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ACUTE EFFECTS OF METHYLPHENIDATE ON ENERGY BALANCE IN HEALTHY MEN AND WOMEN

by

CLAUDIO LORELLO

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THESIS DEFENCE

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Abstract

This thesis attempts to clarify the impact of methylphenidate hydrochloride (MPH) on key components involved in energy balance, specifically, resting energy (REE) and postprandial energy expenditure (PEE), substrate oxidation, energy intake and appetite. A double-blind, randomized, placebo-controlled, cross-over study was conducted to measure any differences between MPH and placebo treatments. MPH and/or placebo were administered orally (0.5 mg/kg) to seven healthy males (age: 19-37y, BMI: 19.8-30.5 kg/m^2, body fat: 8.1-23.6%) and seven healthy females (age: 20-26y, BMI: 20.6-32.4 kg/m^2, body fat: 18.8-42.1%). Indirect calorimetry was used to calculate energy expenditure variables while energy intake variables were measured during an *ad libitum* buffet-type lunch. Body composition was measured with dual energy x-ray absorptiometry (DEXA). The post-prandial energy expenditure (PEE) phase was measured over a 3-hour period. Vital signs (BP and HR) were assessed pre- and post-administration of MPH or placebo in every session. Results demonstrate that resting energy expenditure (REE) during MPH treatment increased over values obtained during the placebo session (1727.4 kcal/24h vs. 1612.3 kcal/24h, $p<0.001$). No changes in fasting respiratory exchange ratio (RER) were noted; however, significant decreases in post-prandial RER were found during the 30- to 90-min time interval ($p<0.01$). Although PEE continually decreased with time as expected, MPH treatment resulted in significantly greater PEE values at 90-min (MPH: 1946.9 kcal/24h ± 290.0 vs. placebo: 1856.5 kcal/24h ± 260.3, $p<0.005$). No statistical differences in side effects were noted between MPH and placebo treatment. Methylphenidate hydrochloride seemed to have a significant affect on energy expenditure and energy intake variables resulting in a potential net caloric deficit without significant changes in vital signs commonly associated with psychostimulant use.

Keywords: Methylphenidate hydrochloride, energy balance, thermic effect of food, dual energy x-ray absorptiometry

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CHAPTER I - Introduction

Energy balance is governed by a multifaceted neuroendocrine system consisting of central and peripheral signals, such as neurotransmitters and neuropeptides. The aforementioned agents play a key role in short-term and/or long-term regulation of energy balance. Essentially, energy balance is comprised of energy intake and energy expenditure. Energy intake is a product of hormonal, gastro-intestinal, metabolic, neurological, environmental and psychosocial factors whereas energy expenditure is a product of physical activity, metabolic rate and the thermic effect of food. Weight gain and obesity results from a chronic energy imbalance, where energy intake exceeds energy expenditure.

Multiple biochemical signals are associated with the regulation of food intake and energy expenditure. These signals include neurotransmitters such as DA, norepinephrine and serotonin. On a more global level, there are circulating hormones such as insulin and leptin that strongly exert their influences on energy metabolism and energy reserves both centrally and peripherally.

Dopamine is the most recently discovered catecholamine (Carlsson, 1966; Carlsson, Falck, & Hillarp, 1962). Until the 1950's, it was simply considered to be an intermediate in synthesizing the catecholamines norepinephrine and epinephrine. Specifically, the dopaminergic system is divided into three major categories and is based on the length of the DA fibres. They are: the ultra short system, the intermediate-length system, and the long system. Of particular importance to this introspection is the long system, which is comprised of long connections that make up the mesolimbic DA projections.

Dopamine synthesis originates from the amino acid, tyrosine. The rate-limiting step in its synthesis is the conversion of L-tyrosine to L-dopa by the enzyme tyrosine hydroxylase (TH). L-

dopa is finally converted to DA by L-aromatic amino acid decarboxylase so rapidly that there are only trace L-dopa levels in the brain (Carlsson, 1966; Carlsson et al., 1962).

Regulation of the rate of DA synthesis in dopaminergic neurons primarily involves the regulation of TH activity through three major mechanisms (Sutoo & Akiyama, 2003). First, DA and other catecholamines (especially norepinephrine) function as end-product inhibitors of TH by competing for a binding site on the enzyme. Second, pre-synaptic DA receptors, or DA autoreceptors, also regulate the rate of tyrosine hydroxylation. These receptors are activated by DA released from the nerve terminal resulting in feedback inhibition of DA synthesis. Last, DA synthesis also depends on the rate of impulse flow. As would be expected, an increased rate of impulse flow increases the rate of tyrosine hydroxylation.

