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**The Effects of Food Deprivation and Weight Loss on Food Hedonics
and the Relative-Reinforcing Value of Food**

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**The Effects of Food Deprivation and Weight Loss on Food Hedonics and the Relative-
Reinforcing Value of Food**

by

JAMEASON CAMERON

B.Sc., University of Ottawa, 2006

THESIS

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ABSTRACT

Food is a primary reinforcer. There is strong evidence that when animals are chronically deprived of calories, the reward of a food stimulus becomes more salient. Recently leptin has been implicated in food reward. Typically the rewarding value of food is separated into the “liking” or pleasure/palatability component generated by the stimulus, and into the “wanting” or appetitive/incentive component. The goal of this current study was examine whether plasma leptin concentrations were related to food hedonics and food reinforcement in humans and to investigate the effect of food deprivation on these variables. Fourteen apparently healthy obese adults (n= 9 women and 5 men; age =33.5± 7.8) with BMI (kg/m²) between 30-45 were subjected to 8 weeks of caloric deprivation (-700kcal/day). Plasma leptin (ELISA), body weight and composition (DEXA), food reinforcement and food hedonics were measured pre- and post-intervention. Post weight loss palatability was rated significantly higher for the food reinforcers than that measured pre weight loss (p<0.01). No significant effect of the chronic food deprivation was noted for the reinforcing value of food. A significant negative correlation was observed between changes in palatability and those in body weight expressed as relative changes (r = -.62; p<0.05). No significant correlations were noted between changes in leptin and those in palatability or the reinforcing value of food. However, in a subgroup that lost the greatest percent of initial body weight (7-8%), food was more reinforcing post intervention (p<0.05). These findings demonstrate that chronic caloric deprivation can increase the subjectively rated palatability of preferred food items. The subgroup may be a caveat illustrating that a greater relative weight loss can lead to food becoming more rewarding.

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**PART ONE: EMPIRICAL, THEORETICAL
AND METHODOLOGICAL CONSIDERATIONS**

CHAPTER I

INTRODUCTION

There is strong evidence that metabolic status drives several fundamental animal behaviours, including appetitive and affective responses to feeding, drinking and drug taking (Friedman 1992; Kelley and Berridge 2002; Kennedy 1972; Mayer 1955; Steller 1954). Food deprivation, or a significant loss of body weight due to nutritional restriction over time, alters not only short-term peripheral cues of meal initiation/termination (le Roux and Bloom 2005; Otto et al. 2001; Ravussin et al. 2001; Stock et al. 2005) but also long-term central cues reflecting global adiposity status (Considine et al. 1996; Rosenbaum et al. 2002; Schwartz et al. 2000; Woods et al. 1979; Woods et al. 1998). Current dogma in studies of feeding behaviour agree that each of these peptide messengers acts in concert to defend a steady body weight by forming a body-brain link at the level of the central nervous system (CNS), where cascading interconnections influence feeding via neuropeptides and biogenic aminergic neurotransmitters (Horvath et al. 2004; Jobst et al. 2004; Schwartz et al. 2000; Smith and Gibbs 1981; Woods et al. 2001; Yeomans and Gray 2002).

Since its discovery in 1994 (Zhang et al. 1994), the major role of the OB protein leptin in this brain-gut axis is theorized as being deep-rooted in the signalling of body energy reserves. Indeed, leptin signalling is integral to normal feeding; when leptin is simply not produced (*ob/ob* mouse) or whether there is a defective leptin receptor (*db/db* and *fa/fa* mice) hereditary obesity ensues as marked by chronic hyperphagia. Leptin is produced by adipose tissue, and via saturable transport (Caro et al. 1996; Pelleymounter et al. 1995; Schwartz et al. 1996a) is able to cross the blood-brain barrier (BBB) to effect

several physiological processes, including feeding (Ahima et al. 1996), thermogenesis (Friedman and Halaas 1998; Pellemounter et al. 1995) and food reward (Figlewicz 2003; Fulton et al. 2000). The long form of the leptin receptor (LRb) is thought to be the main receptor—in the large cytokine class I family of leptin receptors—to be involved in leptin's role in energy balance in the CNS (Flier 2004). Furthermore, the high expression of LRb in the hypothalamus, and especially the anorexigenic/orexigenic neuropeptide seesaw in the arcuate nucleus of the hypothalamus, has been the primary focus of much of the current research on leptin and feeding. Though this arcuate-focused model has subjugated much of the attention for brain mechanisms of feeding—and the leptin modulation thereof—there is now evidence that leptin is involved in two reward signalling pathways, the mesoaccumbens dopamine pathway (Fulton et al. 2006a; Hommel et al. 2006; Jo et al. 2005) and endocannabinoid signalling in perifornical lateral hypothalamic neurons (Jo et al. 2005).

As with animal models, human obesity is associated with high plasma leptin concentrations (Considine et al. 1996) and both short (Doucet et al. 2004; Weigle et al. 1997)- and long-term (Keim et al. 1998; Nicklas et al. 1997; Wisse et al. 1999) caloric deprivation result in significant decreases in plasma leptin levels. There also exists a strong correlation between cerebrospinal fluid (CSF) and serum leptin, but obese persons have been shown to demonstrate CSF/serum ratios of leptin to be about 1/5 of the levels observed in thin persons (Caro et al. 1996; Schwartz et al. 1996a). More pointedly, due to the hyperbolic nature of the resulting CSF to serum leptin curve, the term “leptin resistance” has been employed to describe the saturable component of leptin transport and the unresponsiveness of the obese population to the chronic elevations in plasma

leptin concentrations (Banks 2001). Thus it is feasible that weight-loss paradigms discuss behavioural changes that accompany a significant and chronic loss in body weight by examining the effects of decreased serum leptin levels, and the resulting decrease in leptin signalling at the level of the brain.

As if to promote the survival of species, it appears that in times of significant food deprivation (dieting, famine, etc.) that animals—including humans—sense food as being more palatable and more reinforcing (Berridge 1991; Cabanac and Lafrance 1990; Carr 1996; Epstein et al. 2003; Raynor and Epstein 2003). Much still remains to be learned of these observed behavioural resultants of the proposed “thrifty genotype”(Neel 1962), but one can be certain that are yet to be discovered roles for leptin in the most integrated of all behaviours, feeding. At a glance the concept of food deprivation causing eventual increases in food consumption and food liking may seem axiomatic, but in actuality this conceptualization is both incomplete and inconclusive. What must be acknowledged is that feeding behaviour is not merely analogous to refilling a fuel tank in response to a dipping needle; it is a heterogenous compilation of multiple environmental and cognitive influences.

Rationale

Over the short period of time leading to the new millennium there is evidence of obesity expanding to epidemic proportions, where numbers as high as 23% of adults in Canada are obese, i.e., BMI>30 kg/m² (CCHS 2004). Current estimates attribute between 25-40% of the pathophysiology of obesity to genetic markers (Ravussin and Bouchard 2000), leaving a rather large percentage of the population at a predisposition to the fractions of gene products contributing to energy imbalances, i.e., environment-specific

phenotypic expressions. Note, however, if food is limited and energy expenditure is high, the weight of those subpopulations displaying genetic susceptibility will scarcely differ from subpopulations demonstrating normal genetic backgrounds (Hofbauer 2002).

In dieting, energy intake is limited and overall caloric intake is reduced. As a consequence this restriction can eventually lead to aberrant overeating, thereby defeating the original purpose of this implementation (Franklin et al. 1948). Though it is tempting to attribute such lapses in the control of feeding behaviour to compensatory endocrine-based changes in short- (ghrelin, glucagon-like peptide 1, ect.) or long-term (leptin and insulin) feeding signals, it is imperative that the neuronal-based pathways of reward and the impact of psychological mediators are also considered. Thus, there is a need to determine why, given the fact that even genetically predisposed persons should be able to sustain healthy weights, that there is little overall success in maintaining levels of reduced weight (Wadden et al. 1989). Taken together, the successful maintenance of weight-reduction can be prescribed with an understanding of the short-and long-term signals involved in feeding, and in appreciating the role of food restriction with regards to food reinforcement.

There is also limited information regarding weight-loss and its effects on subjective hedonic ratings (how much food is “liked”) or its effects on objective testing of reinforcement and the work done to obtain a desired food item when given alternative choices. Taking into account that in most situations of dietary restriction there is a need to limit foods high in fat and so called empty calories (candy, chocolate, etc.), it would seem to logically follow, then, that such instances would provide an increased wanting of the limited object—analogue to more salient craving. Further complicating the matter is the

observance that obese persons have been shown to find high-fat foods more reinforcing than low-fat foods (Epstein et al. 1991). Since dieting has emerged at the forefront as the means to lose weight, then there is a need to study how physiological and psychological sensations of hunger and satiety are affected by the internal state of the body.

A promising path has been paved with respect to adiposity signals and their possible role in mediating food reward. When leptin is administered intraventricularly, it attenuates the rewarding impact of food-restriction-sensitive stimulation (Fulton et al. 2000), where animals significantly decrease rates of brain stimulation reward. It may be that long-term adiposity signals like leptin actively signal reward pathways of current body reserves, thereby intrinsically making food more attractive—more rewarding—when a significant loss in weight is detected.

Objectives

The objectives were to quantitatively assess the following: 1) whether or not subjective ratings of hedonics—specifically palatability—change with caloric deprivation and weight loss, 2) whether or not selected food items increase in their reinforcing value—that is, the amount of effort allotted to performing simple button-presses to work for food items—following an 8-week period of weight loss, and 3) whether or not changes in individual leptin profiles have the potential to positively increase the reinforcing value or palatability of the selected food items after the weight loss period.

Hypotheses

It was hypothesized that: 1) participants would subjectively rate their liking for the selected food as being more pleasurable upon following the deprivation regimen (e.g. the intensity of palatability will increase, as measured by visual analogue scales), 2)

following the period of energy deprivation (vs. baseline controls) the reinforcing effect of snack foods would be more salient, i.e, a significant increase in the reinforcing value of snack food as measured by the willingness of the participant to work more at button-presses in order to receive more snack food points, and the final hypotheses, 3) the primed decrease in leptin levels would influence the potential increase in the reinforcing value of selected food items and food palatability following the weight loss period.

Definitions

For the purpose of this proposed study caloric restriction will be defined as a 700 kcal decrease in daily food consumption. This time period of decreased calories—the so-called deprivation stage—will be implemented for a period of 8 weeks and adherence will be monitored by weekly communication between participant and dietician. Important is the fact that it is not the specific amount of weight loss, or even the methods employed to lose the weight loss that is of specific relevance to the main questions, but it is merely important that there is a significant decrease in body fat reserves from baseline to post-treatment.

The diet composition will reflect the Dietary References Intakes for Canadians. Carbohydrate will have to account for 55% of calories, preferably from low glycemic index foods with high fiber content ranging from 25 to 35 grams per day. Fat will have to provide 27% of calories and saturated fat, trans fat and cholesterol will have to be as low as possible. Finally, 18% of calories will have to come from protein.

Work will be defined as the willingness to perform simple button-presses on a computer joystick. It is to be understood that the work performed during the computer

task is internal work, thereby indicating insignificant changes in energy expenditure as a result of performing this task.

Reinforcement will be defined as the willingness of the participant to perform simple button presses to obtain selected food items that were previously determined to be a preferred treat (such as chips or chocolate); this will be contrasted with the choice of selecting alternative reinforcers (fruit or vegetable) under changing schedule demands (Bulik and Brinded 1994). Reinforcement and reward are to be understood as being analogous when presented in the text. In order to measure the reinforcing value of food, the behavioural economics paradigm will be used to assess a potential increase (or decrease) in participant motivation to perform a series of computer tasks (simple button presses) so as to receive specific quantities of either of the reinforcing items of attraction—"healthy food" or so-called "snack food".

The behavioural economics paradigm is defined as a tool that can be used to objectively measure factors that influence choice. This is accomplished by providing access to alternative activities or reinforcers that have pre-determined constraints with respect to accessibility, and subsequently examining the response patterns. Of note is the potential of this paradigm to differentiate the relative-reinforcing value of 2 or more stimuli: by comparing the response patterns to obtain the alternatives, the relative reinforcing value is obtained. Simply put, the reinforcing value of snack food, or any commodity, can be viewed as a function of the constraints on the snack food (cost, response demands) and the other reinforcers available (see Appendix J).

Assumptions, Limitations and Delimitations

It is assumed that the principles of the behavioural economics paradigm are validated as viewed by several other authors (Bulik and Brinded 1994; Bulik et al. 1998; Raynor and Epstein 2003).

Presumably, all participants will answer honestly to all pre-screening questions and follow the requested protocol, i.e., adhere to the caloric restriction, fast during the designated hours, fully consume the standardized breakfast and/or snacks which will have been provided to them, and answer truthfully to all questionnaires that are presented to them.

It must also be assumed that the methods in which data will be collected are accurate and have been validated. This includes the accuracy in which visual analogue scales assess hunger, appetite, fullness, and palatability; also included is the computer program measuring the accuracy of responding to the button press; finally, all anthropometric and food-weighing tools are also assumed to be accurate.

As suggested in the assumptions, due to the fact that much of the dietary reporting is accrued via personal testimonial documented by the participants, there exists the persistent subjective self-reporting limitation observed in most studies involving feeding behaviour (i.e. significant amounts of data are collected beyond the confinement of the laboratory).

As might be expected, utilizing a convenience sample as opposed to a random sample of participants significantly diminishes the population validity; hence, the generalizability of the results will be applicable to a smaller range of individuals.

Significance of the Study

In the past half-century the prevalence of obesity has grown to epidemic proportions (Jequier 2002; Zigman and Elmquist 2003). Particularly, people are consuming ever-greater amounts of energy dense fatty foods and display highly irregular patterns of eating (Raynor and Epstein 2003); consequently, billions of dollars are spent each year trying to control energy intake with fad-diets and pharmaceuticals.

If it can be shown that food restriction (as typically seen in dieting) positively affects the relative-reinforcing value of food—thereby making preferred food items more attractive—this study would afford evidence for the need to focus on motivational factors that influence eating. When the goal is to reduce body weight and combat problems of eating pathology, potential findings may demonstrate a need to focus on alternatives to feeding, thereby combating antecedent precursors to a lapse in control.

CHAPTER II

REVIEW OF LITERATURE

This review of the literature pertinent to the submitted thesis has been revised from its original version, and has been submitted to and accepted for publication in the *Journal of Applied Physiology Nutrition and Metabolism*. The review article, entitled Getting to the bottom of feeding behaviour: Who's on top? (Cameron & Doucet, in press), has therefore been included here in its final form as accepted by the journal's referees because it remains, in the thesis author's opinion, a most appropriate review of literature for the submitted thesis.

**Getting to the bottom of feeding behaviour:
Who's on top?**

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Running head: A commentary on top-down vs. bottom-up modulators of feeding

ABSTRACT

Traditionally there has been a tendency to focus on peripheral “bottom-up” feeding-related signals and their resulting downstream actions on hypothalamic centers when studying the feeding behaviour of animals. A problem with this hierarchal approach emerges especially with respect to acquiring a human model attempting to explain what is ultimately a distributed control of feeding and energy balance. This review is focused on illuminating the means by which we have come to understand the complexities of feeding, and takes the next step in an attempt to propose a distinctive “top-down” view of this composite behaviour. It is argued that in evolutionary terms humans demonstrate behaviours unique to all species as represented by an expanded forebrain and the resultant psychological “non-homeostatic” mediators of feeding. Emphasis is placed on a distributionist “two-tier” model arguing that traditional short-term (CCK, ghrelin, peptide YY, GLP-1, etc.) and long-term (insulin and leptin) feeding signals may be actively suppressed by the nested nuclei and projections of cortical-limbic brain areas. It is the motivational state (dependent on depletion-repletion signals of hunger and satiety) that in turn has the capability to modulate how rewarding or how palatable a food item may be perceived; thus, both sides of the two-tiered model of feeding behaviour are complimentary and interdependent all at once. In the end, this paper is both commentary and critical review. This synthesis purports that as evolutionary processes spawned consciousness, the psychology of hunger and the present-day discordance of gene-environment interaction forever changed the feeding behaviour of Homo sapiens.

Key Words: appetite, gut peptides, arcuate nucleus, limbic system, food reward, hedonics

Introduction

It was approximately 2.5 million years ago when a unique species of hominid first began to delineate from the line of primitive apes, where such evidence is attributed to the finding of prehistoric tools alongside the remains of our “Stone Age” *Homo habilis* counterparts (Leakey et al. 1964). In such a period in the evolution of humankind (*Homo sapiens*), the development of a more sophisticated forebrain was arguably one of the primary physiological mechanisms that concluded, what Darwin would later coin in the mid 1800s, the process of natural selection in the origin of our species. In the early days of evolution, it will be later argued that the brainstem and other “primitive” brain regions harboured the primary circuitry involved in the interpretive processes guiding feeding behaviour, but in the present environment of plenty, it will be further disputed that it is the higher cortical association areas and pathways of reward which dominate in what is essentially a conscious choice—goal directed behaviour. Irrespective of the timeframe of our species (*Homo*), a constant truism is that our survival is dependent on the innate drive to find food. In the days of the hunters and gatherers, however, the environment was more restrictive, where food came at the cost of vigorous physical activity and the energy cost of survival undoubtedly moulded neuronal circuits into those that would best produce behaviours of energy conservation. It would not be illogical to postulate that at these relatively early points in evolution that it would have been beneficial to have central brain signals that facilitated both the ingestion of larger meals and the deposition of such meals into fat stores. In fact, such lines of thought have led some scientists to the “thrifty gene” hypothesis (Neel 1962), or the idea that in a restrictive environment it would have been beneficial to have genes that both facilitated the procurement of food (i.e. genes

producing musculoskeletal adaptations) and allowed the ingestion of larger volumes of such food (i.e. genes promoting metabolic and behavioural adaptations).

Whether it be a thrifty gene or not, in the present day environment of readily available and easily accessible food, humankind is now in the midst of a new challenge, a sort of reverse famine, where in the affluent countries there is no longer a need for such stringent protective mechanisms to thwart starvation. Evidence for this new physiological challenge can be explicated in simple terms by the fact that merely three decades ago obesity was considered a rare disease (Loos and Rankinen 2005) and over the short period of time leading to the new millennium there is evidence of obesity expanding to epidemic proportions, where numbers as high as 23% of Canadian adults are considered obese (i.e. BMI > 30 kg/m²) (CCHS 2004). The existence of such a sudden and drastic increase in overall body energy reserves cannot be attributed to an abrupt evolutionary change via natural selection; it would seem then, that changes must be attributed to an obesogenic environment, not to changes in the human genome. Notwithstanding the lifestyle issues concerning the change in environment, the neural mechanisms that once proved advantageous to our ancestors in situations of “feast or famine” have arguably turned to facilitate the prevalence of obesity.

Thus, if genes and gene products ultimately mediate all bodily functions, and given the clues offered by monogenic forms of obesity, the question that arises is whether it will be possible to utilize clinical cases in order to come to successful experimental conclusions regarding the pathophysiology of obesity and related feeding behaviours. In order to arrive at any form of agreement on whether such a feat is possible, one must first

begin by describing how such results could be quantified, i.e., How do we measure the physiological processes involved in the control of food intake?

Motivation and Behaviour

In order to examine the controlling elements of food intake one must begin by defining these actions in terms of behaviours. Human behaviour can be broadly defined as any action (or reaction) contingent to the given environmental pressures. Ultimately, as *Homo sapiens* have evolved across many millions of years via natural selection, our behaviours can be said to be a consequence of both inherited elements and learned responses. Barring any philosophical debate, one must concede that physical processes govern each of our actions. Accordingly, a conscious decision to reach for a potato chip (the behaviour) is made by a biological system (the brain), which is then reduced to its chemical components, which are then further reduced to physical matter. Given this heuristic framework our present actions are the result of the culmination of past events; further, behaviour is the end product of the interaction of the nervous and endocrine systems, and by convention, as these systems increase in complexity so does the capacity to learn new responses. In fact, from the appearance of *Homo erectus* 1.7 million years ago to the present day, the brain size has nearly doubled—from 800ml to 1500ml—without any considerable change in body size (Halloway 1996). Such is the hypothesis that it is during this relatively short period of time that we developed feeding behaviours unique to any other species of animal. In developing an expanded forebrain, we acquired brain structures which not only made possible a level of cognition yet to be seen on Earth, but also increased the need to procure vitally important glucose to fuel a larger brain mass.

