., E. Saltzman and S. B. Roberts (2001). "Dietary fiber and weight regulation." Nutr Rev **59**(5): 129-39.

Institute of Medicine, Food and Nutrition Board, Panel on the definition of dietary fiber (2001). Dietary reference intakes : proposed definition of dietary fiber, National Academy Press.

Jenkins, D. J., T. M. Wolever, R. H. Taylor, et al. (1982). "Slow release dietary carbohydrate improves second meal tolerance." Am J Clin Nutr **35**(6): 1339-46.

Jimenez-Cruz, A., A. N. Gutierrez-Gonzalez and M. Bacardi-Gascon (2005). "Low glycemic index lunch on satiety in overweight and obese people with type 2 diabetes." Nutr Hosp **20**(5): 348-50.

Kaline, K., S. R. Bornstein, A. Bergmann, H. Hauner and P. E. Schwarz (2007). "The importance and effect of dietary fiber in diabetes prevention with particular consideration of whole grain products." Horm Metab Res **39**(9): 687-93.

Karhunen, L. J., K. R. Juvonen, A. Huotari, A. K. Purhonen and K. H. Herzig (2008). "Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans." Regul Pept **149**(1-3): 70-8.

Kerckhoffs, D. A., G. Hornstra and R. P. Mensink (2003). "Cholesterol-lowering effect of beta-glucan from oat bran in mildly hypercholesterolemic subjects may decrease when beta-glucan is incorporated into bread and cookies." Am J Clin Nutr **78**(2): 221-7.

Kong, F. and R. P. Singh (2008). "Disintegration of solid foods in human stomach." J Food Sci **73**(5): R67-80.

Langhans, W., F. Grossmann and N. Geary (2001). "Intrameal hepatic-portal infusion of glucose reduces spontaneous meal size in rats." Physiol Behav **73**(4): 499-507.

Lavin, J. H. and N. W. Read (1995). "The effect on hunger and satiety of slowing the absorption of glucose: relationship with gastric emptying and postprandial blood glucose and insulin responses." Appetite **25**(1): 89-96.

Levine, A. S., J. R. Tallman, M. K. Grace, S. A. Parker, C. J. Billington and M. D. Levitt (1989). "Effect of breakfast cereals on short-term food intake." Am J Clin Nutr **50**(6): 1303-7.

Lovshin, J. A. and D. J. Drucker (2009). "Incretin-based therapies for type 2 diabetes mellitus." Nat Rev Endocrinol **5**(5): 262-9.

Ma, Y., J. A. Griffith, L. Chasan-Taber, et al. (2006). "Association between dietary fiber and serum C-reactive protein." Am J Clin Nutr **83**(4): 760-6.

Mayer, J. (1955). "Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis." Ann N Y Acad Sci **63**(1): 15-43.

McIntosh, M. and C. Miller (2001). "A diet containing food rich in soluble and insoluble fiber improves glycemic control and reduces hyperlipidemia among patients with type 2 diabetes mellitus." Nutr Rev **59**(2): 52-5.

McKeown, N. M., J. B. Meigs, S. Liu, P. W. Wilson and P. F. Jacques (2002). "Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study." Am J Clin Nutr **76**(2): 390-8.

Mundinger, T. O., D. E. Cummings and G. J. Taborsky, Jr. (2006). "Direct stimulation of ghrelin secretion by sympathetic nerves." Endocrinology **147**(6): 2893-901.

Naslund, E., B. Barkeling, N. King, et al. (1999). "Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men." Int J Obes Relat Metab Disord **23**(3): 304-11.

Nilsson, A. C., E. M. Ostman, Y. Granfeldt and I. M. Bjorck (2008). "Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects." Am J Clin Nutr **87**(3): 645-54.

Nilsson, A. C., E. M. Ostman, J. J. Holst and I. M. Bjorck (2008). "Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast." J Nutr **138**(4): 732-9.

Oesch, S., C. Ruegg, B. Fischer, L. Degen and C. Beglinger (2006). "Effect of gastric distension prior to eating on food intake and feelings of satiety in humans." Physiol Behav **87**(5): 903-10.