Dopamine reuptake is accomplished almost exclusively by a membrane carrier known as the dopamine transporter (DAT). DAT serves two purposes in that it can transport DA into and out of the nerve terminal depending on the concentration gradients. Using adenosine triphosphate (ATP) provided by the Na^{+}/K^{-} pump, the DAT recollects DA soon after its release. This is crucial to nerve transmission since the interaction of DA with both the pre- and post-synaptic receptors is time-dependent (Solanto, Arnsten, & Castellanos, 2001).

The fate of released DA also depends on an enzyme known as monoamine oxidase (MAO) which converts some of the released DA into dihydroxyphenylacetic acid (DOPAC) after reuptake by the nerve terminal (Comings & Blum, 2000; Potter, Moshirfar, & Castonguay, 1999).

Fundamentally, through its high affinity for binding with the DAT, MPH thus acts as a DA reuptake inhibitor. Any compound that inhibits the function of DAT almost completely blocks the reuptake of DA (Cooper, Bloom, & Roth, 2003; Solanto et al., 2001). MPH was first synthesized in the 1940s and was later marketed as Ritalin® in the 1960s. MPH has been shown to successfully

reduce symptoms in approximately 80% of Attention Deficit/Hyperactivity Disorder (ADHD) children. Presumably, the proposed study represents one of the first attempts to clarify the impact of MPH on key components involved in body weight regulation, such as energy intake and expenditure, substrate oxidation, and appetite. The data obtained may yield a clearer understanding of how MPH influences energy balance, which may have important implications for the potential use of MPH as a pharmaceutical intervention for adult obesity.

Rewarding Effects of Food

It has been shown that humans can be driven to eat due to the anticipated pleasure-producing effects of high-fat, high-carbohydrate foods, reflecting the notion that palatable food is inherently reinforcing (Raynor & Epstein, 2003; Saelens & Epstein, 1996). This is especially true in obese individuals where the reinforcing value of food coincides with total caloric intake (Hanlon, Baldo, Sadeghian, & Kelley, 2004; Martel & Fantino, 1996a; Ravussin & Bouchard, 2000; Saelens & Epstein, 1996).

Anti-obesity agents that target DA are still relatively new but it has been well established that DA found in the nucleus accumbens is strongly implicated in mediating the rewarding value of food (Berridge & Robinson, 1998; Salamone, Correa, Mingote, & Weber, 2003). Individuals with low brain DA levels due to overactive transport or reduced DA signalling are more motivated to overeat (or abuse substances) than individuals with normal DA function; hence, increasing brain DA levels with MPH should theoretically attenuate the appetitive food seeking eating behaviour (Horvitz, 2000; Noble, 2000; Seeman & Madras, 2002).

Rationale

The newly appreciated view that obesity is a chronic disease has sparked interest in potential drug therapies. Recent trials have targeted serotonergic neurotransmission with some success

(Barkeling, Elfhag, Rooth, & Rossner, 2003; James et al., 2000; Leung, Neil Thomas, Chan, & Tomlinson, 2003; Luque & Rey, 2002; Walsh, Leen, & Lean, 1999). Anti-obesity agents targeting DA metabolism and signalling are less understood; however, recent findings from both animal and human studies suggest that rapid reuptake/metabolism of intrasynaptic DA resulting in reduced brain DA transmission may be related to the development of obesity; hence, raising central DA levels may reduce the rewarding value of food making it easier to reduce energy intake (Davis, Strachan, & Berkson, 2004; Hernandez & Hoebel, 1988; Leddy et al., 2004; Martel & Fantino, 1996b; Wang et al., 2001).

An efficient and safe method of increasing brain DA levels is with use of orally-administered MPH (Seeman & Madras, 2002) which slows the reuptake of intrasynaptic DA allowing it to have a prolonged effect (Volkow et al., 1998). For decades, MPH has been used for the treatment of childhood and adult attention deficit-hyperactivity disorder (ADHD) (Schachter, Pham, King, Langford, & Moher, 2001). One of its most commonly reported side effects is anorexia with weight loss, suggesting that it may be useful in the treatment of obesity (Efron, Jarman, & Barker, 1997; "Physicians' desk reference,"; Schachter et al., 2001). MPH may also increase energy expenditure given that DA increases sympathetic tone; hence, it should theoretically increase both resting energy expenditure (REE) as well as the thermic effect of food constituting two of three factors that contribute to total energy expenditure (Matsumoto et al., 2001; Tappy, 1996). Seemingly, few have attempted to quantify MPH's effects on energy metabolism in healthy adults.

Objectives

This thesis attempts to clarify the impact of methylphenidate hydrochloride (MPH) on key components involved in energy balance, specifically, resting energy (REE) and postprandial energy expenditure (PEE), substrate oxidation, energy intake and appetite.

Hypotheses

Based on current knowledge, we hypothesize that: (1) MPH will produce a reduction in food intake (measured in kilocalories) compared to placebo, (2) MPH will reduce consumption of rewarding, energy dense, high-fat and/or high-sugar foods but have little effect on consumption of foods low in calories, fat or sugar and (3) data will show a trend of increased REE and thermic effects of food favouring MPH versus placebo and (4) that the MPH-induced reductions in food intake will be moderated by reductions in the reinforcing/rewarding value of food.