Another property that is inherently germane to feeding behaviour is the concept of motivation. Motivation adds direction to behaviour in that processes such as psychological wanting and physiologic needing are translated between mind and body; it is motivation that turns potentially dull stimuli into salient objects of attraction. Hunger and thirst are examples of motivation based on physiologic needs, so strong are these motivations that they are projected as drives leading to operant behaviours—the respective seeking and consuming of food or water. It is motivation that leads us to seek specific objects at specific times; that is to say, motivation can be explicit: we seek food when hungry, water when thirsty, sex when aroused, sleep when tired, etc. Note that a physiological drive state is not equivalent to motivation, but any deprivation may in fact add increased (or decreased) incentive value to the goal object. In fact, the importance of drive state with respect to incentive (“wanting”)-and hedonic (“liking”)-value will be discussed further in the later portion of this review. Integral to this line of argument, it is believed that emergent psychological factors accompanying the expanded forebrain are extensively involved in the amplified incidences of obesity and feeding disorders in modern societies; furthermore, the importance of neurotransmitters in reward and the role of the mid-brain will be argued as being the primary avenues for explaining the etiology of obesity. Indeed, the idea of neural correlates of motivated behaviour is not a new concept, as Steller (1954) proposed over a half century ago a model of central motive states. His theory was founded on the view that a particular motivation state (such as hunger) is dependent on the combination of arousing excitatory and satiating inhibitory signals processed in the brain; unmistakably, this theory has guided much of the scientific understanding of feeding behaviour.

1. Feeding Circuits as Neural Networks

Ingestive (consummatory) behaviour can be, on a rather simplistic level, explained by a series of parallel interactions of the CNS. Specifically, food-related signals from the physical act of consuming foodstuffs—including the afferent trigeminal stimulation (via the 5th cranial nerve) that transmits fat and oil mouth-feel or the afferent vagal stimulation (via the 10th cranial nerve) that transmits feelings of distension—are processed within the nuclei of the hindbrain. In a reciprocal manner, these stimuli are transmitted and converge to the real-time processing stations of the hypothalamus and associated cortico-limbic structures, eventually leading to goal-directed motor programs that either facilitate or impede the further ingestion of food. In such a model there is an information relay between peripheral autonomic and endocrine organs that act as input systems to the aforementioned oversimplified integrator. More than this, via a vast array of sensory systems the CNS simultaneously processes internal stimuli as a function of the input from external stimuli. For the purpose of this review, external stimuli will be divided into visual and olfactory cues, whereas, internal stimuli are dependent on cues generated in localized areas of the alimentary canal, and are further divided into pregastric (cephalic/chemosensing), gastric (distension/mechnosensing), and postgastric (luminal absorptive mechanisms and coupled release of endocrine hormones/metabolites) stimuli (Berthoud 2000). Internal stimuli can again be divided into information that is processed either as a direct consequence of hormonal/metabolic stimulation from gastrointestinal (GI) processing, or into information that is said to be indirect, such as the affective limbic representation of the emotional glee when anticipating a succulent delicacy. On a theoretical level, stimuli that are said to be interpreted directly will be

viewed in light of drive theory, which focuses on measurable physiological consequences to food-related stimuli. In contrast, the processing of indirect information will be viewed along the lines of a hedonistic theory of feeding, where the same stimuli are evaluated in less discernable pathways via the affective representations of rewards and punishers in the higher brain centers.

The following subsections will be devoted to explanations pertaining to the evolution of an interpretation of feeding behaviour, beginning with the role of the hypothalamus as a sensor of the central circuits and eventually discussing its connectivity with other organs. Nonetheless, a more detailed explanation of the interaction between the indirect vs. direct pathways of feeding—and the consequent surfacing of maladaptive behaviour—will be highlighted as the thesis in the final sections of this review.

1.1 Hypothalamic Circuits and Homeostasis

Walter Canon first proposed the idea of homeostasis in 1925 (Cannon 1939), and since then, it has been well established that the consistency of the internal environment is the result of a system of control mechanisms. Specifically, the hypothalamus (HYP) houses the key neuronal mechanisms for the control of this “internal milieu”. The HYP acts on three major systems: the autonomic nervous system (ANS), the endocrine system, and the nested brain areas involved in motivational systems. As previously noted, when considering feeding behaviour—on a very primitive level—this response can be deconstructed and thought of as motivational states (or drives) that are based upon bodily needs. More than this, whether it is to quench one’s thirst or to eat in response to severe hunger pangs, these drives (whether learned or not) often force the body into action.

The HYP houses several nuclei that are now known to be involved in food intake, but none have received as much attention of late as noted with the arcuate nucleus (ARC). Although the scope of this review limits the room for expansion of all known areas of interest, hypothalamic nuclei that are especially pertinent to feeding are the lateral hypothalamic area, the paraventricular nucleus, the ventromedial nucleus, and the dorsomedial nucleus (Hillebrand et al. 2002). At the cap of the brainstem, the HYP forms the inferolateral walls of the 3rd ventricle, which is continuous with the cerebrospinal fluid. At the base of the HYP lies the ARC (known as the infundibular nucleus in Man), a unique hypothalamic area in that it is overlapped by a structure known as the median eminence. It is here where the normally selective blood brain barrier is absent, allowing ARC axon terminals (but not the cell bodies) to be in direct contact with the blood stream (Hillebrand et al. 2002). Due to the fact that there is direct contact with peripheral satiety signals, the neurons that have terminal axons at the blood brain barrier have been said to be first order neurons.

The ARC coexpresses a high density of two subsets of neurons that either produces orexigenic (anabolic) peptides or anorexigenic (catabolic) peptides. The former consists of a family of neuropeptide Y (NPY) receptors, agouti-gene-related protein (AgRP), the opioids, and a few other amino acids. The latter consists of the pro-opiomelanocortins (POMC) and cocaine-and amphetamine-regulated transcript (CART). It is well accepted that these two dichotomous groups of neuropeptides are actively involved in the central interpretation of feeding signals (Cone 1999; Cowley 2003; Cowley and Grove 2004; Hofbauer 2002; Horvath et al. 2003; Schwartz et al. 2000; Zheng et al. 2003); currently the focus on these messengers is also pointing to not only

the hypothalamic involvement of signalling, but also to levels of the hindbrain and in the neocortex. Notably, from the ARC these first order neurons project to second order neurons in the lateral hypothalamic area, the paraventricular nucleus, the ventromedial nucleus, and the dorsomedial nucleus. Furthermore, amongst other connections, these first and second order neurons project to the dorsal vagal complex in the caudal brainstem, which includes both the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus nerve (Hillebrand et al. 2002).

To summarize, food-related signals from the environment converge with many areas of the brain, often in a reciprocal manner, to influence the cognitive and autonomic representations of the ingested items. More than this, regardless of the means by which the CNS receives feedback regarding feeding status, it is clear that peripheral signals act at very specific central areas of the brain, particularly the ARC. The following sections will explain how the aforementioned feeding circuits are influenced by what are designated as long-term and short-term feeding signals.

2. Regulation of Body Weight

Despite the large day-to-day fluctuations noticed in most patterns of human eating, the body demonstrates a rigorous ability to maintain weight (whether lean or obese), especially adipose tissue mass, within very small deviations. Because the variation of carbohydrate and protein stores in adults is relatively small it has been proposed that body weight regulation is achieved mainly as a function of adipose tissue mass (Jequier and Tappy 1999). Further supporting this view, as there are concomitant adaptive changes in thermogenesis (Doucet et al. 2003; Doucet et al. 2001) and in appetitive behaviour (Doucet et al. 2000a) that accompany a change in adipose tissue

mass, there appears to be adiposity signals communicating the level of fat storage to the brain (Cummings and Foster 2003). A half century ago this was proposed as the lipostatic model (Kennedy 1953) of energy homeostasis, which in fact has guided the central dogma of the current view of body weight regulation.

The present understanding of body weight regulation encompasses the view that there are long-term signals that are activated 1) in proportion to adipose tissue stores, and 2) in conjunction with the amount of energy consumed over an extended period of time, and that there are short-term signals that are activated 1) in proportion to the volume and composition of nutrients ingested, and 2) in conjunction with GIT hormones acting both in paracrine and endocrine pathways (Havel 2001). It is important to note that these short- and long-term signals operate through distinct pathways, but nonetheless act in concert, with increasing amounts of evidence showing collateral input amongst the central ARC circuits.

2.1. Long-Term Feeding Signals

Continuous with the attributes required to be considered a long-term signal, there are several other criterion which also must be met for a peripheral body fat signal to be considered a modulator in body weight regulation. These signals must have access to the appropriate areas of the nervous system and interact with neurons known to regulate food intake, the exogenous administration of the compound should alter body-fat mass, and blockade of the signal should inhibit such changes (Cummings and Foster 2003). To date there are two hormones that fit the above criteria as peripheral adiposity signals, leptin and insulin (see Table 1). As body weight increases (particularly fat mass) there are increases in basal and postprandial levels of insulin; in view of that, there is a significant

positive correlation between body fat content and overall insulin secretion (Havel et al. 1999). Interestingly, changes with insulin profiles can be seen as reflecting specific depots with regard to ones adiposity profile. According to correlation analyses, insulin is released in proportion to visceral fat (Wajchenberg 2000), placing its role less as a total body fat marker and more of an indicator of the distribution of body fat per se.

In accordance with its adipostat role, leptin is secreted by adipocytes and circulates in the plasma at concentrations proportional to fat mass (Murphy and Bloom 2004). Further, in times of energy deprivation it is noticed that leptin levels are markedly reduced (Considine et al. 1996)—even before any changes in body fat can be observed (Doucet et al. 2004). Also, in times of energy deprivation leptin transport across the blood brain barrier is reduced while its transport is increased in times of refeeding (Kastin and Pan 2000). Although a preponderance of obese humans demonstrate relatively elevated levels of leptin, in itself suggesting a resistance to this adiposity signal, when offered recombinant leptin therapy there is modest evidence of improvements in weight loss (Heymsfield et al. 1999). However, the decrease in REE that occurs with weight loss has been shown to be associated to the decrease in leptin levels (Doucet et al. 2000b), and this situation can be reversed with recombinant leptin therapy (Rosenbaum et al. 2002). As such, there is strong evidence to suggest that leptin plays a major role in body weight regulation and further studies into this relatively new hormone are sure to offer integral clues into the functioning of adiposity stores and long-term feeding signals.

2.2. Short-Term Feeding Signals

Due to the fact that food intake is episodic (i.e. not continuous) (Smith 2000), short-term feeding signals are said to be those resulting from, or prior to, a single bout of

eating, or meal. There is extensive evidence that these meal-to-meal signals act directly on the ARC and either directly or indirectly on the dorsal vagal complex to modulate food intake. Overall, there are two main points to consider regarding the short-term regulation of energy intake: meal size and frequency. What is noticed in free-feeding laboratory conditions is that meal size predicts the interval until the following eating episode (de Castro 2000). This so-called “postprandial relationship” suggests that meal size is determined via adjustments to the interval to the next meal—not dependent on mere convenience or learned time cues. Conversely, and in most cases in the Western world, meals are scheduled at specific times of the day, resulting in no significant relationship between meal size and inter-meal interval (de Castro 2000). In this so-called “preprandial relationship” there is however a relationship between the inter-meal interval and meal size; what can be extrapolated is that under daily circumstances, the episodic quality of feeding is lead by associative learning. However, as the period of deprivation (inter-meal) increases there is a shift to respond in a drive-induced manner.

Recalling that internal stimuli can be divided into phases of pregastric, gastric, and postgastric events, and further recalling that there are direct stimuli (i.e. hormonal and metabolic signals) acting on these sensory systems, it would seem that deciphering a schema to manage postprandial satiety could potentially control the deprivation signal so as to minimize macronutrient intake on a continuous basis. Thus, the major question guiding this review shifts from the emphasis of how to measure the control of food intake, to a new question: How can we modulate the control of food intake? In order to answer such a question there is need to return to the orexigenic and anorexigenic pathways located in the ARC and the associated “cross-talk” with the brainstem;

explicitly, the roles of specific molecules or peptides that are released in response to nutrient ingestion—collectively known as satiety signals—are summarized in Table 1.

It is important to note that in a bout of eating there are distinct sets of controls that mediate both the start and end of meals. To date the only messenger offering ample evidence to be considered a meal initiation (orexigenic) signal is ghrelin. From the point that ghrelin was identified (Kojima et al. 1999), much of the support for its role in meal initiation comes from observations that circulating levels increase rather abruptly before, and rapidly decreases after each meal (Cummings et al. 2001). Although it will be later argued that for healthy individuals feeding cues and meal initiation are based more on indirect sensory information, i.e., cognitive and social factors, there is, however, evidence that the termination of meals may be influenced by direct sensory information from peripheral satiety signals. Once an individual responds to feelings of hunger and finally reaches the consummatory stage by beginning to ingest food, orosensory information from the pregastric phase becomes the first line of stimulatory input onto the preabsorptive stimuli of the GIT (Blundell and Finlayson 2004), thereby providing positive feedback for eating. These feed-forward signals send an afferent signal to the hindbrain with the overall message to keep feeding. Negative feedback signals begin early in the gastric phase with distension signals communicated via afferent vagal stimulation. As the eating episode continues and the ingesta move through to the postgastric phase, macronutrients are reduced to their sugar, fatty acid, and amino acid residues.

Table 1. Long- and short-term hormone messengers that modulate feeding.

SIGNALS	PRIMARY SITE OF SECRETION	DOWNSTREAM ACTION				EXOGENOUS ADMINISTRATION		VAGOTOMY & EXOGENOUS ADMIN. OF SHORT-TERM SIGNAL	REFERENCES
		NEUROPEPTIDE	FOOD INTAKE	CENTRAL DOSE	PERIPHERAL DOSE				
LONG TERM									
<i>Insulin</i>	Pancreatic β cells	STM POMC INH NPY	↓	↓	↓	—	(Benoit et al. 2002; Schwartz et al. 1991; VanderWeele et al. 1979)		
<i>Leptin</i>	Adipocytes	STM POMC INH NPY/AgRP	↓	↓	↓	—	(Farooqi et al. 1999; Friedman and Halaas 1998; Murphy and Bloom 2004; Sahu 2003; Schwartz et al. 1996b)		
SHORT TERM									
<i>CCK</i>	Endocrine I cells of the proximal SI	STM CCK ₈	↓	↓	↓	↓ or Abolished	(Gibbs et al. 1973; Hillebrand et al. 2002; Rodriguez-Sinovas et al. 1997; Smith et al. 1981)		
<i>PYY</i> ₃₋₃₆	Enteroendocrine L cells of the ileum & colon	INH NPY (Y2)	↓	↓	↑ or ↓	↓ or Abolished	(Abbott et al. 2005; Batterham et al. 2003; Batterham et al. 2002; Coll et al. 2004; Druce et al. 2004; Hagan 2002; Keil et al. 2000; Okada et al. 1993; Onaga et al. 2002)		
<i>Ghrelin</i>	Oxyntic X/A cells of the stomach	STM NPY/AgRP INH POMC	↑	↑	↓	↑ or Abolished	(Cowley et al. 2003; Horvath et al. 2001; Kamegai et al. 2001; Kojima et al. 1999; le Roux et al. 2005; Tschop et al. 2000; Wren et al. 2001a; Wren et al. 2001b)		

The table is to be read with the understanding that each of the parameters is responding to *increases* in each of the respective short- and long-term signals. STM=stimulates; INH=inhibits; CCK=cholecystokinin; PYY₃₋₃₆=peptide YY₃₋₃₆; POMC=proopiomelanocortin; NPY=neuropeptide Y; AgRP=agouti-related protein. ↑ or ↓, increases and decreases food intake, respectively.

Depending on the stimuli produced by the digested food and their products, the short-term regulation of feeding will be influenced by two mechanisms of volume detection: 1) digestion products that stimulate GIT chemoreceptors, with the eventual release of blood borne peripheral satiety signals (CCK, peptide YY, GLP—1, apolipoprotein A-IV, etc.), and 2) GIT mechanoreceptors in the stomach and in the proximal small intestine that respond to ingesta, with the eventual communication to the hindbrain and sometimes further downstream to the HYP and other forebrain areas. This method of volume detection has been proposed to offer the negative feedback signals for eating (Smith 2000). In consequence, with this model, as the bout of eating ensues there comes a point where the positive orosensory feedback will equal the negative volume detection feedback, causing consumption to decrease. As a result, as the postgastric stimuli increase and the rate of eating slows, the negative feedback signals begin to dominate until satiation ends the episode of feeding. It is this idea of privation and subsequent compensation—in other terms “bottom up” control—that has dominated much of the theory on food intake and feeding behaviour, especially in recent years.

3. Feeding Behaviour: “Top-Down” or “Bottom-Up”?

Up to this point this review has focused on a metabolically driven homeostatic-like model of food intake control. In such a model the phylogenetically older brain areas, i.e., the vagus, brainstem and HYP are viewed as direct pathways—a series of communication highways—that are proposed to be bottom-up mediators of feeding behaviour. The “cross-talk” between these distinct pathways influences the neural circuits involved in the short-and long-term feedback signals implicated in the initiation of behavioural, autonomic, and endocrine responses (Berthoud 2004). This representation,

however, is incomplete and only characterizes one limb of an integrated two-tier system guiding feeding behaviour. The other limb of this model consists of so-called indirect pathways; here, indirect can be considered as a “top down” pattern of organization involved in the interpretation of external and internal stimuli (see Fig 1).

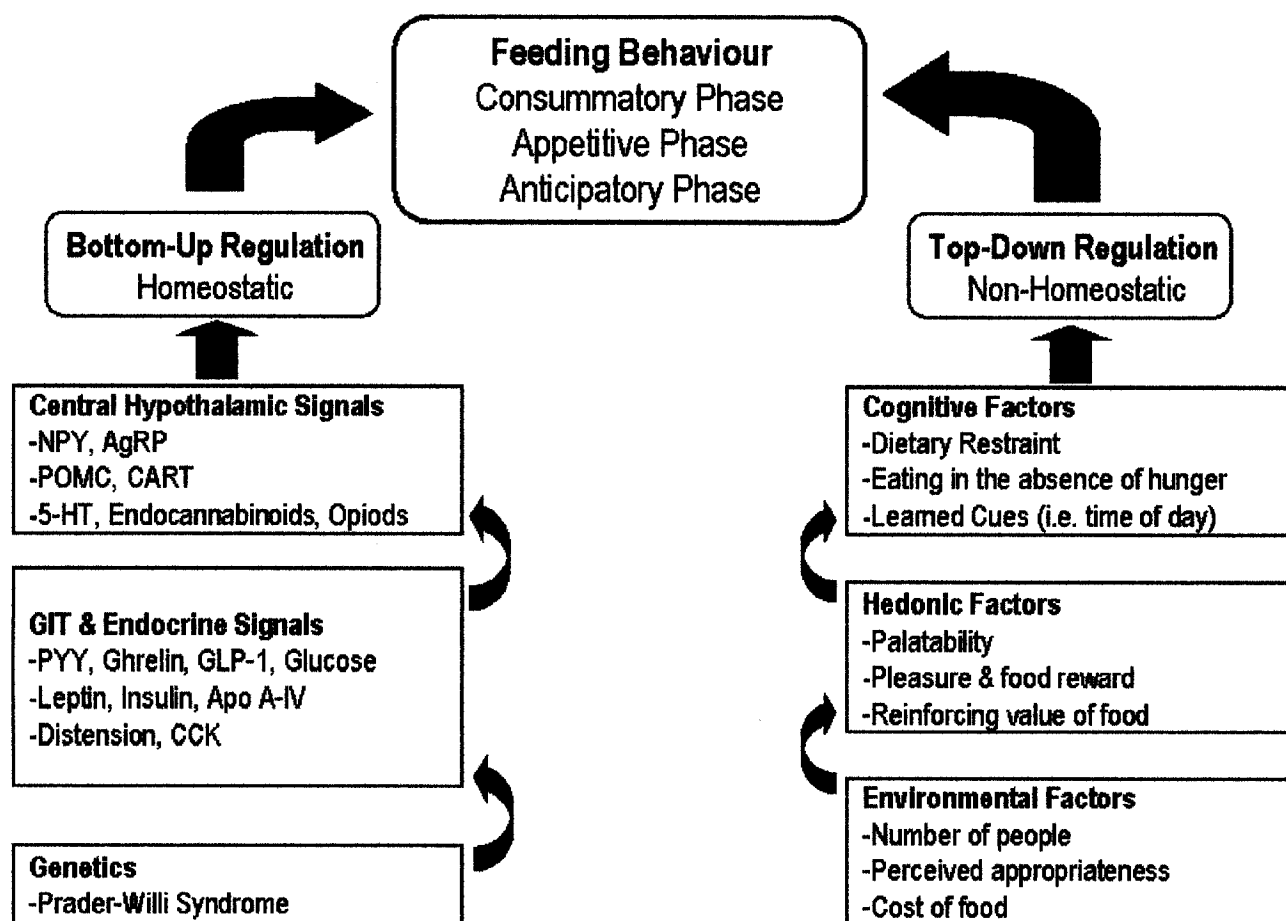


Figure 1: Demonstrating the two-tier regulation of feeding and suggesting that non-homeostatic factors may actively suppress the bottom-up regulators of feeding behaviour.