Pal, S., S. Lim and G. Egger (2008). "The effect of a low glycaemic index breakfast on blood glucose, insulin, lipid profiles, blood pressure, body weight, body composition and satiety in obese and overweight individuals: a pilot study." J Am Coll Nutr **27**(3): 387-93.

Pasman, W. J., V. M. Blokdijk, F. M. Bertina, W. P. Hopman and H. F. Hendriks (2003). "Effect of two breakfasts, different in carbohydrate composition, on hunger and satiety and mood in healthy men." Int J Obes Relat Metab Disord **27**(6): 663-8.

Penicaud, L., C. Leloup, A. Lorsignol, T. Alquier and E. Guillod (2002). "Brain glucose sensing mechanism and glucose homeostasis." Curr Opin Clin Nutr Metab Care **5**(5): 539-43.

Plum, L., B. F. Belgardt and J. C. Bruning (2006). "Central insulin action in energy and glucose homeostasis." J Clin Invest **116**(7): 1761-6.

Plum, L., M. Schubert and J. C. Bruning (2005). "The role of insulin receptor signaling in the brain." Trends Endocrinol Metab **16**(2): 59-65.

Rask, E., T. Olsson, S. Soderberg, et al. (2001). "Impaired incretin response after a mixed meal is associated with insulin resistance in nondiabetic men." Diabetes Care **24**(9): 1640-5.

Rehfeld, J. F. (2004). "A centenary of gastrointestinal endocrinology." Horm Metab Res **36**(11-12): 735-41.

Ritter, R. C. (2004). "Gastrointestinal mechanisms of satiation for food." Physiol Behav **81**(2): 249-73.

Robertson, M. D., J. M. Currie, L. M. Morgan, D. P. Jewell and K. N. Frayn (2003). "Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects." Diabetologia **46**(5): 659-65.

Rolls, B. J. and E. A. Bell (1999). "Intake of fat and carbohydrate: role of energy density." Eur J Clin Nutr **53 Suppl 1**: S166-73.

Rolls, B. J., V. H. Castellanos, J. C. Halford, et al. (1998). "Volume of food consumed affects satiety in men." Am J Clin Nutr **67**(6): 1170-7.

Sakata, T., H. Yoshimatsu, T. Masaki and K. Tsuda (2003). "Anti-obesity actions of mastication driven by histamine neurons in rats." Exp Biol Med (Maywood) **228**(10): 1106-10.

Samra, R. A. and G. H. Anderson (2007). "Insoluble cereal fiber reduces appetite and short-term food intake and glycemic response to food consumed 75 min later by healthy men." Am J Clin Nutr **86**(4): 972-9.

Samra, R. A., T. M. Wolever and G. H. Anderson (2007). "Enhanced food intake regulatory responses after a glucose drink in hyperinsulinemic men." Int J Obes (Lond) **31**(8): 1222-31.

Schenk, S., C. J. Davidson, T. W. Zderic, L. O. Byerley and E. F. Coyle (2003). "Different glycemic indexes of breakfast cereals are not due to glucose entry into blood but to glucose removal by tissue." Am J Clin Nutr **78**(4): 742-8.

Schuit, F. C., P. Huypens, H. Heimberg and D. G. Pipeleers (2001). "Glucose sensing in pancreatic beta-cells: a model for the study of other glucose-regulated cells in gut, pancreas, and hypothalamus." Diabetes **50**(1): 1-11.

Schulze, M. B., M. Schulz, C. Heidemann, A. Schienkiewitz, K. Hoffmann and H. Boeing (2007). "Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis." Arch Intern Med **167**(9): 956-65.

Schwartz, M. W., S. C. Woods, D. Porte, Jr., R. J. Seeley and D. G. Baskin (2000). "Central nervous system control of food intake." Nature **404**(6778): 661-71.

Seimon, R. V., K. L. Feltrin, J. H. Meyer, et al. (2009). "Effects of varying combinations of intraduodenal lipid and carbohydrate on antropyloroduodenal motility, hormone release and appetite in healthy males." Am J Physiol Regul Integr Comp Physiol.

Sheu, W. H., C. H. Hsu, Y. S. Chen, C. Y. Jeng and M. M. Fuh (1994). "Prospective evaluation of insulin resistance and lipid metabolism in women receiving oral contraceptives." Clin Endocrinol (Oxf) **40**(2): 249-55.