Definitions

For the purpose of this study, obesity is defined as a consequence of chronic imbalance of energy where energy intake is greater than energy expenditure. This imbalance results in excess body adipose tissue deposit that leads to adverse pathologies. .

Energy expenditure will be defined as a sum of basal metabolic rate, physical activity and thermic effect of food. These three elements comprise total energy expenditure (kcal) (Brooks, 2000).

Assumptions, Limitations and Delimitations

Presumably, all participants will answer honestly to all pre-screening questions and follow the requested protocol (i.e. fasting, fully consume the standardized breakfast 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 (VAS) assess hunger and appetite. Additionally, it must be assumed that the indirect calorimetry systems that are in place are able to accurately calculate energy expenditure values and RER.

Due to the nature of the study, which incorporates a minimum seven-day washout period between sessions, it will take a male participant a minimum of five weeks and a female participant a minimum of four months (women tested only during days 1-5 of menstrual cycle) to complete the study; therefore, the participants may experience some degree of maturation during this time period.

Furthermore, the researchers must be aware of a possible placebo effect, which may occur in such research designs. The placebo effect can be summarized as a measurable, an observable, or a felt improvement in health not attributable to treatment as observed in antihypertensive drug trials in which placebo treatment induces a reduction in blood pressure (Asmar, Safar, & Queneau, 2001; Coca, 1998).

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

It is difficult to dispute the fact that obesity is quickly becoming a global epidemic (Davy, 2004; Katzmarzyk, 2002; Wadden, Brownell, & Foster, 2002). Although individuals are capable of shedding excess body weight (Freedman, King, & Kennedy, 2001), the complexity lies in maintaining the weight loss. Unfortunately, obesity treatment has thus far been relatively

unsuccessful; hence, there is an obvious need to formulate an effective obesity intervention method.

CHAPTER II - Review of Literature

Part A – Energy Expenditure

DA and peripheral tissues

Dopamine receptors are not limited to the central nervous system (CNS). In actuality, dopaminergic (DAergic) neurons can be found in many other neuronal and adrenal tissues such as cardiovascular tissues, lungs, kidney, gastrointestinal tract and endocrine organs (Kuchel, 1999; Missale, Nash, Robinson, Jaber, & Caron, 1998). Challenges in describing the role of DA in the periphery as a catecholamine (hormone secretion, vasodilating, and natriuretic actions) have proven to be difficult since active plasma DA is frequently elusive because free DA concentrations are usually so low that they border the detection limits (Kuchel, 1999). Altered peripheral catecholamine transporter structure and/or function may be implicated in disturbances of the autonomic nervous system, such as occurs in heart disease or hypernoradrenergic hypertension (Eisenhofer, 2001). The neurotransmitter DA is one of the intermediate substances in the biosynthesis of both epinephrine and norepinephrine. DA is also a psychostimulant which seems to induce a variety of cardiovascular and renal physiological responses, including increases in cardiac activity, vasodilation and diuresis (Velasco et al., 2002).

DA infusion and REE

One study conducted on eight post-surgical patients attempted to understand the effects of exogenous dopamine infusion on the patients' metabolism. By monitoring plasma catecholamine levels, the authors noted that dopamine infusion raised REE by approximately 200 kcal/day (1839 ± 171 kcal/day vs. 2071 ± 170 kcal/day) (Nakagawa, Shinozawa, Ando, Aikawa, & Kitajima, 1994). Both epinephrine and norepinephrine levels increased following the DA infusion. Notably,

plasma levels of epinephrine and norepinephrine remained slightly elevated (1867 ± 141 kcal/day) after exogenous infusion of DA cessation (Nakagawa et al., 1994).

These findings were supported by an earlier study which found a significant increase in REE in response to two dopamine infusion rates of 5 and 10 μg/kg·min), corresponding to a 6% and 15% increase, respectively, when compared with pre-infusion values (Ruttimann, Schutz, Jequier, Lemarchand, & Chiolero, 1991). Infusion of DA also induced significant metabolic changes. Researchers noted significantly increased glycaemia, plasma free fatty acid (FFA) concentrations, and insulin plasma concentrations at the various DA infusion rates (Ruttimann et al., 1991).

Pharmaceuticals and the dopamine transporter (DAT)

The DAT is a member of the Na^+/Cl^--dependent transporter family which additionally includes the transporters for NE (67% identical gene sequence), serotonin (49%) and GABA (45%) to name a few (Reith, Xu, & Chen, 1997). Peak levels of DAT protein expression seem to be prominent in nigrostriatal and mesolimbic DA neurons (Gainetdinov, Jones, Fumagalli, Wightman, & Caron, 1998). MPH has been shown to have a particularly high affinity for the DA and NE transporters, which in turn inhibits (or out competes) both DA and NE reuptake. MPH is substantially less efficient in inhibiting serotonin reuptake (Kuczenski & Segal, 1997).