It appears that from an evolutionary standpoint, the bottom-up limb can account for the powerful mechanisms protecting the lower limits in body weight regulation, but the signal seems to be too weak to protect against the upper limits. Now there are many indirect stimuli acting to condition preferences such as those for readily available

palatable foods, or acting as social factors such as eating in a group. Over time as the network of brain centers became increasingly more sophisticated—largely due to neuroplasticity—modern humans have acquired entirely new methods to guarantee adequate energy reserves. In short, as evolutionary processes spawned consciousness, the psychology of hunger forever changed the feeding behaviour of *Homo sapiens*. In respecting the interconnectedness between the two sides of Figure 1, it is proposed that the circuits of the homeostatic limb can be overridden by the powerful non-homeostatic stimuli. These non-homeostatic stimuli follow pathways that include, but are not limited to, cortico-limbic regions contained within the amygdala, hippocampus, and thalamus; mesostriatal dopamine-gated circuits contained within the nucleus accumbens and ventral tegmentum; and prefrontal cortex regions predominantly within the orbitofrontal projections. Together, these brain areas form a model for central processing and the body of a theoretical model for the “top down” control of food intake. What is important to note here is that unconditioned physiologic signals such as those mentioned as homeostatic do not operate in a mechanistic manner. Plainly, under day-to-day (non-experimental) conditions the rise and fall of a particular peptide hormone does not causally determine specific behaviours. Although the role of homeostatic signalling in feeding behaviour must be appreciated, physiologic signals act more as cues (Blundell and Stubbs 1999)—rather like predisposing agents—for feeding behaviour. Hence hunger and satiety both have a substantial learned element.

3.1 Learning as a Top Down Regulatory Method

The point here is that there need not be a deprivation or homeostatic signal in order to initiate a drive state or to continue consummatory behaviour; once an animal

learns simple stimulus-response relationships, stimuli that were once meaningless become powerful cues with the potential to initiate goal-directed motor programs. Simply put, humans *learn* how and when to initiate feeding: we discover very early that the general feeling of malaise created by the rumbling of a hunger pang or light-headedness of hypoglycaemia are often associated with a lack of food. In this sense humans have also learned to overeat—breaks at work can lead to learned time cues for eating in the absence of hunger, and as an added threat to body weight regulation, it has been well documented that as few as one extra person at meal time can lead to a 33% increase in caloric consumption (de Castro 2000).

As a means to explain how learning is potentiated, extensive research has indicated that the hippocampus is a crucial structure for incorporating and storing sensory information; for the most part it participates in recording the memories of an experience, including where and when and with whom it occurred (Nestler and Malenka 2004). For example, if an individual is at a restaurant and is brought to a gratified state from indulging in chocolate cheesecake, the amygdala—another limbic area—is thought to be communicating a message indicating pleasure to the hippocampus, thereby committing this experience to memory. Intensity of the stimulus, subsequent arousal of these limbic regions, and synaptic levels of dopamine (DA) can all determine whether successive exposure will elicit a “relapsed” response (Nestler and Malenka 2004). Additionally, specific roles for the amygdala with respect to learning have recently been illuminated, where its importance in stimulus-response and response-reinforcement associations was established (Arana et al. 2003; Pickens et al. 2003). In this respect the amygdala is involved in the motivational aspects of learning; it is the extended network arising from

amygdalar nuclear projections that mediates the transfer of the representation of otherwise neutral stimuli into meaningful predictors that become conditioned motivational influences of behaviour (Everitt et al. 2003). Another highlight of the hippocampus' role can be demonstrated in feeding, such that we are able to recall that a certain amount of food or a certain type of food has in the past produced a level of satiation. In this respect, before one even begins to eat, there is a conscious (and arguably subconscious) restraint on the volume of food that will be eaten. Again, this is a result of stimulus response learning, defined by the close association of the oral stimuli of feeding and the post-oral consequences committed to memory.

What is more, in order to truly understand feeding behaviour, there must be an attempt to incorporate one of the most ambiguous concepts in psychology into this model—emotion. Although a thorough definition of emotion is beyond the scope of this review, what can be simply deduced is that emotions (or at least the brain areas thought responsible for emotions) emerged rather early in the timeframe of evolution, as demonstrated by the informal title of the limbic (emotional) brain—the mammalian brain. On a primordial level emotion may be simply defined as a series of brain activities that lead an animal to learn to either avoid a potentially aversive stimulus (somewhat analogous to a negative reinforcer) or to approach a potentially pleasant stimulus (analogous to the positive reinforcer). While the former is commonly referred to as fear, and is widely characterized in animals with an associatively learned response of freezing (Fanselow 1980), the latter has been a great deal harder to typify, and much of the remainder of the review will argue the importance of the role of this phylogenetically older response with respect to feeding.

4. Pleasure as Common Currency: Food as a Reward

Eating is often related to pleasure, with typical responses to highly palatable foods as heavenly, divine, and even euphoric. The nucleus accumbens (NAc) is a brain region that appears to play a crucial role in behaviours related to natural reinforcers, such as ingestion, sexual behavior, incentive and instrumental learning (Wang et al. 2001). Arising from the ventral tegmental area, its dopaminergic innervation plays a key role in many of these functions. It is important to recognize that the Nac is not a homogeneous mass, but is divided between shell and core. The NAc shell serves as a vital link between cortical circuits and hypothalamic brainstem circuits—a pathway known to be important in the control of food intake—whereas the NAc core is less involved in feeding per se, but is involved in learning and the execution of instrumental actions (Kelley 2004).

What is interesting is that feeding has been found to increase extracellular DA concentrations in the NAc; accordingly, increased DA has been shown over many models to contribute to the reinforcing effect of euphoria (Wang et al. 2001). Further, it was found that rats fed ad libitum on rat chow displayed a significant increase in DA efflux in the NAc when eating a novel palatable food (Rolls et al. 1986) and that injection of DA into the NAc can in itself stimulate feeding (Swanson et al. 1997). At the opposite spectrum, when there is a deficiency in DA like that seen in tyrosine-hydroxylase gene knockout mice, animals are hypophagic and die of starvation (Szczypka et al. 2001). Taken together, what this suggests is that the brain systems proposed by Mogenson (1980) over twenty years ago to translate motivation into action are heavily involved both in the drive to feed (incentive salience) and in the hedonic interpretation of pleasurable stimuli—that is to say—the affective processing of the qualities of the liked

items. If ingesting a certain food elicits a pleasurable experience, such behavioural reactions are usually reinforced by proper reward, i.e., repeating this behaviour (food seeking) or continuing to eat this food (food intake). In this manner, the prevailing “top-down” controls can bring a person to snacking behaviour when in the sated state, or even allow one to continue a bout of eating after a 7-course meal if presented with a novel palatable food. Integral to this signalling pathway is the NAc-HYP pathway: this route has been clearly demonstrated as constituting an important communication route between the striatal and hypothalamic mechanisms controlling motivating behaviour (Kelley 2004).

Thus, we believe that it is the cortico-limbic areas of the brain that dominate feeding behaviour. Specifically, in an environment with readily available and highly energy dense food, the rewarding aspects of food compete and actively suppress other feeding related signals. It is here where the idea of pleasure (or more fitting—reward) as a common currency is substantiated, which is further supported by Rolls (1999) as being the solution that evolution has developed to produce the most suiting behaviour. This offers an explanation as to why, when given a barrage of anorexigenic signals, humans still manage to overconsume even at gluttonous levels. Even more intriguing is the idea that hyperphagia and obesity are not necessarily maladaptations, but rather a phenotype that is exploited to guarantee survival. Consequently, this review is brought to its final question: How do we know food is rewarding and what impact does this have on food-seeking behaviour?

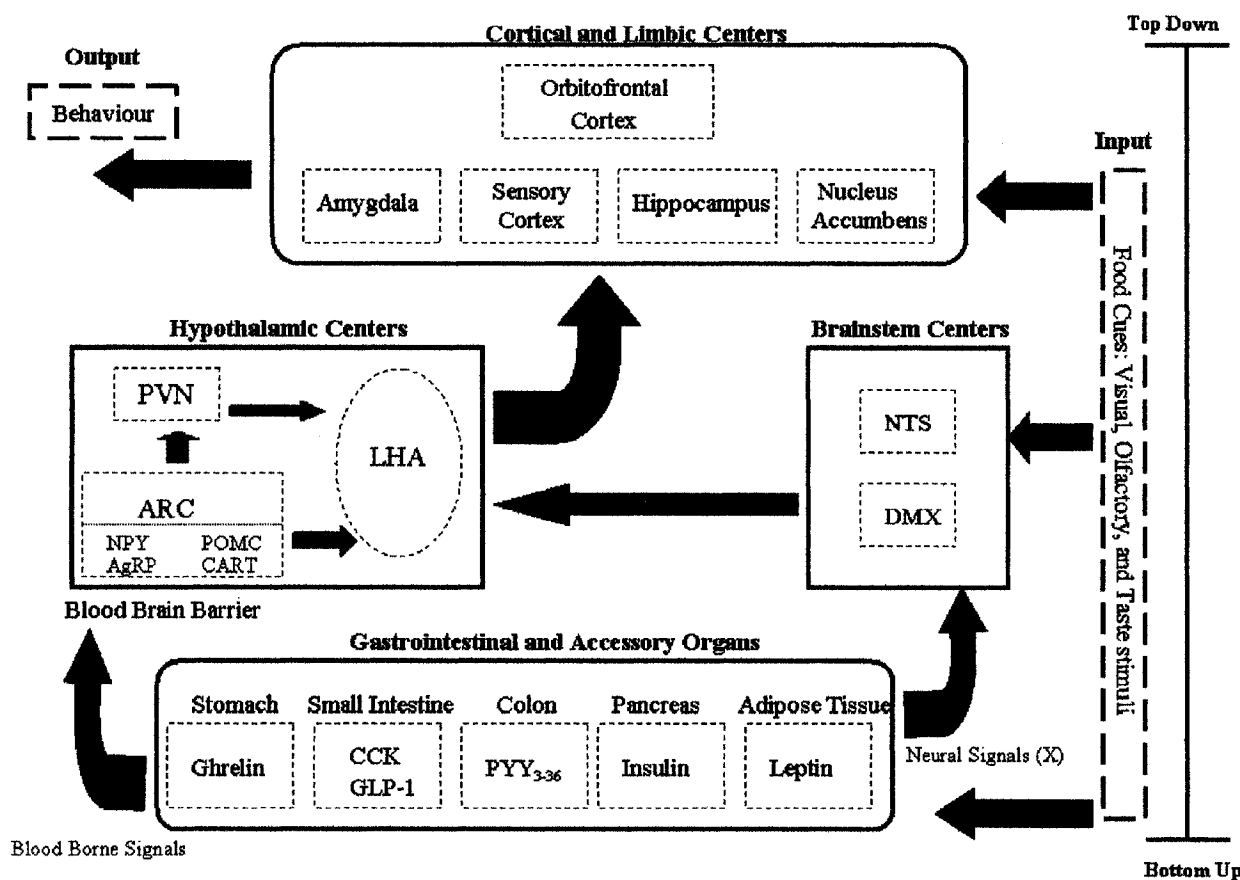


Figure 2: External stimuli (the input) from food are interpreted in a multimodal manner; this interpretation may be dependent on the motivational state of each individual (e.g. hunger and satiety). When fasted for an extended period of time “bottom-up” signals from gastrointestinal and accessory organs are proposed to drive feeding behaviour in a powerful manner, eventually influencing the cortical and limbic centers to promote consummatory behaviour. But the feeding effect of the “bottom-up” signals may be suppressed by “top-down” signals in times of hunger, i.e., a sudden loss of appetite following a significant stressful situation and arousal of limbic centers. Conversely, when in the sated state, indirect “top-down” signals may continue to promote consummatory behaviour in the absence of hunger, i.e., as conditioned associations and learning interact with the reward pathways involving the nucleus accumbens and amygdala to present powerful signals to continue feeding. CCK=cholecystokinin; PYY₃₋₃₆=peptide YY₃₋₃₆; POMC=proopiomelanocortin; CART= cocaine and amphetamine regulated transcript; NPY=neuropeptide Y; AgRP=agouti-related protein; GLP-1=glucagon-like-peptide-1; ARC=arcuate nucleus; LHA=lateral hypothalamic area; NTS= nucleus tractus solitarius; DMX=dorsal motor nucleus of the vagus.

4.1 Answers from Brain Stimulation

In what might be the most convincing evidence for the role of food as a reward, brain stimulation studies during the late 1960s and throughout the 1970s demonstrated that humans would work to obtain electrical stimulation of some sites of the brain (including the lateral HYP) (Olds 1977; Rolls 1975), which was by definition rewarding.

What is more, the rewarding quality of the brain stimulation appeared to mimic the rewarding quality of food; surprisingly, it was found that animals would work harder to obtain brain stimulation when hungry (Hoebel 1969), but when an animal was fed to satiety, it was later found that the group of lateral HYP neurons under observation ceased to respond to food (Rolls et al. 1986). It must be noted that evidence offered with human brain reward stimulation suggests that while the experience is certainly rewarding—patients could be found compulsively self-stimulating over thousands of repeated presses—there was no evidence of self-described pleasure in either case (Heath 1972; Portenoy et al. 1986). Observations such as these helped to lay the framework that disentangled the concept that rewards must be pleasurable; it is part of the incentive salience hypothesis that attempts to verify that under various circumstances (i.e. addiction) a reward need not be both pleasurable and desired at the same time (Berridge and Robinson 1998).

Further substantiating the role of the lateral hypothalamus in motivational behaviour, it has been found that a considerable collection of similar neuronal populations responded to merely the sight of food in chimpanzees (Ono et al. 1980), but not to non-food items (Mora et al. 1976). All told, there is significant support that animals perform operant responses (work) to stimulate populations of brain nuclei, particularly those involved in feeding, which in effect suggest a mode for which food can be considered to have endogenously rewarding qualities. Hence it is argued that opposed to acquiring immeasurable numbers of instinctual responses, animals (including *Homo sapiens*) have evolved in a manner to maximize the common currency of reward for behaviours not only restricted to feeding, but more generally—for survival. Concerning

the role of reward in food-seeking behaviour, this question can undoubtedly be partially answered with the physiological process involved in homeostatic control mechanisms, but many signs point to psychological factors dominating food-seeking behaviours. Further highlighting the importance of the homeostatic-like mediation of feeding, it is interesting to note that decerebrate rats—rats that have a complete disconnect between forebrain and brainstem projections—will not seek food and die unless chronically fed. Though these rats still respond to bottom-up signalling in that they are sensitive to meal-initiation- and termination signals in a similar manner as seen with the intact controls, they cannot discriminate between a fed and food-deprived state as they do not demonstrate a hyperphagic response to food deprivation (Grill and Kaplan 2002). Two points of interest surface from this model: 1) forebrain projections—most probably those in communication with the HYP-NAc network—appear to be integral for the animal to be motivated to engage food items, i.e., demonstrate a normal food-seeking response, and 2) the role of the HYP as an energy reserves sensor and its part in energy balance is paramount to survival.

4.2. Incentive Salience and Reward

The rewarding properties of food guiding feeding behaviour are said to be divided in two functional components: 1) the “liking” or the pleasure/palatability component generated by the stimulus, and 2) the “wanting” or the appetitive/ incentive motivation component generated by the stimulus (Berridge 1996). In utilizing various experimental designs, it has been determined that these two processes are mediated by separate neural substrates. Specifically, opioid and benzodiazepine/GABA neurotransmitter systems in the pallidal circuits are mainly involved in the liking component (Yeomans and Gray

2002), whereas, mesotelencephalic dopamine neurotransmitter systems in the amygdala appear to be involved mainly in the wanting component (Berridge 1996). Such evidence can help explain behaviours commonly found in people trying to lose weight or to maintain a level of reduced-weight. In either case, the incentive salience that draws the person to “want” to eat their favourite food—often against the will of restraint—might compel them to approach and engage a greasy snack, but once the initial reward is achieved, there is a decrease in the “wanting” and motivation to eat. Similarly, a study has shown that in monkeys trained to anticipate a reward through conditioned stimuli, maximal dopaminergic activity preceded the reward, and declined during the reward itself (Schultz et al. 1993). This may offer an explanation for the remorse experienced by many restrained eaters and dieters, for once the powerful initial urges and desires are quenched in engaging food stimuli, people are left with psychological emotions of helplessness—feeling as though they are powerless—mere slaves to the common currency of reward.

Further complicating the matter is the observance that obese persons have been shown to find high-fat foods more reinforcing than low-fat foods (Epstein et al. 1991). In fact, a promising hypothesis is that given obese populations have been demonstrated to show reduced levels of striatal DA (specifically with D₂ receptors)—even showing an inverse association between BMI and dopamine D₂ receptors (Wang et al. 2000)—and that DA is involved in reward, it is thought that overeating has emerged as a compensatory mechanism to ameliorate a deficiency in the reward circuitry (Wang et al. 2001). Consequently as natural selection has shaped behaviour regulation mechanisms via chemical transmitters, and given that stimulating these reward circuits mimics an

event that would normally provide a huge gain in fitness, then the emergence of obesity can arguably be thought of as an illusory gain in fitness (Nesse 2002) casting its veil via genes and their subsequent control of behaviour. The relevance for present day *Homo sapiens* is that our so-called structural machinery, our genes and their products, have arguably been fostered to excel in Stone Age-like environments (Lichtenstein 1999). What is more, research suggests that genetic adaptations to the available food supply ceased prior to the Paleolithic period—that is, the preagricultural period leading up to around 10,000 B.C. (Eaton and Konner 1985). Taken together this evidence implies that there is perhaps much more at work when considering the problem of obesity, mainly in our interactions with an obesogenic environment. Although this explanation has a purely behaviourist tone, the point here is not that we are ultimately powerless, but that we are overtly predisposed to making certain choices—such as when we experience a surge of DA from the VTA to the NAc—especially those concerned with survival.