Slavin, J. and H. Green (2007). "Dietary fibre and satiety." Nutrition Bulletin **32**(SUPPL.1): 32-42.

Slavin, J. L. (2005). "Dietary fiber and body weight." Nutrition **21**(3): 411-8.

Smith, G. P. (1998). Satiation: from gut to brain. New York, Oxford University Press.

Smith, P. M. and A. V. Ferguson (2008). "Neurophysiology of hunger and satiety." Dev Disabil Res Rev **14**(2): 96-104.

Song, W. O., O. K. Chun, S. Obayashi, S. Cho and C. E. Chung (2005). "Is consumption of breakfast associated with body mass index in US adults?" J Am Diet Assoc **105**(9): 1373-82.

StatisticsCanada (2005). Nutrition: Findings from the Canadian Community Health Survey, Statistics Canada.

Stubbs, R. J., C. G. Harbron and A. M. Prentice (1996). "Covert manipulation of the dietary fat to carbohydrate ratio of isoenergetically dense diets: effect on food intake in feeding men ad libitum." Int J Obes Relat Metab Disord **20**(7): 651-60.

Thorburn, A., J. Muir and J. Proietto (1993). "Carbohydrate fermentation decreases hepatic glucose output in healthy subjects." Metabolism **42**(6): 780-5.

Timlin, M. T. and M. A. Pereira (2007). "Breakfast frequency and quality in the etiology of adult obesity and chronic diseases." Nutr Rev **65**(6 Pt 1): 268-81.

Toft-Nielsen, M. B., S. Madsbad and J. J. Holst (1999). "Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients." Diabetes Care **22**(7): 1137-43.

Tucker, L. A. and K. S. Thomas (2009). "Increasing Total Fiber Intake Reduces Risk of Weight and Fat Gains in Women." J Nutr.

Verdich, C., A. Flint, J. P. Gutzwiller, et al. (2001). "A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans." J Clin Endocrinol Metab **86**(9): 4382-9.

Verdich, C., S. Toubro, B. Buemann, J. Lysgard Madsen, J. Juul Holst and A. Astrup (2001). "The role of postprandial releases of insulin and incretin hormones in meal-induced satiety--effect of obesity and weight reduction." Int J Obes Relat Metab Disord **25**(8): 1206-14.

Wang, P. Y., L. Caspi, C. K. Lam, et al. (2008). "Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production." Nature **452**(7190): 1012-6.

Weickert, M. O., M. Mohlig, C. Koebnick, et al. (2005). "Impact of cereal fibre on glucose-regulating factors." Diabetologia **48**(11): 2343-53.

Weickert, M. O., M. Mohlig, C. Schofl, et al. (2006). "Cereal fiber improves whole-body insulin sensitivity in overweight and obese women." Diabetes Care **29**(4): 775-80.

Weickert, M. O. and A. F. Pfeiffer (2008). "Metabolic effects of dietary fiber consumption and prevention of diabetes." J Nutr **138**(3): 439-42.

Weickert, M. O., J. Spranger, J. J. Holst, et al. (2006). "Wheat-fibre-induced changes of postprandial peptide YY and ghrelin responses are not associated with acute alterations of satiety." Br J Nutr **96**(5): 795-8.

Williams, G., C. Bing, X. J. Cai, J. A. Harrold, P. J. King and X. H. Liu (2001). "The hypothalamus and the control of energy homeostasis: different circuits, different purposes." Physiol Behav **74**(4-5): 683-701.

Willis, H. J., A. L. Eldridge, J. Beiseigel, W. Thomas and J. L. Slavin (2009). "Greater satiety response with resistant starch and corn bran in human subjects." Nutr Res **29**(2): 100-5.

Wolever, T. M., J. E. Campbell, D. Geleva and G. H. Anderson (2004). "High-fiber cereal reduces postprandial insulin responses in hyperinsulinemic but not normoinsulinemic subjects." Diabetes Care **27**(6): 1281-5.

Wolever, T. M., D. J. Jenkins, A. M. Ocana, V. A. Rao and G. R. Collier (1988). "Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response." Am J Clin Nutr **48**(4): 1041-7.