Drugs raise resting extracellular levels of DA several-fold but seem to reduce the extent to which DA is released from nerve endings (Seeman & Madras, 2002). A recent study concluded that orally administered MPH (average dose 0.8 ± 0.11 mg/kg) significantly increased extracellular DA in brain. Studies using positron emission tomography found that therapeutic doses of oral MPH (0.25–1.0 mg/kg) induced significant DAT blockade (50–75%) in the human brain (Volkow et al., 2001). A standard therapeutic dose of 0.5 mg/kg is expected to block more than 60% of DATs (Volkow, Wang, Fowler, & Ding, 2005).

MPH and energy expenditure

One known study investigated the effects of MPH on energy expenditure in children with ADHD. As one might expect, the researchers noted a significant decrease in the physical activity component of daily energy expenditure in the sample of children they studied (Butte, Treuth, Voigt, Llorente, & Heird, 1999); nonetheless, more noteworthy was the fact that the relative resting energy expenditure ($kJ \cdot kg^{-1} \cdot min^{-1}$) also showed a significant decrease (Butte et al., 1999). Thus, MPH has an apparent influence on two energy expenditure components – physical activity and basal metabolic rate. Nevertheless, it is important to note that the mentioned study was conducted on developing children diagnosed with ADHD and the effects of MPH on energy expenditure in individuals without ADHD are unknown. Furthermore, it is unknown whether MPH would have any effect on the TEF.

In a more recent study assessing the cardiovascular, and hence peripheral effects of MPH, it was found that MPH administration significantly increased pulse rate, blood pressure and epinephrine levels in blood plasma (Volkow et al., 2003). Further, the increases in blood pressure were significantly correlated with MPH-induced increases of plasma epinephrine levels ($r>0.82$, $P<0.0005$) (Volkow et al., 2003). Finally, these observed increases of epinephrine in plasma were correlated with DA increases in the brain striatum ($r=0.85$, $P<0.0001$) (Volkow et al., 2003) suggesting a commonality between MPH's central dopaminergic effect and a DA-induced peripheral epinephrine effect.

Part B – Energy Intake

Feeding is a complex process responsive to sensory information related to sight and smell of food, previous feeding experiences, various receptors and hormonal signals. DA released in specific brain regions is associated with pleasurable and rewarding events and may reinforce

positive aspects of feeding (Szczypka, Rainey, & Palmiter, 2000); thus, DA may mediate the integration of sensory cues related to appetite initiating the search for food and its consumption (Szczypka et al., 2000). Dopaminergic neurons in the substantia nigra and ventral tegmental areas of the brain project to the caudate putamen and nucleus accumbens (NAC) where they modulate movement and reward (Horvitz, 2000). In the present manuscript, focus will be on the NAC since it also projects to the lateral hypothalamus that regulates feeding.

Regulation of ingestive behaviour

Ingestive behaviour is a complex process that involves short-term and long-term regulation coupled with the control of body weight and body composition (Havel, 2001; Rosenbaum, Hirsch, Murphy, & Leibel, 2000; Schwartz, Woods, Porte, Seeley, & Baskin, 2000). The net outputs are neural and chemical signals that regulate the various components of ingestive behaviour including hunger, satiety, and thirst (Williams et al., 2001). Furthermore, numerous psychological and cognitive factors, such as socio-cultural influences, eating habits, learning and experience, preferences, and emotional status can also influence ingestive behaviour (Havel, 2001; Williams et al., 2001).

DA and feeding behaviour

As previously mentioned, the mesolimbic dopaminergic system (MDS) has been shown to be implicated in feeding behaviour. Studies have demonstrated that the MDS is activated upon the ingestion of food and presumably MDS activity is related to the rewarding properties of foods (Martel & Fantino, 1996b).

The NAC is the major target of mesolimbic DA neurons originating in the ventral tegmental area of the mesencephalon (Cooper et al., 2003; Solanto et al., 2001). Food-seeking behaviour is separated into an appetitive (anticipatory) phase intended to search and approach the food reward,