4.3 Intrinsic Drive and Hedonics

Further, since palatability, or the “liking” component of food reward involves the convergence of taste with the individual’s physiological state and associative history, then an explanation for an initially pleasant stimulus becoming dull or unattractive becomes increasingly evident. So, in continuing with the greasy snack example, although the physical stimulus is constant, it is generally noted that with continued exposure there is a decrease in the subjectively rated pleasantness of the taste, appearance, and smell of the food (Hetherington 1996). This phenomenon was coined in the mid-eighties as sensory-specific satiety (Rolls 1986). Sensory specific satiety can be further explained by the fact that it is noticed that with continued exposure to the same food item there is a

discernable and rather abrupt change in the overall hedonic rating, i.e., the perceived sensory qualities of the item are not absolute (Rolls et al. 1983) though the change in liking is specific to the unchanging sensory characteristics of the item itself. Attempts have been made to explain sensory specific satiety with neurophysiological and behavioural observations, where conclusive evidence has shown that lateral HYP neurons of a monkey that no longer responded to a food that was fed to satiety, once again responded when the animal was given a novel food item (Rolls et al. 1986).

Not to be confused with this experience is a concept coined as alliesthesia (Cabanac 1971). While sensory specific satiety describes the change in hedonic ratings noticed with increasing satiety, alliesthesia illustrates how homeostatic elements (physiological drive states) can alter the rewarding or incentive value of a stimulus. Quite plainly, alliesthesia explains that there is a change in the pleasure of a sensation that is related to the internal state of the animal; in this sense, a normally relaxing sit in the hot tub may be pleasurable with cooler air temperatures, but on a hot summer day it may seem totally unacceptable. In the likelihood of suitable behaviours emerging from balancing reward and punishment, Cabanac (1979) argued that it is pleasure and displeasure that seem to provide the motivation to display useful behaviours. In either case, evolution has assuredly left a mark on how we initiate, maintain, and diversify our patterns of feeding.

Studies of food deprivation and the rewarding qualities of food will no doubt be topics sought out to further describe alliesthesia. A promising path has been paved with respect to adiposity signals and their possible role in mediating food reward. When leptin is administered intraventricularly, it attenuates the rewarding impact of food-restriction-sensitive stimulation (Fulton et al. 2000), where animals significantly decrease rates of

brain stimulation reward. It may be that long-term adiposity signals like leptin actively signal reward pathways of current body reserves, thereby intrinsically making food more attractive—more rewarding—when a significant loss in body energy reserves is detected. One must recall that brain reward was an early adaptation, and evolution has selected brain reward as a mechanism to reinforce behaviours that promote the survival of the species. Ostensibly, much like several other phenomenon related to feeding behaviour in light of the heuristic models presented in this review, such lines of thought seem axiomatic; yet proving causality with respect to such a vastly integrated and most often redundant system involved in feeding will be exhausting, at best.

5. Conclusion

On this terra firma that has been sculpted across billions of years and perilous climates, life has literally existed as an organismal survival of the fittest—or more pointedly via natural selection—constantly imprinting its mark with subtle changes in genes and gene products. Food-related signals from the environment, which are arguably the most salient of stimuli, are mediated by the interplay of the successive processing of physiological and psychological stimuli. It appears that primitive brain regions might have dominated feeding behaviour in the early stages of evolution, but in time cortico-limbic and cortico-striato-thalamo-cortical loops have arguably emerged as the dominant integrators of interoceptive information. Where previous hominids arguably had their quest for food primarily mediated by a vagal-brainstem-hypothalamic thoroughfare—a bottom-up highway to the brain—*Homo sapiens* have come to a point where the dominant mediators of feeding behaviour purportedly have turned to indirect, peripheral non-homeostatic stimuli. This is not to say that the top-down controllers have a monopoly

on goal-directed feeding behaviour, as it is important to note that the brainstem has been shown as a bottom-up integrator able to control behavioural and autonomic functions. What is apparent though is that competing behaviours are actively suppressed, and that in our quest for pleasure and reward humans have learned many conditioned-and stimulus-reinforcement associations, which have facilitated overeating in our environment of energy-dense and palatable foods. It is the motivational state (dependent on depletion-repletion signals of hunger and satiety) that in turn has the capability to modulate how rewarding or how palatable a food item may be perceived; thus, both sides of the two-tiered model of feeding behaviour are complimentary and interdependent all at once. In an attempt to regulate both sides of this representation, thereby making an effort to control the regulation of body weight, there must be a conscious effort to sustain central and peripheral satiety signals and one must take further care to control hunger. Emergent psychological factors now encompass each and every food choice; whether it be deciding what, when, with whom, or how much to eat we are not without enduring cultural and social pressures each influencing feeding behaviour. Much like the intrinsic mystery of the evolution of humankind, a comprehensive model of feeding behaviour still remains elusive, and might still never be fully understood. What is sure though is that we are driven by a quest for reward and pleasure—too often however, the motivation behind this pursuit for happiness now leads to poor food choices and ever fattening waistlines.

CHAPTER III

METHODOLOGY

Methods used for the data collection process in the present study are detailed in article format within the Methodology section in the article entitled The Effects of Food Deprivation on Food Hedonics and the Relative-Reinforcing Value of Food. To include them here as well would be redundant for the reader, and it was therefore deemed appropriate to describe the methodology within the article itself.

PART TWO: RESULTS OF THE STUDY AND DISCUSSION

CHAPTER IV

RESULTS AND DISCUSSION OF THE EXPERIMENT IN ARTICLE FORMAT

This chapter presents the results of the present study, as well as the discussion and analysis of the findings. These are presented in article-style format within the article entitled The Effects of Food Deprivation on Food Hedonics and the Relative-Reinforcing Value of Food, for the eventual submittal of the findings as a manuscript to a peer-reviewed journal. The results of this study are presented in the Results section of said article, followed by the Discussion of the findings.

**The Effects of Food Deprivation on Food Hedonics and
The Relative-Reinforcing Value of Food**

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ABSTRACT

Food is a primary reinforcer. There is strong evidence that when animals are chronically deprived of calories, the reward of a food stimulus becomes more salient. Recently leptin has been implicated in food reward. Typically the rewarding value of food is separated into the “liking” or pleasure/palatability component generated by the stimulus, and into the “wanting” or appetitive/incentive component. The goal of this current study was examine whether plasma leptin concentrations were related to food hedonics and food reinforcement in humans and to investigate the effect of food deprivation on these variables. Fourteen apparently healthy obese adults ($n=9$ women and 5 men; age $=33.5 \pm 7.8$) with BMI (kg/m^2) between 30-45 were subjected to 8 weeks of caloric deprivation (-700kcal/day). Plasma leptin (ELISA), body weight and composition (DEXA), food reinforcement and food hedonics were measured pre- and post-intervention. Post weight loss palatability was rated significantly higher for the food reinforcers than that measured pre weight loss ($p<0.01$). No significant effect of the chronic food deprivation was noted for the reinforcing value of food. A significant negative correlation was observed between changes in palatability and those in body weight expressed as relative changes ($r = -.62$; $p<0.05$). No significant correlations were noted between changes in leptin and those in palatability or the reinforcing value of food. However, in a subgroup that lost the greatest percent of initial body weight (7-8%), food was more reinforcing post intervention ($p<0.05$). These findings demonstrate that chronic caloric deprivation can increase the subjectively rated palatability of preferred food items. The subgroup may be a caveat illustrating that a greater relative weight loss can lead to food becoming more rewarding.

Key words: Reinforcement; Deprivation; Hedonics; Leptin; Reward

1. Introduction

There is strong evidence that metabolic status drives several fundamental animal behaviours, including appetitive and affective responses to feeding, drinking and drug taking (Friedman 1992; Kelley and Berridge 2002; Kennedy 1972; Mayer 1955; Steller 1954). Food deprivation, or a significant loss of body weight due to nutritional restriction over time, alters not only short-term peripheral cues of meal initiation/termination (le Roux and Bloom 2005; Otto et al. 2001; Ravussin et al. 2001; Stock et al. 2005) but also long-term central cues reflecting global adiposity status (Considine et al. 1996; Rosenbaum et al. 2002; Schwartz et al. 2000; Woods et al. 1979; Woods et al. 1998). Since its discovery in 1994 (Zhang et al. 1994), the major role of the OB protein leptin in the abovementioned brain-gut axis is theorized as being deep-rooted in the signaling of body energy reserves. Leptin is produced by adipose tissue, and via saturable transport (Caro et al. 1996; Pelleymounter et al. 1995; Schwartz et al. 1996a) is able to cross the blood-brain barrier (BBB) to effect a wide range of behaviours; although leptin as an adipostat in the arcuate nucleus-focused model has subjugated much of the attention for homeostatic mechanisms of feeding, there is a growing body of evidence showing that leptin is also involved in the signaling of food reward (Figlewicz 2003; Fulton et al. 2000; Fulton et al. 2006b; Hommel et al. 2006).

As with animal models, human obesity is associated with high plasma leptin concentrations (Considine et al. 1996) and both short- (Doucet et al. 2004; Kolaczynski et al. 1996; Weigle et al. 1997) and long-term (Keim et al. 1998; Nicklas et al. 1997; Wisse et al. 1999) caloric deprivation result in significant decreases in plasma leptin levels.

There also exists a strong correlation between cerebrospinal fluid (CSF) and serum leptin (Caro et al. 1996; Schwartz et al. 1996a), and it is yet to be established if this reduction in CSF leptin can modulate food reward within physiological ranges. As if to promote the survival of species, it appears that in times of significant food deprivation (dieting, famine, etc.) that animals, including humans, sense food as being more palatable and more reinforcing (Berridge 1991; Cabanac and Lafrance 1990; Carr 1996; Epstein et al. 2003; Raynor and Epstein 2003). One way to objectively measure the reinforcing value of food is with a behavioural economics paradigm (Rachlin 1989; Saelens and Epstein 1996). By discriminating the absolute amount of work done to obtain particular food items of choice, one can determine if food becomes more or less reinforcing—the more work done to acquire the item, the more reinforcing it is said to be. The hedonic value of food or the subjectively rated liking for food is typically measured by intensity of the sensation as scribed on a ratio scale. Each of these behavioural measures of feeding have been described as being dissociable at the level of the CNS and can be categorized as either food “wanting” or “liking”(Berridge 1996).

In the present study we sought to determine whether plasma leptin concentrations were related to food hedonics and food reinforcement in humans and to elucidate the effect of weight loss on these variables. We chose a prolonged 8-week energy deficit of 700 k/cal per day in order to obtain significant changes in body energy reserves, thus decreasing leptin signaling at the level of the brain. The main objective was to investigate whether the reinforcing value of the snack food would increase along with an increased subjective rating of palatability following the weight loss, and whether these measures would be associated with reduced plasma leptin.

2. Methods

2.1 Participants

Seventeen men and women were recruited through 2 advertisements in a major local newspaper. Of these participants, the results of 14 obese individuals (5 men and 9 women) completed the weight loss program presented in this study. All participants were first screened over the telephone and then subsequently in a screening session to ensure that they met the following inclusion criteria: within the BMI range of 30-45, waist circumference range (≥ 102 cm Male; ≥ 88 cm Female), weight-stable (± 2 kg for 6 months), sedentary (no more than 30 min moderate intensity twice/ week), without food allergies, non-smoker, relatively healthy, regular menstrual cycle (28-35 days), not pregnant, and not taking any medication. Participants who agreed to volunteer gave their written informed consent to participate in this study, which received approval from the University of Ottawa Ethics Committee.

2.2. Design and Procedure

2.2.1 Screening visit

During the first visit to the laboratory, participants were measured, weighed (while wearing a standard hospital gown) and had their waist circumference assessed in the pre-prandial state. Following this, each participant was asked to complete a questionnaire to indicate his or her favourite snack food and favourite fruit/or vegetable. For this decision, they were asked to circle their choice from a comprehensive list of common products (chips, candies, cakes, and chocolate bars; Appendix C) or if the choice was not on the list, they were asked to indicate what their favourite food items were. In this manner each participant would have his or her single favourite snack food

and fruit/or vegetable as reinforcers for the relative-reinforcing value of food paradigm. Following the completion of the consent forms, participants were sent home and required to fill out a 3-day dietary recall to return to the dietician the following visit.

2.2.2. Weight stabilization & weight loss diet

In order to control for variance in individual feeding patterns, there was a weight stabilization period for the three days leading up to the baseline testing session. The time between the screening visit and the weight stabilization visit was not held constant. However, scheduling was arranged such that female participants were tested on days 1-8 of the follicular phase of the menstrual cycle. Of note, one of the female participants fell slightly beyond the follicular phase and was tested up to day 13 of her menstrual cycle. Weight stabilization was accomplished by balancing energy intake with energy expenditure: RMR measures (Deltatrac II metabolic cart, SensorMedics Corporation, Yorba Linda, CA) were adjusted with a physical activity level (PAL) of 1.4 and food intake was then prescribed accordingly so as to approximate energy balance. This stabilization diet was followed for 3 days and on the fourth day participants returned for the baseline visit at 7h30. The weight loss consisted of an 8-week 700kcal a day restriction as previously described (Appendix G), and the diet began the day after the baseline visit.

2.2.3. Baseline and post weight loss

Of note, all measures described below were repeated in the same manner (Appendix H), once pre weight loss (baseline) and once post weight loss. Also, testing for the current study did not commence until 12h00, as the morning session was part of a larger study (Appendix G). Participants arrived at 7h30 fasted from 19h30 the following

evening. After anthropometric measurements were recorded a standardized breakfast of 295 kcal was administered. At approximately 11h00 body composition was measured (DEXA). The current investigation began at 12h00 with the explanation of the computer task. A single practice trial was then administered to familiarize with the joystick controls and program operation. Each participant was then shown what each food portion would look like if they worked entirely for the snack food or entirely for the fruit/ or vegetable. This was done in an attempt to control for reward expectation (Preuschoff et al. 2006) and due to the fact that many of the snack foods were energy dense, a visual representation of food points translated into food items intended to demonstrate how small some of the snack portions could be. Immediately following the practice trial the participants were informed to play the game and that the items of reinforcement would be offered prior to completing the full day session. At ~12h20, after completing the first computer trial a nurse drew a 4-6ml blood sample from each participant. At 12h30 they were required to consume a lunch standardized to their weight stabilization diet. Finally, at 15h30 the second computer task was performed and following the completion of the task the exact amount (in grams) of snack and fruit/ or vegetable food items were weighed on an electronic scale (Scout Pro SP2001, Ohaus Corporation, Pine Brook, NJ) to the nearest 0.1 g and then offered. Participants were told in advance that they were obliged to consume the food at the laboratory.

2.3 Measurements

2.3.1. Food Hedonics: visual analogue scales

During the pre- and post-weight loss sessions desire to eat, hunger, fullness and prospective food consumption (PFC) were rated on a 150 mm VAS that was adapted

from Hill and Blundell (Hill et al. 1984), immediately before a standardized lunch and at 0, 30, 60, 90, 120, 150, and 180 minutes after the ingestion of the standardized lunch test meal. Questions were asked as follows: 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), and 4) “How much food do you think you could eat?” (Nothing at all-A large amount). Palatability, or the hedonic value of food, was also measured in the same manner immediately following the ingestion of the standardized lunch test meal at 13h00 and then again following the ingestion of the food reinforcers at 16h00.

2.3.2. Food reinforcement: progressive ratio computer task

Participants completed 2 computer tasks pre weight loss and 2 computer tasks post weight loss in order to evaluate the relative reinforcing value of snack foods versus fruits and vegetables. For the final analysis, the points earned for each of the computer tasks (12h00 and 15h30) were averaged across schedules for pre- and post- intervention so as to compare 2 times (one pre and one post) as opposed to 4 times. The computer tasks were performed at 12h00 just prior to the 12h30 individually standardized (for weight stabilization) lunch and then again at 15h30 just prior to the offering of food reinforcers. As described elsewhere (Bulik and Brinded 1994; Lappalainen and Epstein 1990) this paradigm is defined as a progressive ratio computer task where the probability of earning food points varies across schedules. The reinforcement schedule remained at VR2 for all 5 trials for the fruit/or vegetable, but increased progressively for the snack food at VR2, VR4, VR8, VR16, and VR32 across the five trials. Thus, on average the reinforcement schedule for the fruit/or vegetable was set to reinforce every second button

push (VR2), and this remained the same across all trials; the reinforcement schedule for the snack food doubled across each trial, such that in the final trial (VR32) snacks were reinforced on every 32nd button press. Participants were told that it would be harder to obtain snack food points as trials progressed, but were not informed of the exact rate of change of the reinforcement schedule. Participants were also showed what a 100g portion of both of their food reinforcers looked like. Food points were earned by selectively working for the food item of choice, and this was accomplished by activating a slot machine-like program with a simple 2-button joystick. Button 2 allowed the user to freely switch between the snack or fruit/vegetable screen during each trial, and button 1 started the slot game. Upon choosing which food item to work for button 1 was pressed to start the slot machine. When the rotating shapes stop with all three shapes matching there is a point registered atop the screen for the designated food item. If the shapes do not match then there are no points allotted and the participant must continue working until a point is gained. Each trial was completed when a total of 10 points was gained. For each of the four computer trials (2 pre- and 2 post-intervention) the presentation of which reinforcer appeared first on the starting screen was counterbalanced across participants. As each of the two computer tasks yielded a total of 50 points, participants consumed the equivalent of 100 food points at the end of the session.

2.3.3. Body Composition

Body composition was assessed baseline and post weight loss by dual energy X-ray absorptiometry (DEXA) using a GE-LUNAR Prodigy module (GE Medical Systems, Madison, WI).

2.3.4. Body Weight

Measurements of weight were conducted baseline and post weight loss using a digital weigh scale (Tanita®). All participants were required to wear standard issue hospital gowns for this measure.

2.3.5. Plasma leptin concentrations

Blood samples were collected from the antecubital vein into EDTA containing tubes. These samples were drawn at ~12h20 in the pre-prandial phase. Blood samples were immediately stored at 4°C, and within the hour were centrifuged at 3500 rpm at 4°C. Samples were then immediately stored at –80°C. Plasma leptin levels were determined with a “Dual Range” ELISA Leptin kit (Linco Research, Inc., St. Louis, MO) that detects relatively low leptin levels of 0.5 ng/mL and does not cross-react with human insulin, proinsulin, glucagon, pancreatic polypeptide, or somatostatin.

2.3.6. Statistical Analysis

To test for differences in the rewarding value of food, pre- and post-weight loss measures of food reinforcement were performed in a within-subjects 2 (time) by 5 (reinforcement schedule) analysis of variance. To test for differences in the hedonic evaluation of food, pre- and post-measures of food palatability were performed in a within-subjects 2 (time) by 4 (mealtime) analysis of variance. Bivariate correlations were used to determine the strength of the relationship between leptin concentrations and various anthropometric and appetitive variables. Partial correlations were utilized to determine whether the noticed changes in palatability with percent change in weight loss were independent of body composition and leptin levels. Effects were considered significant at $p < 0.05$ and data are presented as mean $\pm$ SD unless otherwise specified.

3. Results

Participant Characteristics

Descriptive statistics for the participants (n=5 and 9 for males and females, respectively) are summarized in Table 1. From pre weight loss to post weight loss there were significant decreases in weight ($6.0 \pm 2.8\%$, $p < 0.01$), BMI ($35.4 \pm 4.4 \text{ kg/m}^2$ vs. $33.5 \pm 4.7 \text{ kg/m}^2$; respectively, $p < 0.01$), percent body fat ($42.3 \pm 6.5\%$ vs. $40.8 \pm 6.8\%$; respectively, $p < 0.05$), fat mass ($41.5 \pm 9.3 \text{ kg}$ vs. $38.0 \pm 8.3 \text{ kg}$; respectively, $p < 0.01$) and plasma leptin concentrations ($26.8 \pm 13.9 \text{ ng/mL}$ vs. $17.6 \pm 12.3 \text{ ng/mL}$; respectively, $p < 0.01$). All descriptive statistics for participants were normally distributed and are reported in Table 1. As expected, plasma leptin concentrations dropped $34.2 \pm 29.7\%$ ($p < 0.01$) after the 8 weeks of food deprivation. The delta values for body weight did not significantly differ for males and females ($-7.4 \pm 3.3 \text{ kg}$ vs. $-5.6 \pm 1.7 \text{ kg}$; respectively, $p > 0.5$), nor did the delta values for leptin concentrations between males and females ($-7.9 \pm 4.7 \text{ ng/mL}$ vs. $-10.1 \pm 13.8 \text{ ng/mL}$; respectively, $p > 0.5$).