Wood, P. J., J. T. Braaten, F. W. Scott, K. D. Riedel, M. S. Wolynetz and M. W. Collins (1994). "Effect of dose and modification of viscous properties of oat gum on plasma glucose and insulin following an oral glucose load." Br J Nutr **72**(5): 731-43.

Woodend, D. M. and G. H. Anderson (2001). "Effect of sucrose and safflower oil preloads on short term appetite and food intake of young men." Appetite **37**(3): 185-95.

Woods, S. C. and D. A. D'Alessio (2008). "Central control of body weight and appetite." J Clin Endocrinol Metab **93**(11 Suppl 1): S37-50.

Woods, S. C., T. A. Lutz, N. Geary and W. Langhans (2006). "Pancreatic signals controlling food intake; insulin, glucagon and amylin." Philos Trans R Soc Lond B Biol Sci **361**(1471): 1219-35.

Woods, S. C. and R. J. Seeley (2001). "Insulin as an adiposity signal." Int J Obes Relat Metab Disord **25 Suppl 5**: S35-8.

Wren, A. M., L. J. Seal, M. A. Cohen, et al. (2001). "Ghrelin enhances appetite and increases food intake in humans." J Clin Endocrinol Metab **86**(12): 5992.

Yeomans, M. R., J. E. Blundell and M. Leshem (2004). "Palatability: response to nutritional need or need-free stimulation of appetite?" Br J Nutr **92 Suppl 1**: S3-14.

Zhou, J., R. J. Martin, R. T. Tulley, et al. (2008). "Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents." Am J Physiol Endocrinol Metab **295**(5): E1160-6.

CHAPTER 8
APPENDICES

7.1. Appendix 1. Screening Questionnaires

Recruitment Screening Questionnaires

- Sleep Habits Questionnaire
- Eating Habits Questionnaire
- Food Acceptability List

Consent Form

Recruitment Screening Questionnaires

NAME: _____ AGE: _____

ADDRESS: _____

POSTAL CODE: _____

PHONE # : (____)_____ EMAIL:_____

HEIGHT: _____ WEIGHT: _____ BMI: _____

PARTICIPATION IN ATHLETICS/ EXERCISE:

ACTIVITY _____
HOW OFTEN? _____
HOW LONG? (HRS)_____

DO YOU USUALLY EAT BREAKFAST? YES _____ NO _____

IF YES, WHAT DO YOU USUALLY EAT FOR BREAKFAST?

_____

Women

Are you taking any birth control? _____

In the past 3 months, estimate how many menstrual cycles you have had? _____

Currently, for how many days do you typically experience menstrual flow each cycle?
___1 day ___2 days ___3 days ___4 days ___5 days ___ more than 5 days

Have you ever taken oral contraceptives OR other hormones for amenorrhea (absence of menses)?_____

If yes, when did you stop taking oral contraceptives or other hormones?_____

When was the FIRST day of your most recent period _____

How sure are you about this date? _____

Health Status

Do you have diabetes? YES _____ NO _____

Do you have any other major disease? YES _____ NO _____

If YES, please specify

_____

Are you taking any medications? YES _____ NO _____

Do you have reactions to any foods? YES _____ NO _____

If YES, please specify

_____

Are you on a special diet? YES _____ NO _____

If YES, please specify

_____

Have you recently lost or gained weight? YES _____ NO _____

If YES, please specify

_____

Do you smoke? YES _____ NO _____

How many Alcoholic Beverages do you consume per day? _____ per week? _____

Sleep Habits Questionnaire

1. What time do you normally wake up in the morning?

   during the week:_____

   weekends/ days off:_____

   Explain if needed: _____

2. What time do you normally get out of bed? (if different from the above)

   during the week:_____

   weekends/ days off:_____

3. What is the earliest you would get up in a normal week?

during the week:_____

weekends/ days off:_____

4. What is the latest you would get up in a normal week?

during the week:_____

weekends/ days off:_____

5. How long do you wait to eat after rising

during the week:_____

weekends/ days off:_____

Eating Habit Questionnaire

Choose the appropriate answer to best describe your personal situation.