and a consummatory phase, consisting of fixed response patterns (eating, drinking, etc) linked to the characteristics of the food reward (caloric, metabolic, etc.) (Bassareo & Di Chiara, 1999; Davis & Woodside, 2002; Horvitz, 2000; Martel & Fantino, 1996a, 1996b). While some studies reported a stimulation of DA transmission in the NAC in relation to appetitive as well as consummatory behaviour, other studies reported a relationship only during the consummatory phase (Bassareo & Di Chiara, 1999; Davis & Woodside, 2002; Horvitz, 2000; Martel & Fantino, 1996a, 1996b); therefore, the precise relationship between DA transmission in the NAC and specific phases of motivated behaviour is debated. It is quite possible that this debate arises from the fact that the NAC is subdivided into two compartments, a "shell" and a "core" (Cooper et al., 2003; Solanto et al., 2001). This may be relevant to the current debate over the role of NAC DA in appetitive behaviour. Thus, depending on the specific compartment of the NAC where DA transmission is examined, a different relationship is obtained. It has also been demonstrated that appetitive food stimuli phasically stimulates DA transmission in the core but not in the shell (Bassareo & Di Chiara, 1999; Davis & Woodside, 2002; Horvitz, 2000; Martel & Fantino, 1996a, 1996b). These differences between NAC shell and core suggest that phasic DA transmission in each compartment of the NAC serves different roles in food-seeking behaviour (Bassareo & Di Chiara, 1999; Davis & Woodside, 2002; Horvitz, 2000; Martel & Fantino, 1996a, 1996b).

MPH and energy intake

A recent study attempted to directly analyze the effects of MPH on energy intake. The authors found that most often, a 0.5 mg/kg dosage of MPH was sufficient to reduce the energy intake of a highly palatable food (i.e. pizza) by approximately 34% over one meal (Leddy et al., 2004). It is unknown whether this reduction in caloric intake is sustained over a prolonged period of time.

One of MPH's most commonly reported side effects is anorexia with accompanied weight loss and decreases in BMI, with the largest reductions in BMI occurring in subjects with higher baseline values (Leddy et al., 2004; Schertz, Adesman, Alfieri, & Bienkowski, 1996). The anorexigenic effects of psychostimulants such as MPH have been well documented in human and animal models (Efron et al., 1997; Ishii, Blundell, Halford, & Rodgers, 2003; Klein-Schwartz, 2002; Leddy et al., 2004). Anorexia during MPH therapy seems to increase linearly in accordance to dose where it eventually levels. (Klein-Schwartz, 2002). Unfortunately, the levels of DAT blockade attained by common doses of oral MPH (ranging from 0.3-0.6mg/kg) are not well known and vary from person to person. One study noted that approximately 50% DAT can be achieved with a relatively small dose of 0.25 mg/kg (Volkow et al., 1998). In addition, the study by Volkow et al. also found that increasing the absolute dose from 40mg to 60 mg resulted in an insignificant increase of 2% in DAT blockade.

MPH absorption

Proceeding gastrointestinal absorption and transfer into the bloodstream, the saturable transport of MPH across the blood-brain barrier results in brain MPH concentrations correlated to serum concentrations (Pardridge & Connor, 1973; J. M. Swanson & Volkow, 2003). In accordance, food has been reported to have no effect on MPH pharmacokinetics (Modi, Wang, Hu, & Gupta, 2000). Administering MPH 1 hour before or 2 hours after meals is generally not convenient for children with ADHD due to the malabsorption that may be incurred (Modi et al., 2000). Therefore, ingestion of meals must be timed accordingly. One particular study evaluated the effect of food on MPH doses of 0.15 and 0.3 mg/kg in six healthy participants. Blood samples were collected 1, 2 and 3 hours after the dose was administered. No differences in MPH serum concentrations were noted between the fed and fasted state at any sampling time in either groups.

The authors also remarked that although serum MPH concentrations were slightly lower in the fed state, the difference was not statistically significant (Modi et al., 2000).

Neurotransmitters

Dopamine and serotonin relate to the rewarding effects of food and modulation of meal size and frequency during hyperphagia in obese Zucker rats (Meguid et al., 2000). It is likely that meal size and meal frequency are independently regulated in different yet connected anatomical sites in the brain by these two neurotransmitters (Meguid et al., 2000). Numerous studies have characterized serotonin and the serotoninergic system in the inhibitory role of food intake (Bray, 2000; James et al., 2000). The theory that serotonin acts to inhibit food intake is based on findings that a variety of different serotonin agonists cause dramatic reduction in food intake (Bray, 2000; James et al., 2000). Moreover, a body of evidence exists showing that DA release is regulated in part by serotonin release (Bray, 2000; Comings & Blum, 2000; Meguid et al., 2000).

It is suggested that DA, especially in the NAC, mediates the primary reinforcing characteristics of natural stimuli such as food or illegal drugs (Berridge, 1996; Salamone et al., 2003). Studies have demonstrated that the effects of NAC DA depletion is instrumental for food-seeking behaviour (Berridge, 1996; Salamone et al., 2003; Szczypka et al., 2000). The involvement of NAC DA in aspects of motivation has implications for energy imbalance related disorders such as obesity.

CHAPTER III - Methodology

Participants

In total, 14 healthy adults (7 males and 7 females) participated and completed the study. Posters located at the University of Ottawa and Montfort Hospital were used in order to recruit participants (Appendix 1). To encourage participation, a one-day workshop on lifestyle modification was offered and took place shortly after completion of the study.