Food Liking and Weight loss

As shown in Figure 1, palatability significantly increased in response to weight loss ($p < 0.01$). Post hoc analyses showed no significant difference pre- and post- weight loss for palatability following the lunch meal ($p > 0.5$), but there was a significant increase in the palatability of the food reinforcers offered at the end of the session ($p < 0.01$). Thus palatability was rated significantly higher for the food reinforcers post weight loss than for that of pre weight loss ($140.4 \pm 10.8 \text{ mm}$ vs. $128.2 \pm 19.8 \text{ mm}$; respectively, $p < 0.01$). Additionally, when gender was used as a between subjects factor, there was no significant gender by time interaction for palatability scores pre- and post- weight loss ($p > 0.5$).

Reinforcing Value of Food and Weight loss

The reinforcing value of food data is shown in Figure 2. There was no significant effect for the deprivation (time) period on the reinforcing value of preferred snack food, ($p > 0.1$). Also, there was no significant difference in amount of work done (reinforcement schedule) to obtain points ($p > 0.1$), and there was no interaction between time and schedule ($p > 0.1$). When gender was used as a between subjects factor, there was no significant gender by time interaction for reinforcement scores pre- and post- weight loss ($p > 0.5$). An additional analysis was performed on a subgroup of those who lost the largest percent of initial body weight (7-8%). The rationale being that past research has demonstrated that reward sensitivity is influenced by degree of weight loss (Hao et al. 2006). In this subgroup there was a significant increase in the reinforcing value of the snack food as demonstrated by the increase in total snack points from pre- to post-intervention (63.3 ± 11.5 vs. 85.3 ± 16.2 , respectively, $p < 0.05$). Of note, there was a participant who lost 11% of initial body weight, but was not included in this analysis as the percent change in weight was 3 standard deviations away from the mean.

Leptin, Food Reinforcement and Food Hedonics

As reported above, the 8-week deprivation period did not significantly affect the reinforcing value of food; it was also found that changes in plasma leptin did not significantly influence food reinforcement. The noticed change in palatability was not significantly correlated with changes in plasma leptin (nor adiposity adjusted leptin) or changes in fat mass, but there did exist a significant negative correlation with that of percent change in weight ($r = -.62$, $p < 0.05$). Correspondingly, percent change in weight was a significant predictor (Beta= -2.1 , $p < 0.05$) of the change subjectively rated

palatability of food reinforcers, where percent change in weight accounted for 38% of the variance in palatability (Fig. 3.). Interestingly, when the sample was separated by gender, percent change in weight accounted for 67% of the variance in palatability for females ($r=0.82$, $p<0.01$), but for males the value was below 1% ($r=0.08$, $p>0.5$). For the overall model, the negative correlation between palatability and percent change in weight remained significant when controlling for the percent change in body fat percent, and also remained significant when controlling for the change in adiposity-adjusted leptin.

4. Discussion

One of the main outcomes of this investigation was to test the hypotheses that chronic caloric deprivation resulting in weight loss affects the relative-reinforcing value of food. It was hypothesized that, relative to baseline, participants would perform more work (simple button presses) to obtain snack food points versus fruit or vegetable points post weight loss—in effect indicating that the snack food items increase in reinforcing and rewarding value. This is what has been called the “wanting” component of reward and is thought to be separate from the “liking” component of reward (Berridge 1996). This “wanting” and the neurobiological-correlates (e.g. dopamine) thereof are believed to influence not only food choice, but also the amount of food consumed. Though acute food deprivation (hours) has been shown to influence food “wanting” by positively affecting the relative-reinforcing value of food in humans (Epstein et al. 2003; Raynor and Epstein 2003), to our knowledge there has not been work done to elucidate the effect of a longer deprivation period on this variable. Results from this study demonstrate that after an 8-week hypocaloric period and an average weight loss of ~6.0 kg there is no significant difference in the total amount of work performed to obtain a favourite snack

food (Fig.2.). It is important to note that there were no significant differences in pre weight loss versus post weight loss visual analogue scores for hunger or fullness that immediately preceded each of the computer tasks (see Appendix I). A possible explanation for the lack of significant change in food reinforcement, which was shown to be independent of the abovementioned appetitive variables, is the influence of the behavioural intervention with the dietician. During the 8-week period participants were rigorously monitored by weekly follow-ups of either phone controls or morning visits to the laboratory. Education as to proper food choices was integral for the success of and adherence to the weight-loss diet. That many of the participants reported they did not want to upset the dietician by spoiling their diet is evidence of the weekly control sessions confounding the reinforcing value of food variable.

The subanalysis did, however, demonstrate that larger losses in relative body weight are associated with an increase in the reinforcing value of the snack food. What this suggests is that with greater relative changes in body weight people are more likely to choose to engage in eating highly palatable energy dense snacks when offered the choice between other preferred low calorie foods. A parallel is the change in brain stimulation reward (BSR)—a measure of brain reward circuitry that computes the value of goal objects (Fulton et al. 2004)—that accompanies changes in body weight. Via a chronically implanted electrode, a rewarding electrical stimulation (typically to the lateral hypothalamus) is delivered when the animal performs the operant response of pushing a lever. What is interesting is that this rewarding effect is potentiated by chronic food deprivation and that the ability of this deprivation to enhance BSR is proportional to the degree of weight loss (Carr and Wolinsky 1993). In effect, with greater weight loss

animals will continue pressing the lever for ever smaller amounts of stimulation, which is translated into a leftward shift in the rate-frequency curve. Further, intracerebroventricular leptin administration causes a rightward shift in this curve, restoring the reward value to pre-deprivation levels (Fulton et al. 2000). The abovementioned studies illustrate that leptin plays a modulating role in reward in rodents and that there may be a similar role for leptin in humans.

A secondary hypothesis tested was examining the influence of plasma leptin concentrations on food reinforcement. Hypoleptinemia acts as a negative feedback signal potently influencing feeding behaviour as described by the chronic hyperphagia noted in the *db/db* mouse (Halaas et al. 1995; Lee et al. 1996). Moreover, the strong correlation between plasma and CSF levels of leptin (Banks 2001; Caro et al. 1996) permit the first leap needed to connect reduced peripheral levels of leptin to central (hypothalamic) signalling and the diverging connections formed by the long form of OB protein receptors with deeper brain structures. With the understanding that leptin receptor-expressing cells are found in areas of the brain that are thought to be responsible for goal-directed behaviour and reward—particularly in the nucleus accumbens (Bagnol et al. 1999) and the ventral tegmental area (Figlewicz et al. 2003)—it was hypothesized that the primed decrease in leptin would be correlated with an increase in the reinforcing value of food. However, as reported above the overall model was not significant. It could very well be that the weight loss noticed in this sample was not enough to substantially change CNS levels of leptin. A deeper look at the data also shows that mean post weight loss leptin levels (17.7 ± 7.3 ng/mL) are near those noted to be the point of saturation for leptin transport, which has been shown to be around 20-25 ng/mL (Banks 2001; Caro et al.

1996; Schwartz et al. 1996a). That women dominated the sample, and that mean leptin levels for women post weight loss were ~ 20.3 ng/mL further illustrates that leptin saturation may still have occurred. Taken together this suggests that a chronic caloric deprivation greater than 700kcal/day leading to even greater percent changes in weight and plasma leptin may be required to: 1) increase the rewarding value of food, and 2) demonstrate a correlation between increased food reward and lowered leptin concentrations.

The other main outcome of this investigation was to examine the potential effect that food deprivation leading to weight loss has on the hedonic evaluation of food. Here it was hypothesized that following the deprivation regimen the subjectively rated intensity of palatability would increase. The goal was to test the other aspect of food reward—being the “liking” component of the stimulus—and to help clarify whether “wanting” and “liking” are separate processes of food reward. Indeed, metabolic status has been shown to influence food hedonics (Cabanac 1989; Nisbett 1972) such that food deprivation enhances food palatability. There is however a paucity of information concerning the matter. The results here are interesting in that there was no significant difference in the palatability ratings following the individually standardized lunch meals, but there was a significant difference—namely a $\sim 10\%$ increase—in the palatability rating following the ingestion of the food reinforcers (Fig.1.). A possible explanation for the lack of a significant change in palatability for the lunch meal is that the lunch was relatively bland and low in fat (toast, whole-wheat crackers, low-fat turkey, light mayonnaise, 2% milk, and carrot/apple pieces)—and palatability is often associated with orosensory texture

(Raats et al. 1993), which is typically a function of the quantity and chain length of fat ingested.

Because each of the food reinforcers were already picked as favourite food items, it can be understood that frequent exposure to these items had already produced a preference for that level of nutrient (i.e. fat/salt/sugar)(Bertino et al. 1986; Mattes 1966). Further, it must be clarified that stimuli such as sweet taste and fatty flavour have endogenously rewarding qualities (Berridge 2000); these stimuli powerfully promote approach behaviour and operant learning (Sclafani 2004). The fact that, following weight loss, food reinforcers were rated significantly more palatable in this obese sample is indeed a troubling trend when viewed in light of dieting paradigms. However, the significant negative correlation between palatability change and percent change in weight loss is counter-intuitive to how metabolic status can affect how food is perceived (Fig.3.). Unexpectedly, Figure 3 shows that the greatest increases in palatability occur with the smallest changes in relative weight loss. If this is indeed representative of the obese population, then it might offer an explanation as to the initial difficulty in staying away from palatable foods once weight loss commences. It should be noted that there is a tendency for the overall model to fit best as a quadratic trend ($R^2=0.47$, but not quite significant, $p=0.065$), so precaution must be taken when interpreting the data; when viewed this way, as the extreme is approached to the left, with ever bigger losses in relative weight, the palatability ratings then turn to be predicted as they are with the far right of the curve.

The above data are representative of the ambiguity of palatability depending on a need for energy. At one end, studies have shown an absence of an inverse relationship

between energy content of a preload and the palatability of a subsequent meal (Yeomans et al. 2004); at the other end, paradigms with negative alliesthesia have demonstrated that gastric loads of energy-dense fluids can turn a positive consummatory response to an aversive response (Cabanac and Lafrance 1991). Nonetheless, that palatability increased nearly 10 % from pre- to post- weight loss amongst this obese sample is symptomatic of dietary complication given our current “obesogenic” environment of low cost energy dense food products. To complicate matters further, all else being equal, obese persons show a stronger preference for highly palatable energy dense foods compared to the non-obese (Drewnowski and Holden-Wiltse 1992; Drewnowski et al. 1992); and perceived palatability is positively correlated with the amount of food consumed at a meal (Bobroff and Kissileff 1986; Price and Grinker 1973; Yeomans et al. 1997).

Understanding the factors that influence the motivation to eat is integral to the proper prescription and adherence to dietary change. The observed dissociation between two qualities of reward, wanting and liking, is relevant for several reasons. The fact that motivation to eat the preferred food items was not influenced by weight loss is indicative that wanting does not change over time under the specific conditions of this study. Along with the behavioural intervention of the dietician, there could have existed a hedonic shift (Mattes 2006) in the perceived reward of healthier food choices that occurred during the 8-week intervention. When the participants were reintroduced to the possibility of eating a treat that would have been prohibited under the prescribed diet, they did not differentiate between the reinforcers. There was no increase in the saliency of the snack; hence the appetitive phase of feeding and food selection was not affected. But upon offering the reinforcers following the deprivation period it should be noted that the

consummatory response—specifically, the hedonic evaluation of palatability—did positively change. What this suggests is that if a lasting behavioural change (perhaps a hedonic shift?) can be implemented by modifying the diet towards healthy food choices, then increased palatability may not be of concern if the reinforcing items are healthy food choices. Using this same relative-reinforcing value of food paradigm, Epstein et al. (2003) actually demonstrated the opposite trend with an acute deprivation period of approximately four hours. In a sample of non-obese, non-dieters, the deprivation period significantly increased the reinforcing value of food, but had no significant effect on the hedonic ratings of the food. In the end, it might be that a deprivation period longer than both the 4 hours and the 8 weeks noted above would bring the wanting and liking components of reward in the same direction, that is, increased liking following increased wanting. In fact, given a larger sample size this study might have shown, 1) a quadratic trend did exist for the regression of delta palatability onto percent change in weight, and 2) the predictions of the subanalysis were correct in identifying snack food as being more reinforcing. Under such circumstances food would be both more palatable and more rewarding as a function of metabolic status.

In summary, from pre weight loss to post weight loss food “liking” increased as indicated by higher palatability ratings of the food reinforcers. Conversely, there was no significant difference in food “wanting” or the rewarding value of snack food as there was no significant difference in the work performed to obtain snack points. Changes in leptin were not significantly correlated with either measures of wanting or liking, but post weight loss levels of leptin were similar to those previously demonstrated as apparently

saturating the OB receptor. The subgroup may be a caveat illustrating that a greater relative weight loss can lead to food becoming more rewarding.

PART THREE: CONCLUSIONS AND RECOMMENDATIONS

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The main findings of this study indicate that favourite snack food items do not increase in reinforcing or rewarding value as a result of physiological changes from 8 weeks of food deprivation. However, palatability did change over the course of the intervention, as the hedonic evaluation of food was influenced by the magnitude of percent change in weight. Leptin concentrations were not correlated with either of the abovementioned components of food reward, wanting and liking, respectively.

The role of leptin in signalling body energy reserves and its function in reward are topics that are paramount to the current understanding of feeding behaviour. Recent results support the role of weight loss in reward sensitivity, and in doing so failed to find a role for leptin in this model (Hao et al. 2006). In the current examination of the reinforcing value of food, perhaps a better proxy to leptin would be dopamine when examining the neural correlates of reinforcing behaviour. Indeed studies have demonstrated a role for dopamine in food wanting (Schertzer et al. 1996; Volkow et al. 2002a; Volkow et al. 2002b; Volkow et al. 2003), and given the pharmacological role of dopamine agonists in the current population (e.g. methylphenidate) it would be beneficial to follow this avenue to better interpret not only how food is selected, but also how much food is consumed.

Recommendations and Future Perspectives

It would be interesting to re-examine this sample in six months to a year in order to observe if the reinforcing value of the preferred snack food increased. The sample could be separated into those who maintained weight loss and those who returned to their baseline weight observed before this current 8-week intervention. From this it could also be further clarified if the behavioural intervention of the dietician impacted the reinforcing value of food (assuming that those who maintained the weight loss were still following the prescribed diet). In the same manner, the hypothesized hedonic shift could be evaluated, as those who returned to baseline weight most likely would have returned to uninhibited feeding patterns. Additionally, the experiment could also be repeated with a new sample, but without having weekly follow-ups.

Another potential avenue would be to again use food deprivation as the dependent variable in examining wanting and liking. A shorter term of deprivation—perhaps a few days to a week—but one that is very low in calories (<1200 kcal/day), could be a good model to see if short-term feeding signals influence food reinforcement and food hedonics. That peripheral leptin levels have been shown to rapidly decrease in a matter of hours to days of caloric restriction, peripheral reductions that can even surpass those seen with chronic weight loss, is warrant for the examining of acute changes in leptin and the potential impact on the abovementioned variables. Or in contrast, a longer and more substantial deprivation period would also be an interesting follow-up to this current study. Much of the research on weight loss is limited to following merely six months to a year; accordingly a longitudinal study would certainly be relevant when examining food reward.

Due to the fact that peripheral leptin was the physiological marker of an assumed central effector response, our data are limited in explaining what must be ultimately studied in real-time. Although peripheral and CSF levels of leptin are correlated, the jump from physiology to theory ultimately begins at this level. However, due to financial limitations and lack of sophisticated machinery (e.g. fMRI) it must be accepted that these limitations exist, especially when studying humans. Finally, due to the nature and the timeline of the current study—being a Masters project—the small sample size is certainly a limitation and could be increased so as to more accurately predict population characteristics.

PART FOUR: CONTRIBUTION OF COLLABORATORS

CHAPTER VI

STATEMENT OF CONTRIBUTION OF COLLABORATORS

The collaborators involved in the conception and writing of this thesis (J.C. and E.D.) contributed as follows: J.C. and E.D. collaborated to write the published Review of Literature; J.C. was the primary author of this review. J.C. and E.D. were involved in the elaboration of the experimental design. J.C. and M.J.C. recruited all participants and collected all the data. Stephanie Willbond performed the ELISA analysis for plasma leptin. J.C. and E.D. interpreted the findings. Finally, J.C. wrote the submitted thesis article. None of the collaborators had any financial motivation in the conception of writing this thesis.

PART FIVE: REFERENCES AND APPENDICES

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Table 1. Participants' characteristics before and after weight loss

Variable	Value	
	Pre-Loss	Post-Loss
Age (y)	33.6 ± 2.1 (19.0-42.0)	33.6 ± 2.1 (19.0-42.0)
Weight (kg)	104.9 ± 5.6 (82.5-152.2)	99.6 ± 5.6 (76.6-146.5) ¹
BMI (kg/m ²)	35.6 ± 1.1 (30.5-43.9)	33.7 ± 1.2 (28.5-42.3) ¹
% Body fat	42.3 ± 1.7 (33.3-55.2)	40.8 ± 1.8 (28.8-52.6) ²
Fat Mass (kg)	41.5 ± 2.5 (29.6-63.4)	38.0 ± 2.4 (25.2-52.3) ¹
Leptin (ng/ mL)	26.8 ± 3.7 (7.6-55.1)	17.7 ± 3.3 (2.0-48.2) ¹

Data are expressed as mean ± SEM; range in parentheses; n=9 and 5 in groups of women and men, respectively.

¹ P < 0.01.

² P < 0.05.

FIGURE CAPTION

Figure 1. Changes in the subjectively rated visual analogue scale (VAS) scores (mm) for palatability of the food reinforcers offered at the end of the testing session (16h00). Post weight loss, participants rated palatability as being more intense ($p<0.01$); error bars are expressed as $\pm$ SEM.

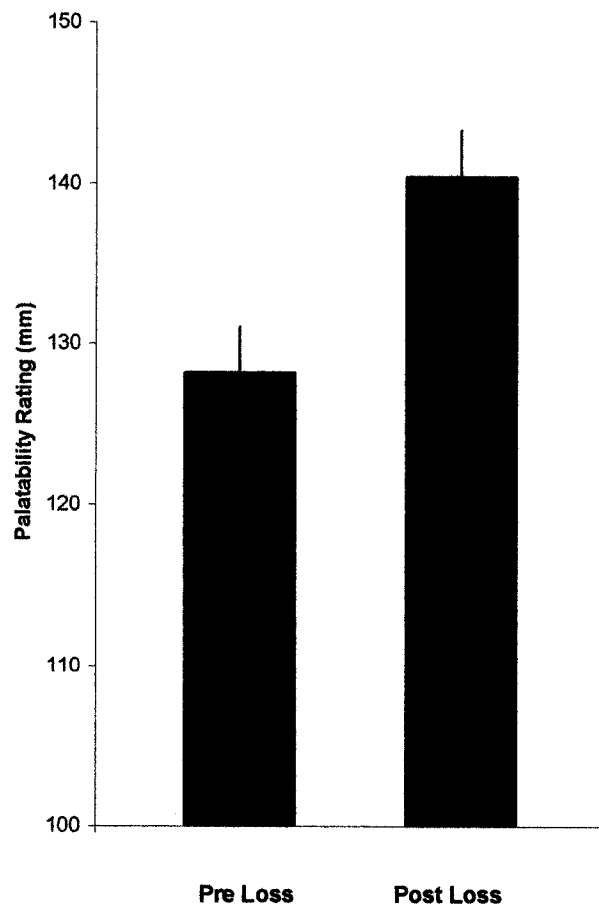


FIGURE CAPTION

Figure 2. Average percent change in the total points earned for the snack food reinforcer pre- and post- weight loss ($p>0.1$). The reinforcement schedule doubled from levels 1-5 (initially set to reinforce every 2 button presses, then 4, then 8, then 16, then 32); error bars are expressed as $\pm$ SEM. Only snack food points are presented graphically due to the fact that fruit/vegetable points are mirror opposites for any given reinforcement schedule; however it is necessary to report total baseline points for snack food ($X=47.4$, $SD \pm 22.6$) and fruit/vegetable ($X=52.6$, $SD \pm 22.6$) and total post points for snack food ($X=42.8$, $SD \pm 31.3$) and fruit/vegetable ($X=57.1$, $SD \pm 31.3$).