1. How often are you dieting?

Never____ rarely _____ sometimes _____ often _____ always _____

2. What is the maximum amount of weight (in pounds) that you have ever lost within one month?

1-4 _____ 5-9_____ 10-14 _____ 15-19 _____ 20+ _____

3. What is your maximum weight gain within one week?

0-1 _____ 1.1-2 _____ 2.1-3 _____ 3.1-5 _____ 5.1+ _____

4. In a typical week, how much does your weigh fluctuate?

0-1 _____ 1.1-2 _____ 2.1-3 _____ 3.1-5 _____ 5.1+ _____

5. Would a weight fluctuation of 5lbs affect the way you live your life?

Not At all _____ slightly _____ moderately _____ very much _____

6. Do you eat sensibly in front of others and splurge alone?

Never _____ rarely _____ often _____ always _____

7. Do you give too much time and thought to food?

Never _____ rarely _____ often _____ always _____

8. Do you have feelings of guilt after overeating?

Never _____ rarely _____ often _____ always _____

9. How conscious are you of what you are eating?

Not at all _____ slightly _____ moderately _____ extremely _____

10. How many pounds over your desirable weight were you at your maximum weight?

0-1 _____ 2-5 _____ 6-10 _____ 11-20 _____ 21+ _____

Food Acceptability

Please indicate with a rating between 1 and 10 how much you enjoy the following foods (1= not at all, 10 = very much) and how often you eat them (never, daily, weekly, monthly)

		Enjoyment?	How often?
1	Pasta	_____	_____
2	Rice	_____	_____
3	Potatoes (Mashed, roasted)	_____	_____
4	French fries	_____	_____
5	Pizza	_____	_____
6	Bread, Bagels, Dinner rolls	_____	_____
7	Sandwiches, Subs	_____	_____
8	Cereal	_____	_____
9	Cake, Donuts, Cookies	_____	_____
10	Beans in Tomato sauce	_____	_____

Will you be able to eat beans in tomato sauce
YES _____ NO _____

At the end of each of the sessions, you will be provided with pizza. In order to provide you with a meal that you will enjoy, we ask that you rank the following pizzas according to your personal preferences (i.e. **1, 2, 3**) in the space provided. If you do **NOT** like a particular type of pizza, then do not rank it, but place an "**X**" in the space provided.

Pepperoni (Cheese, pepperoni) _____

Deluxe (cheese, pepperoni, peppers, mushrooms) _____

Three Cheese (mozzarella, cheddar, parmesan) _____

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title: The Role of Insoluble Fiber in Food Intake Regulation, Appetite and Blood Glucose in Healthy Young Adults

Investigators: Dr. G. Harvey Anderson, PhD
Department of Nutritional Sciences, University of Toronto
Phone: (416) 978-1832
Email: harvey.anderson@utoronto.ca

Dr. Bohdan Luhovyy, PhD
Department of Nutritional Sciences, University of Toronto
Phone: (416) 978-6894
Email: bohdan.luhovyy@utoronto.ca

Ati Hamedani, MSc student
Department of Nutritional Sciences, University of Toronto
Phone: (416) 978-6894
Email: ati.hamedani@utoronto.ca

Funding Source:

Funding for this project is provided by the Bell Institute of Health and Nutrition, General Mills Inc. The project has been peer-reviewed and approved for its scientific merits.

Background and Purpose of Research:

In 2004, almost 60% of adult Canadians were overweight or obese. This is a serious health concern as it is associated with many common health risks, including increased blood sugar, blood lipids and blood pressure. Obesity, the most common nutrition problem in Canada, can in many cases be treated through changes in our diet (what we eat and/or how much we eat). It is important to find food-based solutions for the prevention and treatment of overweight and obesity. The results from this study will be used to better understand the health benefits of eating high fibre cereals for breakfast. The purpose of this study is to determine the effect of high fibre cereal eaten at breakfast on food intake, fatigue (tiredness), satiety and blood glucose response.

This study will have overall 40 participants.

Invitation to Participate:

You are being invited to participate in this study. If you chose to participate, you will be asked to meet with us on two or five occasions approximately 3 days apart. On the first of the five sessions, you will consume water as breakfast. For the additional four sessions, you will be asked to consume cereal. For the two sessions, you will be asked to consume

breakfast cereal only. Your appetite and blood glucose after consuming the cereal/water will be measured. Each session will require up to 4 ½ hours of your time.