Participants were non-smokers, their weight had not varied more than 2kg in previous 6 months, no known food allergies, no history of previous MPH use or allergy to MPH, no history of ADHD as measured by the Wender-Utah Rating Scale (Appendix 2), no current use of antidepressants, thyroid medication, or any medication that could affect appetite, normal blood pressure, no history of cardiac problems or symptoms suggestive of any cardiac condition, no history of diabetes or insulin resistance, no excessive use of alcohol or alcoholism, nor current addictions to opiates, cocaine or stimulants, not a restrained eater based on cut-score on Three Factor Eating Questionnaire (Appendix 3), no history of glaucoma, no personal or family history of seizure disorders, not currently taking MAO inhibitors, pressor agents, coumarin, anticonvulsants, phenylbutazone, or tricyclic antidepressants, no history of thyroid disease, no personal or family history of motor tics or Tourettes's Syndrome. Any interested candidate was required to weigh $\leq$ 120 kg in order to accommodate the recommended maximum dosage of MPH of 60 mg/day. All descriptive statistics have been summarized in Table 1.

Design

A randomized, double-blind, placebo-controlled, crossover laboratory study was conducted. Participants visited the laboratory for one screening visit and four experimental sessions. The order in which participants received medication (MPH or placebo) and underwent experimental

test sessions (energy intake and energy expenditure) was counterbalanced by a computerized randomization scheme. The study was conducted within 18-months at the Behavioural Metabolic Research Unit (BMRU) located at the Montfort Hospital.

Procedures

Interested participants were screened via telephone to determine if they met basic inclusion criteria and eligible participants were then invited for thorough screening, which took place at the laboratory. During the initial laboratory visit, written informed consent was obtained from all participants. To fully assess inclusion criteria, a complete demographic, medical, psychological and nutritional history was completed by clinical interview, physical (medical) examination, and questionnaires. Participants then rated all of the foods used in the standardized breakfast food and ad libitum buffet-eating portion of the study using an "Appreciation of Certain Foods" questionnaire (Appendix 4). Individuals who rated 50% of foods lower than moderate liking (lower than a 3 on a 5-point rating scale) were excluded from the study. As a precautionary measure, participants were then given a single dose of MPH (0.5 mg/kg) to ensure they would not become ill during the experimental test sessions. This is the only occasion in which participants were aware of receiving MPH. A drug effects/side effects checklist (Appendix 5) was completed and vital signs (blood pressure and pulse rate) were monitored before administration of the test dose and 1-hour following administration. Although there were no such instances in this study, anyone who reported or showed severe side effects such as systolic blood pressure exceeding baseline reading by 20 mmHg, diastolic blood pressure exceeding the baseline reading by 10 mmHg, overall blood pressure > 160/100, or resting pulse rate increased by >20 beats/minute from the baseline reading would have been excluded from the study. Subjective side effects were measured for 19 potential side effects (e.g., headache, nausea, nervousness) by having participants

rate the intensity of their symptoms using the following scale: 1=none, 2=mild, 3=moderate and 4=severe. The participant was notified of their inclusion or exclusion from the study approximately 2 weeks after the screening visit and, if included, was scheduled for four half-day (5-6 hours) experimental test sessions scheduled at least one week apart. Two of the four experimental test sessions evaluated energy intake variables and the remaining two days assessed energy expenditure variables.

Preliminary Assessments

a) Questionnaires

As previously mentioned, all participants underwent a telephone-screening questionnaire (Appendix 6). The information provided on the telephone-screening questionnaire was used to aid the researchers in deciding whether a potential candidate may be invited for more thorough screening later.

The participants were also asked to rate all of the foods that were used in the standardized breakfast food and ad-libitum buffet-eating portion of the experiment. This required the participant to rate their like/dislike for all test foods using a Likert scale from 1 to 5 (Appendix 4). A ranking of "1" indicates "I do not like at all" and a ranking of "5" indicates "I like a lot". If a potential participant ranked more than 50% of the buffet food items a 2 or less that participant would be excluded from further testing.

In addition, an extensive 51-question food habits self-report questionnaire with true/false and multiple-choice questions was be used to assess the participant's eating behaviour and level of restraint. The three-factor eating questionnaire (TFEQ) (Appendix 3) incorporates three concepts of human eating behaviour: (a) cognitive restraint of eating, (b) disinhibition, and (c) hunger (Stunkard & Messick, 1985). As previously mentioned, the TFEQ was administered to assess

aspects of individual dietary habits but particularly excessive dietary restraint that would limit eating in the laboratory. A cut score of 10 in section (a) was used to identify and exclude restrained eaters from the study.

During the screening session, a single dose of MPH was given to participants in order to ensure they would react adversely to the drug during experimentation. Hence, a drug effects questionnaire (DEQ) (Appendix 7), which asked participants to indicate on a 150-mm line (from "Did not like at all" to "Liked very much") whether they believed to have received the MPH or the placebo and how much the enjoyed the effects of the drug. This question was asked immediately after the termination of the session.