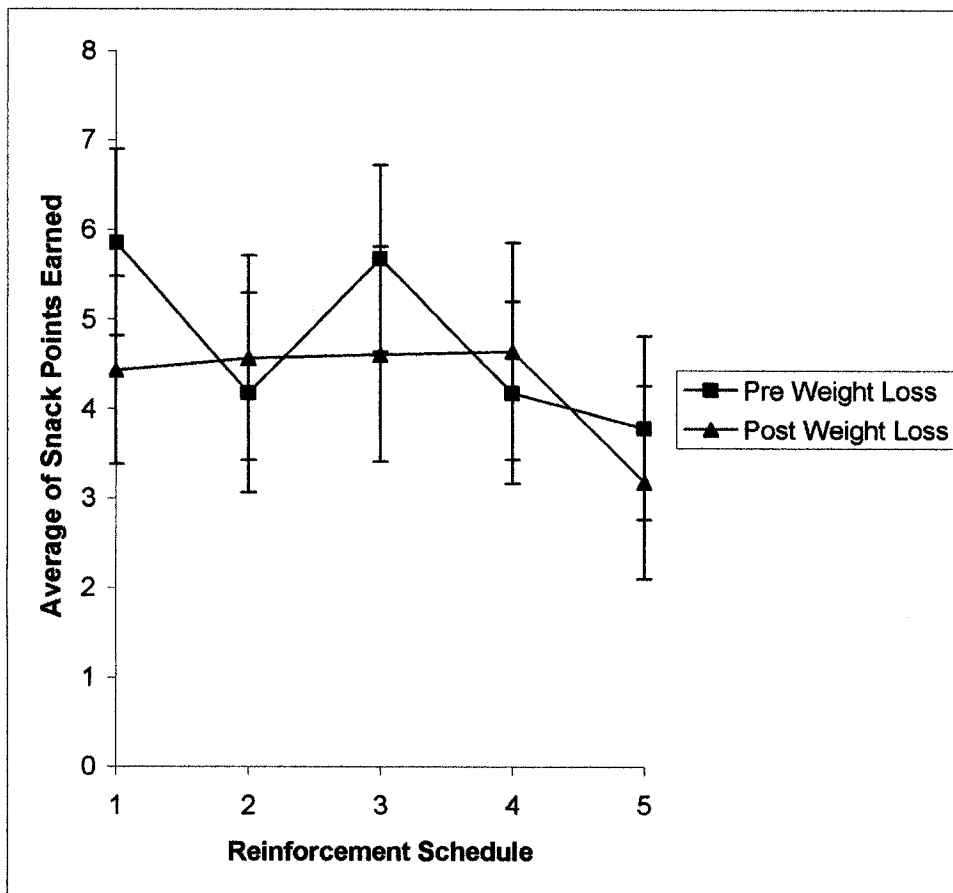
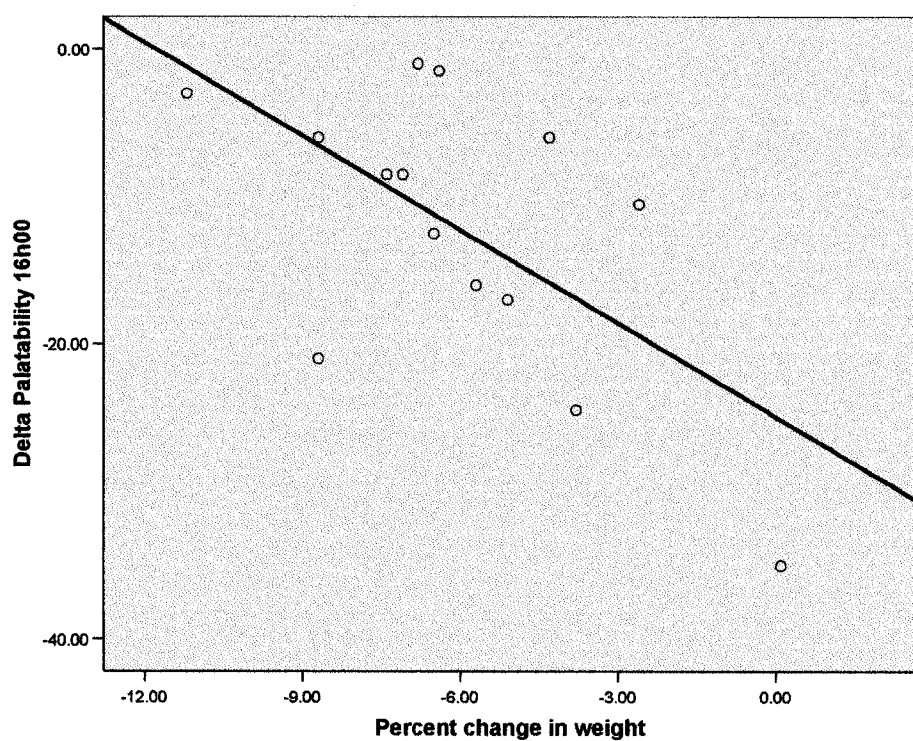


FIGURE CAPTION

Figure 3. Relation between change in palatability (VAS score, mm) and percent change in body weight (kg) for an 8-week deprivation period of 700kcal/day: $R^2=0.38$, $P<0.05$.



APPENDIX A

Recruitment Poster (English and French)



Université d'Ottawa • University of Ottawa

Volunteers needed

FOR A WEIGHT LOSS STUDY

Masters thesis research project:

Principal Investigator: Éric Doucet (Ph.D)

Masters student and Research Coordinator: Marie-Josée Cyr (Dt.P), Jameason
Cameron, B.Sc.

**Behavioral and Metabolic Research Unit, University of Ottawa School of Human
Kinetics**

Selection criteria:

- Women or men aged 18 to 55 years;
- Obese ($30 \text{ kg/m}^2 < \text{BMI} < 45 \text{ kg/m}^2$);
- stable weight for the last 6 months;
- not regularly engaging in physical activity;
- non-smoker;
- not diabetic;
- No major health problems;
- Women with a regular menstrual cycle

For more information, please contact Jameason Cameron (Study
Coordinator), Behavioral and Metabolic Research Unit at

Jameason	Jameason	Jameason	Jameason	Jameason	Jameason	Jameason	Jameason	Jameason	Jameason	Jameason
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POUR UNE ÉTUDE DE PERTE DE POIDS

Unité de recherche sur le comportement et le métabolisme
École des sciences de l'activité physique de l'Université d'Ottawa

- Femmes ou hommes âgés entre 18-55 ans;
- Obèse ($30 \text{ kg/m}^2 < \text{IMC} < 45 \text{ kg/m}^2$);
- Poids stable lors les derniers 6 mois;
- ne pas pratiquer régulièrement d'activité physique;
- non fumeurs;
- non diabétiques;
- Pas de problèmes de santé majeurs;
- Femmes ayant un cycle menstruel régulier

Pour de plus amples renseignements, veuillez appeler Jameason Cameron (coordonnatrice de recherche), Unité de recherche sur le comportement et le métabolisme.

[illegible]

APPENDIX B**Telephone and Screening Questionnaire (English and French)**

MEAL FREQUENCY

Phase	Visite	Date (j/m/a)			Initiales du sujet			Code du sujet (temporaire)		
P-SC	tel									

Eng

PRE-SCREENING QUESTIONNAIRE

Legend : E = exclusion

Questions	Answer	
	Yes	No
➤ Where did you hear about this study?		
➤ What is your age? Between 18 and 55 years?	☐	E
➤ What is your weight?		
➤ What is your height?		
➤ BMI $30\text{kg/m}^2 < \text{BMI} < 40\text{kg/m}^2$?	☐	E
➤ What is your waist circumference? $\geq 102\text{cm}$ M or $\geq 88\text{cm}$ F	☐	E
➤ Do you smoke?	E	☐
➤ Have you been weight stable ($\pm 2\text{ kg}$) for the past 6 months?	☐	E
➤ Do you practice physical activity less than twice a week?	☐	E
-How many minutes per week?		
-Which activities?		
➤ Are you vegetarian?	E	☐
➤ Do you have any food allergies?	☐	☐
If yes, which ones?		
➤ Have you had a medical checkup in the last 12 months?	☐	☐
➤ Do you take any medications?	☐	☐
-If yes which ones?		
➤ Do you suffer from diabetes?	E	☐
➤ Do you suffer from heart problems? Which ones?	E	☐
➤ Do you suffer from hypertension?	E	☐
➤ Do you have any thyroid gland problems?	E	☐
➤ Do you suffer from any other health problem not mentioned in this questionnaire? If yes, which ones?	☐	☐
➤ Would you accept that we take blood samples at these visits?	☐	E

Initiales de l'évaluateur : _____

MEAL FREQUENCY

Phase	Visite	Date (j/m/a)			Initiales du sujet			Code du sujet (temporaire)			
P-SC	tel										

Fr

QUESTIONNAIRE DE PRÉ-SÉLECTION

Légende : E = exclusion

Questions	Réponse	
	Oui	Non
➤ Où avez-vous entendu parler de cette étude?		
➤ Quel est votre âge? Entre 18 et 55ans?	☐	E
➤ Quel est votre poids?		
➤ Quelle est votre taille?		
➤ IMC $30\text{kg/m}^2 < \text{IMC} < 40\text{kg/m}^2$?	☐	E
➤ Quelle est votre circ. de taille? $\geq 102\text{cm}$ M ou $\geq 88\text{cm}$ F	☐	E
➤ Est-ce que vous fumez?	E	☐
➤ Avez-vous un poids stable ($\pm 2\text{kg}$) depuis au moins 6 mois?	☐	E
➤ Pratiquez-vous de l'activité physique à raison de moins de 2 fois par semaine?	☐	E
-Combien de minutes d'activité physique continue pratiquez-vous par semaine?		
-Quelles activités pratiquez-vous ?		
➤ Êtes-vous végétarien?	E	☐
➤ Avez-vous des allergies alimentaires	☐	☐
-Si oui, lesquelles?		
➤ Avez-vous eu un examen médical dans la dernière année?	☐	☐
➤ Prenez-vous des médicaments?	☐	☐
-Si oui, lesquels?		
➤ Souffrez-vous de diabète?	E	☐
➤ Souffrez-vous de problèmes cardiaques? Si oui, Lequel?	E	☐
➤ Souffrez-vous d'hypertension?	E	☐
➤ Est-ce que votre médecin vous a déjà dit que vous aviez des problèmes de glande thyroïde? Si oui, Lequel?	E	☐
➤ Souffrez-vous de tout autre problème de santé qui n'a pas été mentionné qui n'a pas été mentionné dans le présent questionnaire? Si oui, Lequel?	☐	☐
➤ Accepteriez-vous qu'on effectue des prises de sang lors de	☐	E

Initiales de l'évaluateur : _____

APPENDIX C

Appreciation of Certain Foods (English and French)

FOOD APPRECIATION

- 1- Ask the participant to give his level of appreciation of each of the foods of the buffet and the other meals.
- 2- Specify that on the appreciation scale, number 1 represents a food that he does not like at all and that number 5 represents a food that he likes a lot.

Meat and substitutes	I do not like at all				I Like it a lot
Natural peanut butter	1	2	3	4	5
Almonds	1	2	3	4	5
Turkey breast, slice	1	2	3	4	5
Milk products					
Cheddar cheese < 20 % fat	1	2	3	4	5
Yogurt < 2% fat (all flavors, plain)	1	2	3	4	5
Partially skim milk (2%)	1	2	3	4	5
Grain products					
Crackers (wheat thin)	1	2	3	4	5
Whole wheat bread	1	2	3	4	5

Fruits and vegetables					
Carrot	1	2	3	4	5
Raisins	1	2	3	4	5
Apple	1	2	3	4	5
100% pure orange juice	1	2	3	4	5

Commentaires : _____

Food Appreciation

1. Circle one (1) of your favourite snack foods out of the following three (A to C) categories, i.e. not one out of each category.

A. Cake & Desserts

Ah Caramels

Chocolate Cheesecake

Hostess Twinkies

Hostess Cup Cakes

Hostess Ding-Dongs

McCain's Chocolate

McCain's Marble

McCain's Banana

Strawberry Cheesecake

Haagen Dasz Chocolate

Haagen Dasz Chocolate chip cookie dough

Haagen Dasz Chocolate peanut butter

Haagen Dasz Cookies and Cream

Haagen Dasz Strawberry

Haagen Dasz Vanilla

Haagen Dasz Vanilla Fudge Brownie

Two bite chocolate brownies

Two bite banana brownies

B. Candy

Baby Ruth

Butterfinger

Chocolate-coated raisins

Chocolate-coated peanuts

Cadbury's Caramilk
Coffee Crisp
Hershey's Milk Chocolate
Hershey's Milk Chocolate with Almonds
Jersey Milk
Junior Mints
Kit Kat
Licorice (black)
Licorice (red)
Mars
M & Ms chocolate
M & Ms peanut
Milky Way
Oh Henry
Reese peanut butter Cups
Reese Pieces
Skittles
Skor
Smarties
Snickers
Three Musketeers
Tootsie Roll
Twix
York Peppermint Pattie
Wonder Bar

C. Chips (specify favourite flavour)

Cheetos
Doritos
Lay's

Miss Vickie's

Pringles

2. Circle one (1) of your favourite health foods out of the following two categories (i.e. not one out of each category).

D. Fruits

Apple (specify favourite type)

Apricot

Banana

Blueberry

Cheery

Grape

Grapefruit

Honeydew melon

Kiwi

Orange

Peach

Pear

Plum

Prunes

Raspberry

Strawberry

Tangerine

E. Vegetables

Broccoli

Carrot

Celery

Cauliflower

Cucumber

Red Pepper

Green Pepper

Tomatoe

Zucchini

APPRÉCIATION DE CERTAINS ALIMENTS

- 1- Demander au participant de donner son niveau d'appréciation de chacun des aliments contenus dans le buffet et lors des autres repas.
- 2- Spécifier au sujet que sur l'échelle d'appréciation, le numéro 1 représente un aliment qu'il n'aime pas du tout et que le numéro 5 représente un aliment qu'il aime beaucoup.

Viandes et substituts	Je n'aime pas du tout				J'aime beaucoup
Beurre d'arachide naturel	1	2	3	4	5
Amandes	1	2	3	4	5
Poitrine de dinde en tranche	1	2	3	4	5
Produits laitiers					
Fromage cheddar < 20 % MG	1	2	3	4	5
Yogourt < 2% MG (toutes saveurs, nature)	1	2	3	4	5
Lait partiellement écrémé (2%)	1	2	3	4	5
Produits céréaliers					
Crackers (wheat thin)	1	2	3	4	5
Pain de blé entier	1	2	3	4	5
Fruits et Légumes					
Carotte	1	2	3	4	5
Raisins secs	1	2	3	4	5
Pomme	1	2	3	4	5
Jus orange 100% pure	1	2	3	4	5

Commentaires : _____

1. Encercler un (1) de votre collation favori dans les trois catégories (A à C), i.e. pas une par catégorie.

A. Gâteaux et Desserts

Ah Caramels

Hostess Twinkies

Hostess Quatre-quarts

Hostess Ding-Dongs

Gâteau de chocolat McCain

Gâteau de marbre McCain

Gâteau de banane McCain

Gâteau de fromage au chocolat

Gâteau de fromage aux fraises

Petit gâteau au chocolat Deux mordre

Haagen Dasz Chocolate

Haagen Dasz Chocolate chip cookie dough

Haagen Dasz Chocolate peanut butter

Haagen Dasz Cookies and Cream

Haagen Dasz Strawberry

Haagen Dasz Vanilla

Haagen Dasz Vanilla Fudge Brownie

Two bite Chocolate Brownies

Two bite Banana Brownies

B. Bonbon

Baby Ruth

Butterfinger

Raisins enrobé au chocolat

Arachides enrobé au chocolat

Cadbury's Caramilk

Coffee Crisp
Hershey's chocolat au lait
Hershey's chocolat au lait avec Amandes
Jersey Milk
Menthes Junior
Kit Kat
Réglisse (noir)
Réglisse (rouge)
Mars
Chocolat M & Ms
Arachide M & Ms
Milky Way
Oh Henry
Reese peanut butter Cups
Reese Pieces
Skittles
Skor
Smarties
Snickers
Three Musketeers
Tootsie Roll
Twix
Wonder Bar

C. Frites (spécifiez votre saveur favori)

Cheetos
Doritos
Lay's
Miss Vickie's
Pringles

2. Encercler un (1) de votre aliment santé favori dans les deux catégories (i.e. pas un dans chaque catégorie).

D. Fruits

Pomme (spécifiez votre saveur favori)

Abricot

Banane

Bluets

Cerises

Raisin

Pamplemousse

Melon d'eau

Kiwi

Orange

Pêche

Poire

Prune

Pruneau

Framboises

Fraises

Mandarine

E. Légumes

Brocoli

Carotte

Céleri

Chou-fleur

Concombre

Poivron rouge

Poivron vert

Tomate

Courgette

APPENDIX D**Consent Form (English and French)**

Université d'Ottawa • University of Ottawa

Faculté des sciences de la santé
École des sciences de l'activité physique

Faculty of Health Sciences
School of Human Kinetics

CONSENT FORM

**EFFECTS OF HIGH FREQUENCY MEALS ON BODY WEIGHT LOSS, APPETITE
REGULATION AND PYY LEVELS.**

&

**THE EFFECTS OF FOOD DEPRIVATION ON FEEDING BEHAVIOUR, LEPTIN
LEVELS AND THE RELATIVE-REINFORCING VALUE OF FOOD**

Masters thesis research project

Principal Investigator: Éric Doucet (Ph.D)

**Research Coordinators and masters Students: Marie-Josée Cyr (Dt.P), Jameason
Cameron (B.Sc)**

**Faculty of Health Sciences, University of Ottawa
School of Human Kinetics**

1. INVITATION TO PARTICIPATE: You are invited to participate in the above named research study conducted by Marie-Josée Cyr Dt.P and Jameason Cameron, masters candidates supervised by Éric Doucet Ph.D.

2. PURPOSE OF THE STUDY: The aim of this study is to 1) investigate whether using an increased meal frequency pattern (3 meals + 3 snacks/day) will lead to greater weight loss than the conventional low meal frequency pattern (3 meals/day) in response to an equal caloric restriction; 2) examine the daily PYY levels between the two groups; 3) examine the daily variation in appetite between the two group; 4) examine the effects of weight loss on hunger, palatability and the relative-reinforcing value of food, and 5) examine whether changes in plasma leptin correlate with changes in hunger, palatability and the relative-reinforcing value of food. Therefore, if you wish to take part in this study, the intended duration of your participation will be of 12 weeks, including 9 visits to the research unit.