Eligibility:

To participate in this study you must be healthy and between the ages of 18 and 35. You must be a nonsmoker and you cannot be taking any medications. The study will take place in the Department of Nutritional Sciences, Rm 305, 334, 331 and 331A, FitzGerald Building, 150 College Street, Toronto, ON.

Procedure:

To determine eligibility, you will be asked to fill out questionnaires, which ask questions about your age, exercise and eating habits, health status, whether or not you smoke or take any medications. You height and weight will be measured.

If you are eligible, you will be asked to fill out questionnaires about the foods you like. You will be scheduled to meet with us for five sessions over a three week period.

You will be asked to arrive at the FitzGerald Building between 8:00 and 11:00 am. You will be asked to stick to your normal routine, including exercise and to eat a similar meal the night before each session. You will be asked not to eat for 12 hours before arriving at the Fitzgerald Building. You can drink water until one hour before meeting with us.

During each session, you will give blood samples and complete questionnaires at the times outlined in the table below. You will be given a pizza meal 3 hours after consuming the treatment food. Up to a maximum of eleven times during each session, for a total of 55 times over the whole study, you will be asked to provide a small sample of blood by finger prick. Blood will be sampled at baseline (before breakfast) and 15, 30, 60, 120, 180, 195, 210, 255, 240 and 255 minutes after breakfast. You will be asked to complete visual analog scale (VAS) questionnaires measuring your appetite, physical comfort and energy/fatigue as well as the palatability of the treatment and pizza throughout the study sessions. The detailed procedure for each session is summarized below in an example of a session schedule for a 9.00 a.m. arrival.

Time and Activity Schedule for Each Session

Time	Activity
9:00	Arrive in the lab
9:05	Fill in Sleep, Stress, and VAS questionnaires and take baseline blood sample
9:10 – 9:20	Consumption of breakfast (10 minutes)
9:20-12:20	Blood sampling and VAS questionnaires at 15, 30, 60, 120 and 180 minutes
12:20-12:35	Pizza served and eaten at 180 minutes
12:35-1:35	Blood sampling and VAS questionnaires at 195, 210, 255, 240 and

	255 minutes

VAS: Visual analogue scale

Voluntary Participation and Early Withdrawal:

It is hoped that you will complete all five sessions. However, you may choose to withdraw at any time without prejudice.

Early Termination:

Not applicable

Risks:

All of the foods and beverages (water) that you will be asked to consume are prepared hygienically in the kitchen or purchased from the grocery store and present no risk.

After the overnight fast you may feel faint or dizzy.

Great care will be taken when obtaining your finger prick blood samples. The investigator will assist you. You will put a new lancet into the finger prick gun before taking each blood sample and then discard it immediately in the safety container. You will swab your finger with alcohol before and after each finger prick. Some discomfort will be felt as a result of a sharp momentary pain caused as the needle penetrates the skin. However, because the lancet needle is very small the pain felt is usually less than you might experience from skin puncture during vaccination or if a blood sample is taken by a needle inserted in a vein. During the study, there is minimal risk of infection or bruising from 55 finger pricks. However, 11 finger pricks per session my result in some discomfort.

You may experience flatulence and feelings of gastrointestinal discomfort (bloating) from the cereal because some are high in fibre. This seldom happens and there is no health risk associated with these effects.

Benefits:

You will not benefit directly from participating in this study. You will be shown your blood glucose results and if they are abnormal you will be notified and will be advised to seek advice from your doctor. The foods and drinks (water) will be provided free of charge.

Confidentiality and Privacy:

Confidentiality will be respected and no information that discloses your identity will be released or published without your permission unless required by law. Your name, medical history and signed consent form will be kept in a locked filing cabinet in the

investigator's office. Your results will not be kept in the same place as your name. Your results will be recorded on data sheets and in computer records that have an ID number for identification, but will not include your name. Your results, identified only by an ID number, will be made available to the study sponsor if requested. Only study investigators will have access to your individual results.