The Side Effects Checklist (Appendix 5) was used to assess the severity of 14 potential side effects of MPH by having participants rate the intensity of their symptoms using a 4-point rating scale ranging from none to severe.

The Wender Utah Rating Scale (WURS) (Appendix 2) assessed recent and current attention-deficit and hyperactivity symptoms. The 61-item scale is divided into symptoms pertaining to inattention (i.e. do not listen when directly spoken) and hyperactive-impulse symptoms (i.e. feeling restless). Participants were asked to rate the intensity of their symptoms using the following scale: 0-never or rarely, 1-sometimes, 2-often, or 3-very often. The WURS has excellent reliability and diagnostic discriminate validity ($\alpha = 0.89$) (Rossini & O'Connor, 1995). A cut-off score of 46 was used to identify and exclude any potential participant who may have undiagnosed ADHD.

The Beck Depression Inventory (BDI) will be administered to assess current depressive and psychiatric symptoms. The BDI (Appendix 9) is a self-administered 21-item questionnaire that measures supposed manifestations of depression (Beck, Ward, Mendelson, Mock, & Erbaugh,

1961). The BDI demonstrates high internal consistency (α = 0.86 and 0.81 for psychiatric and non-psychiatric populations respectively) (Beck, Epstein, Brown, & Steer, 1988). A cut score of 13 was used to identify and exclude any participants who may have undiagnosed/untreated depression.

c) Anthropometric measurements

Body weight, height, and composition were assessed. A medical exam/questionnaire was also administered in collaboration with a physician. A method called dual-energy x-ray absorptiometry (DEXA) was used to measure body composition (fat-free mass, fat mass, total body fat percentage). Participants were required to lie on the measuring unit's examination table, in hospital garments (with all metal objects removed); while a low-intensity x-ray scanned the entire surface area of the body. The measurement took approximately 15 minutes to complete. The only risk to the participant was a minimal x-ray exposure of less than 0.5 millirems. This is equivalent to less than 1/20th of a day's exposure to sunlight. Coefficient of variation and correlation for percent body fat measured with the DEXA in the 14 participants tested in our laboratory were 1.8 % and r = 0.99, respectively. Height along with hip and waist circumferences were measured using a conventional measuring tape abiding to CSEP standards (Canadian Society for Exercise Physiology et al., 2003). Weight measurements were conducted using a digital weigh scale (Tanita BWB-800S Digital Scale®).

Experimental Sessions

a) Energy Expenditure Measurement Days

7h30- Arrival and completion of 24-hour food intake recall to ensure adherence to a 12-hour overnight fast, along with a pre-test questionnaire determine if participants refrained from vigorous physical activity for at least 24 hours prior to testing, as instructed.. **7h40**- Vital signs

(involving blood pressure and heart rate assessment) and anthropometric measurements (involving height, body weight, and waist circumference recordings). **8h00-** Insertion of a catheter with subsequent blood sampling and administration of short-acting MPH (0.5 mg/kg) or placebo followed by drug effects questionnaires and leisure time activity (e.g., reading, school or class work) for 60 minutes. **9h00-** Re-assessment of vital signs followed by a 20-minute rest period in the supine position. **9h30-** Measurement of resting energy expenditure (REE) using indirect calorimetry. **10h00-** A standardized breakfast was then provided to all participants. A blood sample was taken immediately following the completion of the standardized breakfast and every 30 minutes thereafter for the duration of the session (10h30, 11h00, 11h30, 12h00, 12h30, 13h00). The thermic effect of food (TEF)/post-prandial energy expenditure was evaluated by indirect calorimetry every 60 minutes during a period of three hours (i.e. 10h30-11h00, 11h30-12h00, 12h30-13h00) following the end of the meal, while visual analogue scales (VAS) were completed every 30 minutes during this time period (10h30, 11h00, 11h30, 12h00, 12h30, 13h00). **13h15-** Approximated end of testing session.

b) Energy Intake Measurement Days

9h30- Participants arrived at the laboratory after having consumed their standardized breakfast at home at approximately **8h00**, which was confirmed by interview. Participants also completed a 3-day physical activity record for the purposes of ensuring they did not engage in vigorous physical activity for at least 24 hours prior to the session. Participants who did not adhere to these pre-experimental conditions were rescheduled to a later date. **9h45**- Anthropometric measurements (i.e. Height, weight, waist circumference) and evaluation of hunger using VAS. **10h10**- Insertion of catheter with subsequent blood sampling and administration of MPH or placebo followed by 60 minutes of leisure time activities and evaluation of side effects and vital signs. **11h10**- Twenty