3. BACKGROUND: Few studies have concentrated on the efficacy of increased meal frequency on weight loss and appetite regulation. High meal frequency with a regular pattern has potential role in increasing the level of compliance while following an energy restriction via PYY levels, which favors better control in appetite. Peptide YY is a gut hormone released in the blood after meals and is recognized to inhibit food intake. Peptide YY is secreted from the pancreas and in the gastrointestinal tract. With this research, we want to study if high meal frequency will lead to a greater weight loss than the conventional low meal frequency. Measurements during this protocol will include body composition, energy expenditure, appetite and psychological assessments. Results obtained from this study will enable us to better understand the effects of meal frequency on body weight loss, appetite regulation and PYY level. Also, during this study, data will be collected in order to further understand how dieting affects the subjective rating of hunger, fullness, food

palatability, and willingness to perform simple button-presses to obtain food. It is known that the adipose tissue hormone leptin is a good marker of overall adipose tissue levels, and a goal will be to observe whether or not changes in leptin that will follow weight loss will correlate with expected changes in participant ratings of hunger, fullness, and food palatability; also, it is of interest to observe the effects of the change in leptin on willingness to perform simple button-presses to obtain food. From this experiment, the researchers anticipate further understanding of the influences of food deprivation on how food tastes (liking/hedonics) and on the desire to obtain food (wanting). We aim eventually to be able to design weight loss-weight maintenance programs that have a greater resolution potential.

4. DESCRIPTION OF THE STUDY: Initial visits: You will be asked to visit the research unit for an initial visit (*Initial visit 1*) of approximately 2 hours during which the study as well as the consent form will be explained to you. You can then bring the consent form home so further reading and discussion with family members is made possible. Other questionnaires will also have to be filled out at that moment and your height, weight and waist circumference will be measured for screening purposes. Results from these measurements will then be analyzed in order to determine if you correspond to the inclusion criteria of this present study. If you do correspond and agree to participate in this study, you will be asked to come to the research unit for a second initial visit (*initial visit 2*) which will last for approximately 3 hours. During this visit, your resting metabolic rate will be measured in order to determine your basal energy needs. The dietitian will give you a weight stabilization diet for 3 days. After this, you will have to come back to the research unit for 2 other sessions before the beginning of the weight loss program. Follow-ups will also be necessary during the weight loss program. This research project consists of two 8 week experimental diets (either high or low frequency meals). These sessions of testing are described in details below.

BASELINE ASSESSMENTS DAY (WEEK -2) AND POST DIET SESSION 2 (WEEK 8 + 2 DAYS)

A. Arrival at the laboratory 7h30.

B. Resting (7h30-8h00) – You will have to rest comfortably in the reclining bed for a 30 minute period.

C. Resting Metabolic Rate (8h00-8h30) - After a 30 minute resting period in the supine position a measurement of resting energy expenditure will be done. The measurement of resting metabolic rate takes place early in the morning after an overnight fast. A plexiglass hood will be placed over your head through which fresh air will be drawn. The expired air will be sampled for analysis and percentages of oxygen and carbon dioxide determined for 30 minutes. By measuring the flow rate, we will be able to determine the amount of oxygen that is consumed and derive energy expenditure. This test requires that you lie quietly and relaxed in bed for around 30 minutes. There are no risks associated with this procedure.

D. Body composition (8h30-9h00) - Body weight, height and waist circumference will be measured. A method called dual-photon x-ray (DEXA) will be used to measure bone density, percent fat and percent lean body mass. You will have to lie on an examination table, fully clothed, while a low intensity x-ray will scan the entire body. The measurements takes 20 minutes. The only risk is a minimal x-ray exposure of less than 0.5 millirem. This exposure is less than the naturel background from 1 day of exposure to sunlight.

E. Standardized breakfast test meal and appetite ratings (9h00-12h00) - After an overnight fast, you will be served a variety of foods at 8h30. You will be asked to eat a standardized breakfast test meal, which will consist of whole bread, natural peanut butter and milk (8h30-9h00). Appetite ratings will be measured before and after breakfast and every 15 minutes for a period of 180 minutes. This will be done using a pen and paper on a visual analogue scale. Briefly, desire to eat, hunger, fullness and prospective food consumption (PFC) will be rated. Questions will be asked as follows: 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), and 4) "How much food do you think you could eat?" (Nothing at all- A large amount).

F. Computer Task (12h00-12h25) - You will be required to complete a computer task to assess the amount of work done for a particular reinforcer (snack or fruit/vegetable) that will be allotted towards the end of the session. The computer task is as follows. You will sit in front of a laptop with a joystick which allows you to switch from two separate screens, each representing an opportunity to work for food points: one screen is for your favorite snack food, and the other for your favourite fruit or vegetable. To earn the points you must work for them by pressing a button on the joystick, which in turns starts a slot machine. Points are earned when all three objects on the screen match.

G. Blood Sample For Leptin (12h25-12h30) - A qualified nurse will withdraw a small sample of blood (8-10ml).

H. Subjective VAS ratings (12h30-12h35) -You will be required to complete a rating of VAS for hunger, prospective food consumption, and fullness.

I. Standardized Lunch (12h35-13h00) - You will be asked to eat a standardized lunch test meal.

J. Subjective VAS ratings (13h00-13h05) - You will be required to complete a rating of VAS for hunger, prospective food consumption, palatability, and fullness.

K. Subjective VAS ratings (13h30-15h30) - Every half hour you will be required to complete a rating of VAS for hunger, prospective food consumption, and fullness.

L. Computer Task (15h35) - You will be required to complete the same computer task to assess the amount of work done (simple button-presses on a joystick) for a particular reinforcer (snack or fruit/vegetable) that will be allotted immediately following this test.

M. Offering and Consumption of Reinforcer (16h00-16h30) - You will now be offered the amount of food that is equivalent to the number of food points that you earned during the computer task. You may eat as much of the food as you wish.

N. Subjective VAS ratings (16h30) - You will be required to complete a rating of VAS for hunger, prospective food consumption, palatability, and fullness.
END OF BASELINE SESSION 16h35

O. END OF BASELINE AND POST DIET SESSION 2 16H45

PRE-DIET SESSION (WEEK -1) AND POST-DIET SESSION 1 (WEEK 8 + 1 DAY)

A. Arrival at the laboratory 7h30.

B. Insertion of catheter and PYY blood samples (7h30-14h45) – You will rest comfortably in a reclining bed. An intravenous catheter will be placed in a vein in your arm. Blood samples will be drawn every 30 minutes to measure PYY levels. Eighteen samples of 5 ml will be taken for a total of 90 ml. Insertion of the catheter and blood samples will be performed by a registered nurse.

C. Appetite ratings (7h30-14h45) - Appetite ratings will be measured every 30 minutes for 8 hours. Food will be served to you according to your respective meal plan (high or low meal frequency).

D. Breakfast (8h00- 8h30) - A breakfast will be served consisting of toast, peanut butter, yogurt and a fruit.

E. AM Snack (10h15-10h30) - A midmorning snack will only be served to the high meal frequency group and will consist of crackers, cheese and milk.

F. Explanation of the experimental diet (10h30-11h00) - The dietitian will go through the meal plan as well as portion sizes. Any questions or concerns about the diet will be answered.

G. Lunch (12h00-12h30) - A lunch will be served consisting of a sandwich, vegetables, crackers and milk.

H. PM Snack (14h15-14h30) - An afternoon snack will be served to the high meal frequency group consisting of a fruit, nuts and yogurt.

I. END OF PRE-DIET SESSION AND POST DIET SESSION 2 14h45

CONTROL SESSIONS (WEEK 1 3 AND 5)

A. Arrival at the laboratory 8h00

B. Anthropometric measurements (8h00-8h10) - Body weight will be determined with a standard beam scale, whereas height and waist circumference will be measured with a tape.

C. 24 hour dietary recall (8h10-8h30) - The participant will be asked to fill out a 24 hour dietary recall with the help of the dietitian and any questions regarding their experimental diet will be answered.

D. END of CONTROL SESSIONS 8h30

TELEPHONE CONTROLS (WEEK 0, 2 4 AND 6)

A. The dietitian will call the participant to assess his adherence to the experimental diet and to answer questions.

5. POSSIBLE RISKS/DISCOMFORTS:

The risks associated with this project are low and minimal. The measure of body composition (DEXA) presents a low risk to you. However, it is important to underline that this apparatus will expose you to a minimal radiation (the equivalent of a day in the sun - 0.02-0.05 mRem). The blood samples also present very few risks. However, a small local hematoma (a bruise at the venal puncture) could develop during the few days following the blood sampling. Since the catheter has to be worn for a few hours for certain measures (satiety hormone PYY), it is possible that you will experience a certain discomfort. It is important to note that the risks of infection, of phlebitis (inflammation of the vein) and vaso vagal shock (loss of consciousness) are very low, but still remain a possibility. As for any weight loss program, the energy restriction could make you feel weak and/or tired at the beginning of the program and it might take a certain number of days for your body to adapt to the energy restriction. Hunger will also be an important side-effect throughout. It is important to note that weight relapse is common after weight loss.

6. BENEFITS:

Your participation in this study will allow you to gather information on your body composition as well as on other health indicators (e.g. resting metabolic rate, glucose profile...). Further, you will most likely lose body weight which will lead to improvements of blood lipids such as total cholesterol and LDL cholesterol, blood glucose and quality of life. In addition, certain notions and practical advice on healthy eating will also be offered to you.

7. MONETARY COMPENSATION:

Parking at the research center is free for participants, as are all scientific tests. You will receive a compensation of \$100.00 which will be paid in increments of 25\$ at the beginning of visit initial 2, baseline session, pre-diet and post-diet. You will not be compensated for a session for which you did not show up.

8. CONFIDENTIALITY AND ANONYMITY:

In order to guarantee the confidentiality and anonymity of participants, all precautions and necessary measures will be taken to ensure that results and personal information of participants is kept under the strictest of confidentiality.

- Only the following persons will have access to the material: Principal Investigator, Research Coordinators, and Nurse. Any other individuals involved in the study will not have access to participant's personal information and results.
- The names of participants will not appear on any reports. A number code will be used to identify participants on all research documents.
- All material and information which can be linked to participants will not be made public and will be kept under the strictest confidentiality.
- Participants will not be identified in any way in publications or reports.
- The data collected will be kept in a locked cabinet in the Behavioral and Metabolic Research Unit with restricted access where all participant's folders will be kept. In addition, the computer files will be protected by a password.
- Blood samples will be kept in the research unit's laboratory freezer. Blood samples will be identified by a number code which will not be retraced.
- Data will be destroyed and any blood samples eliminated five years after publication of study results.

9. VOLUNTARY PARTICIPATION

- You are free to refuse to participate and if you choose to participate, you are free to withdraw from the study at any time for any reason. At any moment during this study, the best interests of participants will always prevail upon the objectives of the study.
- The participants will be made aware of new findings that might influence their decision to take part in the present study.

Any information about your rights as a research participant may be addressed to: Protocol officer for ethics in research, University of Ottawa, 550 Cumberland, Tabaret Hall, room 159, Ottawa, Ontario, K1N 6N5; Phone: (613) 562-5841, email: ethics@uottawa.ca.

If I have any questions about the conduct of the research project, I may contact the research coordinators, Marie-Josée Cyr, mcyr105@uottawa.ca, and Jameason Cameron, jcame077@uottawa.ca, at (613) 746-4621 x 6029.

There are two copies of the consent form, one of which I may keep.

Please choose one of the following options:

If I choose to withdraw from the study, I want that all data gathered from me until the time of withdrawal be destroyed ☐

Even if I withdraw from the study, I accept that the data gathered from me be used for this study ☐

Researcher' signature

Eric Doucet, Ph.D.: _____ Date:

Research coordInators' Signatures

Marie-Josée Cyr, M.(Sc).(candidate): _____ Date:

Jameason Cameron, M.(Sc).(candidate): _____ Date:

PARTICIPANT'S SIGNATURE:

I agree to participate in this study,

Date:

Printed Name

Signature



Université d'Ottawa • University of Ottawa

Faculté des sciences de la santé
École des sciences de l'activité physique

Faculty of Health Sciences
School of Human Kinetics

FORMULAIRE DE CONSENTEMENT

EFFETS D'UNE FRÉQUENCE DE REPAS ÉLEVÉE SUR LA PERTE DE POIDS CORPOREL, LA RÉGULARISATION DE L'APPÉTIT ET SUR LES NIVEAUX DE PYY.

&

EFFETS DE LA PRIVATION DES ALIMENTS SUR LE COMPORTEMENT ALIMENTAIRE, LES NIVEAUX DE LEPTINE ET SUR LA VALEUR RELATIVE DE RENFORCEMENT DES ALIMENTS.

Projet de recherche pour thèse de maîtrise

Chercheur principal : Éric Doucet (Ph.D)

Coordinateurs de recherche et étudiants à la maîtrise : Marie-Josée Cyr (Dt.P.) et Jameason Cameron B.Sc.

**Faculté des sciences de la santé, Université d'Ottawa
École des sciences de l'activité physique**

1. VOTRE PARTICIPATION: Vous êtes invités à participer à l'étude mentionnée ci-haut. Ce projet sera dirigé par Marie-Josée Cyr (Dt.P) et Jameason Cameron candidats à la maîtrise, supervisés par Eric Doucet (Ph.D).

2. OBJECTIF DE L'ÉTUDE: Cette recherche vise à 1) examiner si l'utilisation d'un patron de repas à fréquence élevée (3 repas + 3 collations/jour) va mener vers une plus grande perte de poids qu'un patron de repas à fréquence diminuer suite à une restriction énergétique identique; 2) examiner les niveaux de l'hormone peptide YY (PYY) entre les deux groupes; 3) examiner les variations quotidiennes de l'appétit entre les deux groupes; 4) examiner les effets de la perte de poids sur la sensation de faim, la palatabilité et la valeur relative de renforcement des aliments; 5) examiner si les changements de leptine plasmatique sont associés avec des changements au niveau de la sensation de faim et la valeur relative de renforcement des aliments. Ainsi, la durée de votre participation sera de 12 semaines si vous acceptez d'y prendre part et ceci à raison de 9 visites à l'unité de recherche.

3. BUT DE L'ÉTUDE: Peu d'études ont investigué l'efficacité d'une fréquence de repas élevée sur la perte de poids corporel et la régularisation de l'appétit. La fréquence des repas possède un rôle potentiel sur une augmentation du niveau d'adhérence lors d'une restriction énergétique via des niveaux de PYY potentiellement plus élevés ce qui pourrait favoriser un meilleur contrôle de l'appétit. Peptide YY est une hormone provenant de l'intestin qui est relâchée dans la circulation sanguine suite à l'ingestion d'un repas qui est reconnue d'inhiber la consommation d'aliments. Peptide YY est sécrété à partir du pancréas et du

tractus gastro-intestinal. À l'aide de cette recherche, nous visons à étudier si une fréquence de repas élevée induira une plus grande perte de poids en comparaison avec une fréquence de repas diminuée. Des données de composition corporelle, de dépense calorique, mesures d'appétit, ainsi que des données psychosociales seront effectuées. Les résultats de cette recherche permettront de mieux comprendre les effets de la fréquence des repas sur la perte de poids corporel, la régularisation de l'appétit et sur les niveaux de PYY. Pendant l'étude, les données seront recueillies afin de comprendre plus profondément les effets de la perte de poids sur l'évaluation subjective de la faim, de la satiété, de la palatabilité des aliments et de la détermination d'exécuter une motion simple d'appuie sur une touche afin d'obtenir de la nourriture. Leptine est une hormone connue comme étant un bon marqueur des niveaux de tissus gras (tissus adipeux). Le but sera d'observer si les changements de leptine suivant la perte de poids seront associés avec les changements anticipés au niveau de l'évaluation du niveau de la faim, de la satiété et de la palatabilité au niveau des participants. De plus, nous allons observer les effets des changements de leptine sur la détermination d'exécuter une motion simple d'appuie sur une touche afin d'obtenir de la nourriture. À partir de cette recherche, nous anticipons une compréhension plus approfondie sur l'influence de la privation des aliments sur le goût des aliments (aimer/plaisir de consommer des aliments) et sur le désir d'obtenir de la nourriture (vouloir). Ceci aidera éventuellement à développer des programmes de perte et de maintien de poids corporel ayant un plus grand potentiel de résolution.

4. DESCRIPTION DE L'ÉTUDE: Visites initiales: Vous devrez vous présenter à l'unité de recherche pour une brève visite d'environ 2 heures (*visite initiale 1*). Lors de la visite initiale 1, l'étude et le formulaire de consentement vous seront expliqués. Vous pourrez par la suite apporter le formulaire de consentement à la maison afin de le lire plus attentivement et d'en discuter avec les membres de votre famille si vous le désirez. Quelques questionnaires devront également être remplis à ce moment et une mesure de votre taille, poids et circonférence de taille, servant au processus de sélection, sera effectuée. Les résultats de ces mesures seront ensuite rapidement analysés afin de déterminer si vous correspondez aux critères de sélection de l'étude. Si vous répondez aux critères de sélection et acceptez de participer à l'étude, vous devrez vous rendre à l'unité de recherche pour une seconde visite initiale (*visite initiale 2*) qui également sera d'une durée de 3 heures. Lors de cette visite, une mesure de la dépense énergétique au repos sera effectuée afin de déterminer vos besoins énergétiques de base. La diététiste de l'étude vous assignera un régime de stabilisation de poids pour une période de 3 jours. Suite au troisième jour, vous devrez vous présenter à l'unité de recherche pour deux autres sessions avant le début du programme de perte de poids. Des suivis seront également nécessaires pendant le programme de perte de poids. Ce projet de recherche consiste à suivre deux régimes expérimentales de 8 semaines (soit à fréquence de repas élevée ou faible). Les descriptions des mesures qui auront lieu lors de ces visites sont présentées ici-bas.

SESSION PRÉLIMINAIRE (SEMAINE -2) ET SESSION POST-RÉGIME II (SEMAINE 8 + 2 JOURNÉES)

A. Arrivée au laboratoire 7h30.

B. Repos (7h30-8h00) – Vous devrez vous reposer dans un lit pour une période de 30 minutes.

C. Mesure de métabolisme de repos (8h00-8h30) – Cette mesure vise à établir la dépense énergétique de repos en se basant sur la consommation d'oxygène et la production de dioxyde de carbone. Vous devrez vous coucher sur un lit et placer un casque de plastique transparent au-dessus de votre tête et respirer dans celui-ci pendant une période d'environ 30 minutes. Il est également important de souligner que cet appareil assure un apport adéquat en air frais lors de la mesure ce qui réduit considérablement l'inconfort associé à la mesure. Cette mesure ne comporte aucun risque.

D. Composition corporelle (8h30-9h00) - Votre poids corporel et votre taille seront mesurés. La méthode du DEXA (Dual Energy X-ray Absorptiometry) sera utilisée afin de mesurer votre densité osseuse, votre pourcentage de graisse et votre masse musculaire. Pour ce faire, vous devrez vous coucher, vêtu d'une jaquette d'hôpital, sur une table d'examen pendant qu'un rayon-x de faible intensité parcourra votre corps de la tête aux pieds. Cette mesure est d'une durée moins de 20 minutes. La radiation associée à cette mesure est moins de 0.5 millirem, ce qui correspond à une journée d'exposition au soleil.

E. Déjeuner standard et mesure de l'appétit (9h00-12h00) – Suite à une période de jeun, des aliments vous seront servis à 9h00 consistant de pain blé entier, beurre d'arachide naturel et lait (8h30-9h00). Des mesures d'appétit seront administrées avant et après le déjeuner et chaque 15 minutes pour une période de 180 minutes. Ceci sera fait à partir d'un crayon et d'un papier et d'une échelle visuelle analogue. Brièvement, le désir de manger, la sensation de faim, la satiété et l'apport d'aliments prospectif sera mesuré. Les questions seront demandées comme suit: 1) "Dans quelle mesure avez-vous envie de manger?" (Envie très faible- Envie très forte); 2) "Dans quelle mesure avez-vous l'impression d'avoir faim?" (Envie très faible- Envie très forte); 3) "À quel point vous sentez-vous rempli?" (Pas rempli du tout- Très rempli), et 4) "Quelle quantité de nourriture pourriez-vous manger immédiatement?" (Absolument rien- Une grande quantité).