Publication of Results:

The results of the study may be presented at scientific meetings and published in a scientific journal. If the results are published, only the means and not individual values of the subjects will be reported.

Possible Commercialization of Findings:

Results from this study may lead to commercialization of a product, new product formulation, changes in the labeling of a product and/or changes in the marketing of a product; you will not share in any way from the possible gains or profits made by commercial application of findings.

Alternative Treatment/ Therapy:

Not applicable.

New Findings:

If anything is identified during the course of this research which may influence your decision to continue, you will be notified.

Compensation:

You will be paid $42 per session. You will also be reimbursed $6 per session for travel expenses (bus, subway). If you withdraw from the study before completion or are asked to withdraw, you will be paid on the basis of the sessions already completed.

Injury Statement:

Not applicable

Rights of Subjects:

Before agreeing to participate in this research study, it is important that you read and understand your role as described here in this study information sheet and consent form. You waive no legal rights by participating in this study. If you have any questions or concerns about your rights as a participant you can contact the Ethics Review Office at ethics.review@utoronto.ca or call 416-946-3273.

If you have any questions after you read through this information please do not hesitate to ask the investigators for further clarification.

Dissemination of findings:

A summary of results will be made available to you to pick up after the study is done, should you wish to receive it.

Copy of informed consent for participant:

You are given a copy of this informed consent to keep for your own records.

Consent:

I acknowledge that the research study described above has been explained to me and that my questions have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw. As well, the potential risks, harms and discomforts have been explained to me. I understand that I will receive compensation for my time spent participating in the study.

As part of my participation in this study, I understand that I may come in contact with certain confidential information. I agree to keep the confidentiality of such, if any, information unless it is necessary to disclose it to my health care provider(s), or to my legal representative(s).

I hereby agree and give my authorized consent to participate in the study and to treat confidential information in a restrictive manner as described above. I have been given a copy of the consent form to keep for my own records.

Participant Name	Signature	Date
Witness Name	Signature	Date
Investigator Name	Signature	Date

7.2. Appendix 2. Study Day Questionnaires

Sleep Habits and Stress Factors Questionnaire

VAS – Motivation to Eat

VAS – Physical Comfort

VAS – Palatability

VAS – Energy, Fatigue and Satisfaction

Blood Glucose Chart

SLEEP HABITS AND STRESS FACTORS QUESTIONNAIRE

ID: _____
SESSION & TREATMENT: _____
DATE: _____

1. Did you have a normal night's sleep last night?

Yes_____ No_____

2. How many hours of sleep did you have?
_____

3. What time did you go to bed last night?
_____

4. What time did you wake up this morning? _____

5. Recount your activities since waking:

Time	Activity
_____	_____
_____	_____
_____	_____

6. Are you experiencing any feelings of illness or discomfort, other than those from hunger?

Today: Yes ____ No_____
Past 24 hours: Yes ____ No_____

If yes, please describe briefly:
_____

_____

7. What did you have for dinner last night?

_____

8. Females only: on which day of your menstruation are you?

_____

Describe if you've taken any pain medication: _____

9. Are you under any unusual stress? Exams/reports/work deadlines, personal, etc.

Today: Yes ____ No_____
Past 24 hours: Yes ____ No_____

If yes, please describe briefly:
_____

_____

10. Have you been involved in any physical activity within the past 24 hours that is unusual to your normal routine?

Yes_____ No_____

If yes, please describe briefly:
_____

_____

11. Have you had anything to eat or drink, other than water, for the past 11-12 hours?

Yes_____ No_____

If yes, please describe briefly:
_____

Time =

Visual Analogue Scale
Motivation to Eat

DATE: _____

NAME: _____

These questions relate to your "motivation to eat" at this time. Please rate yourself by placing a small "**x**" across the horizontal line at the point which best reflects your present feelings, for example: |——X——|

1. How strong is your desire to eat?

Very weak |———|———|———|———|———|———|———|———|———|———| Very strong

2. How hungry do you feel?

Not hungry at all |———|———|———|———|———|———|———|———|———|———| As hungry as I have ever felt

3. How full do you feel?

Not full at all |———|———|———|———|———|———|———|———|———|———| Very full

4. How much food do you think you could eat?

Nothing at all |———|———|———|———|———|———|———|———|———|———| A large amount

Time =

Visual Analogue Scale
Physical Comfort

DATE: _____
NAME: _____

These questions relate to your physical comfort at this time. Please rate yourself by placing a small "**x**" across the horizontal line at the point which best reflects your present feelings, for example: |——X——|

1. Do you feel nauseous?

Not at all |———|———|———|———|———|———|———|———|———|———| Very much

2. Does your stomach hurt?

Not at all |———|———|———|———|———|———|———|———|———|———| Very much

3. How well do you feel?

Not well at all |———|———|———|———|———|———|———|———|———|———| Very well

4. Do you feel like you have gas?

Not at all |———|———|———|———|———|———|———|———|———|———| Very much

5. Do you feel like you have diarrhea?

Not at all |———|———|———|———|———|———|———|———|———|———| Very much

Time =

Visual Analogue Scale
Energy and Fatigue

DATE: _____
NAME: _____

These questions relate to your energy level and fatigue at this time. Please rate yourself by placing a small "**x**" across the horizontal line at the point which best reflects your present feelings, for example: |-----X-----|

1. How energetic do you feel right now?

Not at all |---|---|---|---|---|---|---|---|---|---| Very energetic

2. How tired do you feel right now?

Not at all |---|---|---|---|---|---|---|---|---|---| Very tired

3. How satisfied with your breakfast do you feel right now?

Not at all |---|---|---|---|---|---|---|---|---|---| Very satisfied

After Breakfast and Lunch

Visual Analogue Scale
Palatability

DATE: _____
NAME: _____

These questions relate to the palatability of the food you just consumed. Please rate the pleasantness of the beverage by placing a small "**x**" across the horizontal line at the point which best reflects your present feelings, for example: |——X——|

1. How pleasant have you found the food?

Not at all pleasant |—|—|—|—|—|—|—|—|—|—| Very pleasant

2. How tasty have you found the food?

Not at all tasty |—|—|—|—|—|—|—|—|—|—| Very tasty

3. How did you like the texture of the food?

Not at all |—|—|—|—|—|—|—|—|—|—| Very much

Blood glucose measurement

ID: _____

Date and Time: _____

Session: _____

Treatment: _____

Monitor: _____

Time	Blood Glucose Reading (mmol/L)
Baseline	
180 min (3 hrs)	
Please record the current time on the timer after lunch completion	
210 min (3 hrs and 30 min)	
225 min (3 hrs and 45 min)	
240 min (4 hrs)	
255 min (4 hrs and 15 min)	

7.3. Appendix 3. Pizza Composition[1]

Nutritional Information per 100g	Pepperoni	Deluxe	Three Cheese
Energy (kcal)	205.9	222.2	239.6
Protein (g)	10.8	11.1	12.5
Carbohydrate (g)	26.5	27.8	31.2
Total Fat (g)	5.9	7.4	7.3

[1] McCain Foods: Deep and Delicious, 5" Pizza

7.4. Appendix 4. Permission for Reproduction of Manuscript

Sarah McCormack

From: ati.hamedani@utoronto.ca
Sent: Monday, May 11, 2009 1:34 PM
To: Sarah McCormack
Subject: Permission

Dear Ms. McCormack,

I am writing to ask permission to publish my recent AJCN article as a chapter within my Masters thesis.

The article is in the current May issue of AJCN and I have cited it below:

Carbohydrate metabolism and diabetes

Atyeh Hamedani, Tina Akhavan, Rania Abou Samra, and G Harvey Anderson Reduced energy intake at breakfast is not compensated for at lunch if a high-insoluble-fiber cereal replaces a low-fiber cereal Am J Clin Nutr 2009 89: 1343-1349. First published online April 1, 2009; doi:10.3945/ajcn.2008.26827

Thanks for the information you provided me over the phone. I would prefer an electronic copy because I need to submit my thesis electronically.

Thank you very much,
Atyeh Hamedani

Permission granted by the copyright owner provided complete credit is given to the original source: Am. J. Clin. Nutr. (year;volume:page range), American Society for Nutrition.
As a courtesy, please notify the author of your intent to use this material.

Per: Sarah L McCormack
American Society for Nutrition