F. Tâche d'ordinateur (12h00-12h25)—Vous serez demandé de compléter une tâche à l'ordinateur afin de déterminer le montant de travail que vous serez prêt à compléter pour un renforcement en particulier (collation ou fruit/légume), qui sera donné vers la fin de la session. La tâche sera la suivante: vous devrez vous asseoir devant un ordinateur portatif avec une manette qui vous permettra de changer entre deux écrans séparés. Chaque écran vous donnera l'opportunité de travailler pour des points afin de recevoir de la nourriture. Un écran sera pour votre collation favorite et l'autre sera pour votre fruit ou légume favori. Pour gagner les points vous devrez travailler en appuyant sur la touche de la manette, qui par la suite changera à un écran de machine à sous. Les points seront gagnés quand les trois figures à l'écran seront identiques.

G. Prélèvements sanguins de leptine (12h25-12h30)—Un prélèvements sanguin d'environ 8-10ml sera pris par une infirmière qualifiée.

H. Mesures de l'appétit (12h30-12h35)—L'appétit sera mesurée à partir d'une échelle visuelle analogue afin de déterminer la sensation de faim, la consommation de nourriture prospective et le niveau de satiété.

I. Dîner standard (12h35-13h00)—Un dîner standard vous sera servi d'un sandwich, légumes, craquelins et lait.

J. Mesures d'appétit (13h00-13h05)—L'appétit sera mesurée à partir d'une échelle visuelle analogue afin de déterminer la sensation de faim, la consommation de nourriture prospective, la palatabilité et le niveau de satiété.

K. Mesures d'appétit (13h30-15h30)—L'appétit sera mesurée à chaque 30 minutes à partir d'une échelle visuelle analogue afin de déterminer la sensation de faim, la consommation de nourriture prospective et le niveau de satiété.

L. Tâche d'ordinateur (15h35-16h00)—Vous serez demandé de compléter une tâche à l'ordinateur afin de déterminer le montant de travail que vous serez prêt à compléter pour un renforcement en particulier (collation ou fruit/légume), qui sera donné vers la fin de la session. Même description qu'au point D.

M. Consommation des aliments de renforcement (16h00-16h30)—Des aliments vous seront servis basés sur le nombre de points que vous avez obtenus lors de la tâche à l'ordinateur. Vous ne serez pas obligé de consommer en entier le ou les aliments qui vous seront servis.

N. Mesures d'appétit (16h30-16h35)—L'appétit sera mesurée à partir d'une échelle visuelle analogue afin de déterminer la sensation de faim, la consommation de nourriture prospective, la palatabilité et le niveau de satiété.

FIN DE LA SESSION PRÉLIMINAIRE 16H35

SESSION PRÉ-RÉGIME (SEMAINE -1) ET SESSION POST-RÉGIME I (SEMAINE 8 + 1 JOURNÉE)

A. Arrivée au laboratoire 7h30.

B. Insertion du cathéter et prélèvements sanguins de peptide YY (7h30-14h45) - Vous reposant confortablement sur un lit à inclinaison, un cathéter intraveineux (petit tube de plastique) sera inséré dans une veine de votre avant-bras par une infirmière qualifiée. Des prélèvements sanguins seront pris chaque 30 minutes afin de mesurer les niveaux de l'hormone peptide YY. Quinze échantillons de 5ml seront prélevés, pour un total de 75 ml de sang. L'insertion du cathéter et les prélèvements sanguins seront effectués par une infirmière qualifiée.

C. Mesure de l'appétit (7h30-14h45) – L'appétit sera mesurée chaque 30 minutes pour une période de 8 heures. Des aliments vous seront servis pendant la journée selon votre plan de repas expérimental (fréquence de repas élevée ou faible).

D. Déjeuner (8h00- 8h30) - Un déjeuner vous sera servi composé de rôties, beurre d'arachide, yogourt and un fruit.

E. Collation en avant midi (10h15-10h30) - Une collation vous sera servi seulement si vous faite parti du groupe de fréquence de repas élevé. Celui-ci sera composé de craquelins, fromage et lait.

F. Explication du régime expérimental (10h30-11h00) – Vous rencontrerez la diététiste de l'unité de recherche. Elle vous expliquera le régime de restriction énergétique et fera une revue de la grosseur des portions. Toutes questions ou préoccupations au sujet du régime seront répondues.

G. Dîner (12h00-12h30) – Un dîner vous sera servi composé d'un sandwich, légumes, craquelins et lait.

H. Collation en après-midi (14h15-14h30) - Une collation vous sera servi seulement si vous faite parti du groupe de fréquence de repas élevé. Celui-ci sera composé d'un fruit, noix et yogourt.

I. FIN DE LA SESSION PRÉ-RÉGIME 14h45

SESSIONS CONTRÔLES (SEMAINES 1, 3 ET 5)

A. Arrivée au laboratoire 8h00

B. Mesures anthropométriques (8h00-8h10) – Votre poids corporel et votre circonférence de taille sera mesurés.

C. Rappel de 24 heures (8h10-8h30) – Vous devrez remplir un rappel de 24 heure de votre consommation alimentaire à l'aide de la diététiste et toutes questions ou préoccupations au sujet du régime sera répondues.

D. FIN DES SESSIONS CONTRÔLES 8h30

CONTRÔLES TÉLÉPHONIQUES (SEMAINE 0, 2, 4 ET 7)

A. La diététiste vous contactera afin d'évaluer votre niveau adhérence au régime expérimental et afin de répondre à toutes questions ou préoccupations au sujet du régime.

5. RISQUES PRÉVISIBLES: Les risques associés à la participation à cette étude sont peu nombreux et très faibles. La mesure de graisse corporelle (DEXA) présente peu de risques pour vous. Il importe toutefois de souligner que cet appareil vous exposera à un minimum de radiation (l'équivalent d'une journée au soleil - 0.02-0.05 mRem). Les prélèvements sanguins présentent également peu de risques. Cependant, un léger hématome local (un bleu à l'endroit de la ponction veineuse) pourrait se manifester pendant quelques jours suite aux prélèvements. Puisque le cathéter devra être porté pendant quelques heures lors des mesures de l'hormone de satiété PYY, un certain inconfort pourrait être ressenti par les participants. Il est à noter que les risques d'infections, de phlébites (inflammation de la veine) et de chocs vaso-vagals (perte de conscience) sont faibles dans de telles conditions, mais il en demeure toutefois une possibilité. Pour le programme de perte de poids, une restriction énergétique pourrait vous rendre faible et/ou fatigué au début de l'intervention. Il se peut que votre corps prendra quelques jours à s'adapter à la restriction énergétique. Une augmentation de la faim pourrait se faire ressentir pendant le programme de perte de poids. Il est également important de mentionner qu'un regain de poids corporel est possible une fois le programme terminé.

6. AVANTAGES: Votre participation à cette étude vous permettra de recueillir de l'information quant à votre composition corporelle ainsi qu'autres indicateurs de santé (i.e. dépense énergétique de repos, profil hormonal...). Il est fort probable que vous subirez une perte de poids corporelle qui mènera à une amélioration de votre profil lipidique (cholestérol total, cholestérol LDL), de votre glycémie (glucose sanguin) et de votre qualité de vie. De plus, certaines notions et conseils pratiques seront véhiculés quant à la saine alimentation.

7. COMPENSATION MONÉTAIRE: Les tests auxquels vous aurez accepté de vous soumettre sont gratuits. Il en va de même pour le stationnement au centre de recherche. Vous recevrez également une compensation financière totale de \$100.00 qui sera payée en incréments de 25\$ au début de la visite initiale 2, session préliminaire, session pré-régime et post-régime. Vous ne serez pas compensés pour une session à laquelle vous étiez absent.

8. CONFIDENTIALITÉ ET ANONYMAT: Afin de garantir la confidentialité et l'anonymat des participants, toutes les précautions et mesures nécessaires seront prises afin d'assurer que les résultats et l'information personnelle des participants soient gardés sous la confidentialité la plus sévère.

- Seules les personnes suivantes auront accès au matériel : chercheur principal, coordonnatrice de recherche et infirmière. Tout autre individu impliqué dans l'étude n'aura pas accès aux informations personnelles ou aux résultats des participants.
- Les noms des participants n'apparaîtront dans aucuns rapports. Un code numérique sera utilisé pour identifier les participants dans tous les documents de recherche.
- Tous les matériaux et l'information qui peuvent être associés aux participants ne seront pas disponibles au public et seront gardés sous la confidentialité la plus sévère.
- Les participants ne seront pas identifiés dans les publications ou rapports.
- Les données recueillies seront gardées dans une armoire verrouillée dans l'Unité de recherche sur le comportement et le métabolisme, dans un local à accès limité. De plus, les documents sur ordinateur seront protégés par un mot de passe.

- Les échantillons sanguins seront gardés dans un réfrigérateur de l'unité de recherche. Les échantillons sanguins seront identifiés par un code numéroté qui ne pourra être retracé.
- Les données seront détruites et les échantillons sanguins éliminés cinq ans suivant la publication des résultats de l'étude.

9. PARTICIPATION VOLONTAIRE :

- Vous avez le choix de refuser de participer à cette étude. Si vous choisissez de participer, vous pouvez vous retirer de l'étude en tout temps pour toute raison. À tout moment lors de cette étude, les intérêts des participants vont prévaloir les objectifs de l'étude.
- Les participants seront avertis de nouvelles trouvailles qui pourraient influencer leur décision à prendre part dans la présente étude.

Toutes informations au sujet de vos droits en tant que participant de recherche peuvent être adressées à : Responsable de la déontologie en recherche, Université d'Ottawa, 550 rue Cumberland, Pavillon Tabaret, salle 159, Ottawa, Ontario, K1N 6N5; Tél. : 613-562-5841, courrier électronique : ethics@uottawa.ca.

Advenant des questions au sujet de la conduite du projet de recherche, vous pouvez contacter la coordonnatrice du projet, Marie-Josée Cyr, (613) 746-4621 x 6029, mcyr105@uottawa.ca et Jameason Cameron {

Il y a deux copies du formulaire de consentement dont une que vous pouvez garder.

SVP choisir une des options ci-dessous :

Si je choisis de me retirer de l'étude, je veux que ☐
toutes données recueillies à mon sujet soient détruites

Même si je choisis de me retirer de l'étude, j'accepte que ☐
les données recueillies à mon sujet soient utilisées pour cette étude

SIGNATURE DU CHERCHEUR :

Eric Doucet, Ph.D.: _____

Date:

SIGNATURE DE LA COORDONATRICE DE RECHERCHE :

Marie-Josée Cyr, M.Sc.(candidate): _____

Date:

Jameason Cameron, M.Sc.(candidate): _____

Date:

SIGNATURE DU PARTICIPANT :

Je consent participer à cette étude,

Date:

Nom imprimé

Signature

APPENDIX F

Study Release/Payment Form (English and French)



Université d'Ottawa • University of Ottawa

Faculté des sciences de la santé
École des sciences de l'activité physique

Faculty of Health Sciences
School of Human Kinetics

SUBJECT COMPENSATION FORM

I, _____, hereby confirm that I have participated in the study entitled "*Effect of High Meal Frequency on Body Weight Loss, Appetite Regulation and Petite YY*" that was conducted by Marie-Josée Cyr, Jameason Cameron and Dr. Éric Doucet of the School of Human Kinetics at the University of Ottawa. For this reason, I am entitled to receive the monetary compensation of 100\$ for the entire weight loss program as stipulated in the consent agreement of this study.

Researcher's signature: _____ Date: _____

Participants signature: _____ Date: _____

(Please note that payment will take at least 2 weeks from the date that this document has been signed).

Subject mailing address:

For administrative use ONLY

Account #: _____

Approved on: _____

APPENDIX G

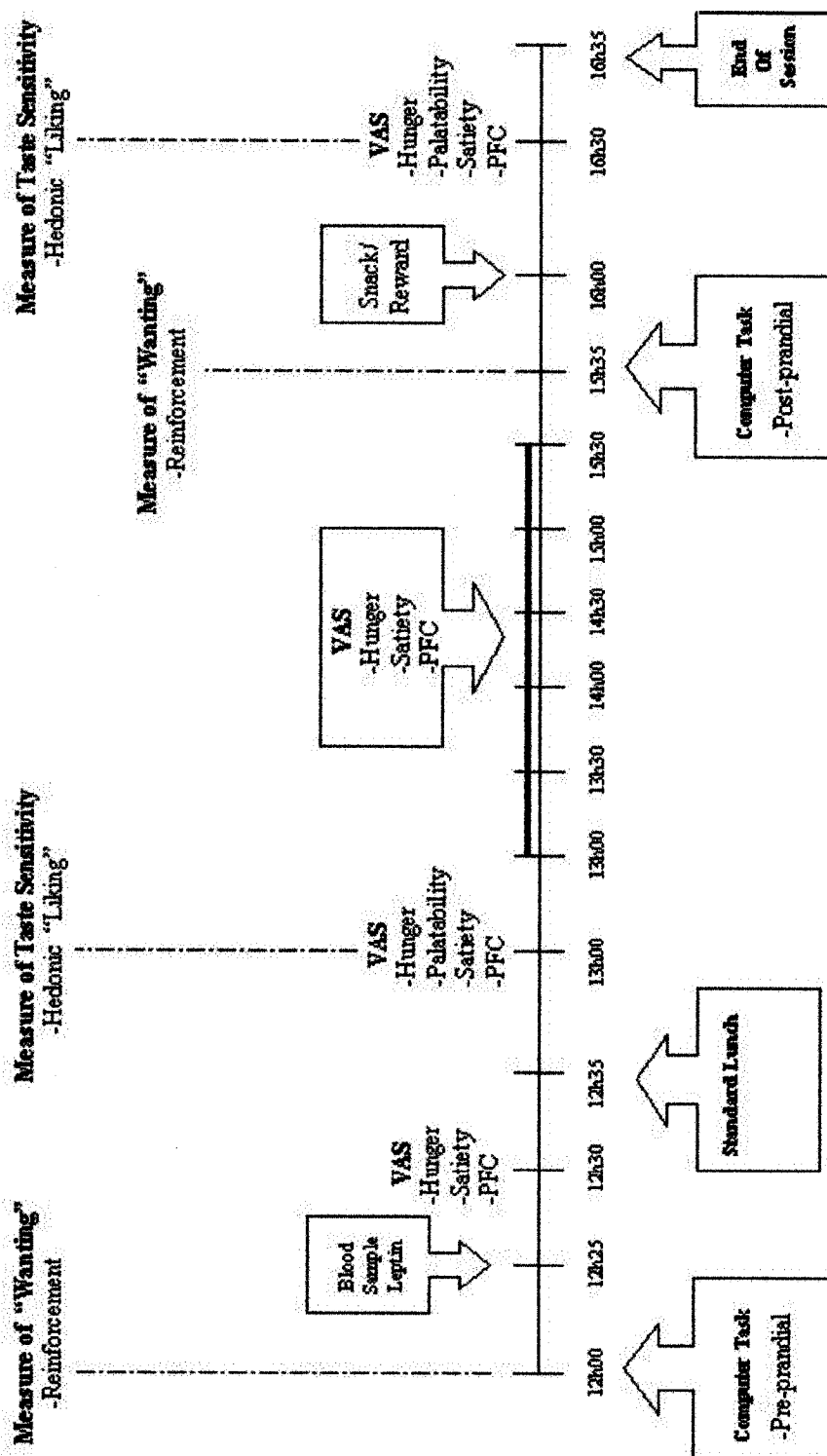
Protocol for 8-week weight loss

Meal Frequency and Weight Loss

The experiment presented here was embedded in the design of an 8-week weight loss study investigating the role of meal frequency in weight loss and peptide signaling. For this larger study, participants were randomized to 1 of the 2 groups as follows: the high meal frequency (HMF) (3 meals + 3 snacks/day) and the low meal frequency (LMF) (3 meals/day). Women and men were stratified evenly into both experimental arms. A meal had to be composed at least from 3 food groups from the Canadian Food Guide and a snack was represented by one source of carbohydrate (grain products or fruits and vegetables) and one source of protein (meat and substitutes or milk products). Both groups were subjected to an energy restriction of 700 kcal of their total caloric needs per day for a period of 8 weeks. The participants had the flexibility to select their food within the meal plan that was individually designed for them based on their daily caloric prescription. The macronutrient composition was reflective of the Dietary References Intakes for Canadians. Carbohydrate was accounted for 55% of calories, preferably from low glycemic index foods with high fiber content ranging from 25 to 35 grams per day. Fat had to provide 27% of calories and saturated fat, trans fat and cholesterol had to be as low as possible. Finally, 18% of calories had to come from protein. As for meal timing, it varied among participants. A time period of at least 4 hours but no more than 6 hours between main meals for the LMF group was instructed.

For the current study there was a need to control for variance in diet, thus there was a requisite weight stabilization phase of 3 days, where upon beginning participants were required to arrive at the lab at 7h30 after an overnight fast from 19h30 the previous evening. After resting in the supine position for 20 minutes, a 30-minute resting metabolic rate (RMR) measurement was made. RMR was then used to prescribe a weight stabilization diet aimed at equalizing energy intake (EI) with energy expenditure (EE): this was accomplished by multiplying the RMR measure by a Physical Activity Level of 1.4. A nutritionist then spent 90 minutes describing and prescribing the 3-day stabilization diet, which followed the recommendations from the Canadian Diabetes Association (CDA).

APPENDIX H
Protocol for Current Study



APPENDIX I

Table for VAS appetite scores

Table 2. Average visual analogue scores pre- and post- weight loss at times immediately before the offering of the lunch (12h30) and food reinforcers (15h30).

Variable	Value (mm)	
	Pre-Loss	Post-Loss
Hunger 12h30	101.4 ± 23.6 (58.0-138.0)	102.6 ± 27.8 (39.0-148.0)
Fullness 12h30	47.9 ± 30.2 (5.5-113.0)	30.7 ± 15.9 (1.0-67.5)
Hunger 15h30	73.2 ± 35.0 (28.0-130.0)	65.4 ± 33.3 (9.0-113.0)
Fullness 15h30	58.3 ± 25.8 (10.5-98.0)	65.2 ± 31.7 (18.5-127.0)

Data are expressed as mean ± SD; range in parentheses; n=9 and 5 in groups of women and men, respectively. There are no significant differences in pre- vs. post- weight loss values.

APPENDIX J

Behavioural economics paradigm figure

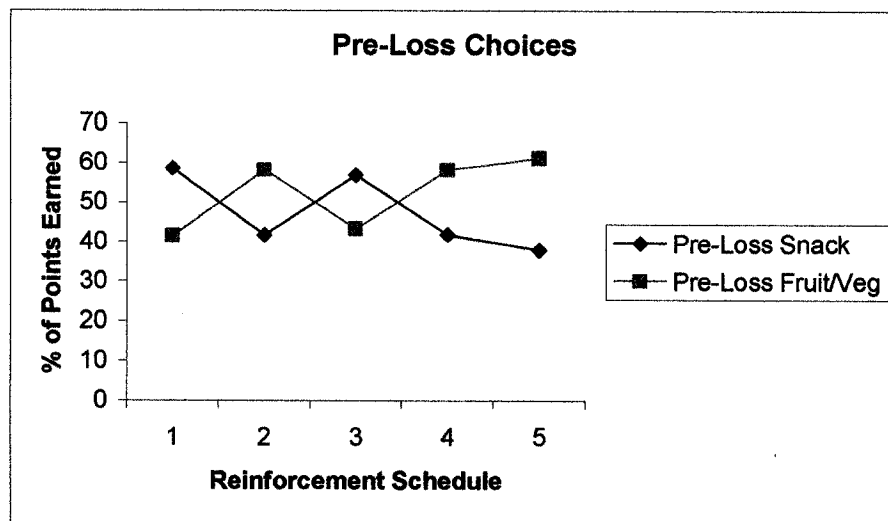


Figure 4. The 3rd reinforcement schedule demonstrates the shift in the willingness to work for snack food points (i.e. the relative-reinforcing value) with the constraint of more button-presses required to earn a single point.