minutes of resting in the supine position followed by re-assessment of vital signs. **11h25-** Assessment of hunger using visual analogue scales (VAS), as well as the reinforcing value of food using a questionnaire (Appendix 8) developed and validated by (Goldfield, Epstein, Davidson, & Saad, 2005). **11h30-** Standardized buffet meal. Evaluation of energy intake (kilocalories consumed) from a standardized mixed meal buffet-style eating methodology with hunger re-evaluated every 30 minutes for three hours (12h00, 12h30, 13h00, 13h30, 14h00, 14h30, 15h00) following completion of the meal. Water consumption was also measured during the ad-libitum buffet. A blood sample was taken prior to serving of the standardized buffet and post-prandial blood samples were taken every 30 minutes (12h30, 13h00, 13h30, 14h00, 14h30, 15h00) following the completion of the standardized buffet meal. **15h15-** Approximated end of experimental session.

Experimental Measurements

a) Assessment of vital signs

Assessment of vital signs involves measurement of blood pressure and heart rate which was taken by a qualified registered nurse.

b) Anthropometric measurements

As conducted in the preliminary visit, a research assistant measured body weight and height prior to commencing each experimental session.

c) Questionnaires

The participant was asked to complete a 3-day physical activity record to ensure they did not partake in any intense physical activity prior to the test sessions.

d) Visual Analogue Scales

Participant's hunger levels just prior to the ad-libitum buffet lunch were assessed using 150mm visual analogue scales (VAS). In total, four questions were asked: (a) "How strong is your desire to eat?", (b) "How hungry do you feel?", (c) "How full do you feel?" and (d) "How much food do you think you could eat?".

e) Resting energy expenditure (REE)

The indirect calorimetry system (Deltatrac II, SensorMedics, Yorba Linda, CA) was calibrated before each test. After a 20-minute rest period in the supine position, a measurement of REE was performed. In order to obtain RER measurements, a Plexiglas hood was placed over the participant's head through which fresh air was drawn. The expired air was sampled and analyzed for percentages of oxygen and carbon dioxide averaged per minute and determined for 30 minutes. With this measurement, the researchers are able to determine the rate of oxygen (L/min) consumption and derive energy expenditure (kcal). The Deltatrac II system has a coefficient of variation and correlation for VO_2 measurement in the 14 participants tested in our laboratory were 0.97 % and r = 0.95, respectively.

f) Post-prandial energy expenditure (PEE)

The PEE was measured using the exact methodology described above. The post-prandial period was 3 hours. The first PEE measurement was conducted 30 minutes following completion of the standardized breakfast and then 30-minute measurements were completed once every 60 minutes thereafter.

g) Food intake

Food intake was assessed by calculating kilocalories consumed during the ad-libitum buffet-style eating in the two test sessions (MPH vs. placebo) using a standardized buffet eating methodology as described by Arvaniti et al. (2000). All buffet foods were weighed on an

electronic scale (calibrated daily) before and after consumption to obtain the amount consumed to the nearest 0.1 g. Energy and macronutrient intake was calculated based on grams of each food consumed using valid and reliable energy/gram data provided by computer software (Food Processor® SQL Version 9.6, ESHA Research, Salem, OR, USA). Twenty-four hour food recalls were used to assess adherence to experimental instructions regarding food intake the day before test sessions.

Statistical Analysis

All statistical analyses were performed using Statistical Product and Service Solutions software, version 12.0 (SPSS Inc., Chicago, IL). Differences between MPH and placebo in fasting REE and RER were analyzed using paired-samples t-tests. Changes in vital signs (BP & HR) were evaluated using a 2 (condition: MPH vs. placebo) x 2 (time: pre- and post-administration of dose) repeated measures ANOVA. Finally, a 2 (condition: MPH vs. placebo) x 3 (time: 30-, 90-, 150-min) repeated measures ANOVA was conducted to assess changes in post-prandial energy expenditure and RER. Effects were considered significant at $P < 0.05$ and data are presented as means ± SD except where otherwise specified.

Ethics

Ethical approval for this study was granted from the University of Ottawa Research Ethics Committee, the Montfort Hospital Research Ethics Board and also received approval as a clinical trial under Health Canada legislation (CTA No. 102138 Ritalin). Written informed consent was obtained from all subjects.

CHAPTER IV – Results

SECTION 1. ENERGY METABOLISM

The Results section is presented in the form of two papers. The first focuses on elements of energy expenditure and has been formatted and submitted to the International Journal of Obesity as a short communication in accordance to the guidelines for publication in its integral form. The paper is entitled: Orally Administered Methylphenidate Increases Resting and Post-prandial Energy Expenditure in Healthy Adults. Whilst the second focuses on elements of energy intake and has been formatted and submitted to the International Journal of Clinical Nutrition as a full article in accordance to the guidelines for publication in its integral form. The paper is entitled: Effects of Methylphenidate on energy intake and dietary fat in adults: A mechanism of altered reward value of food?

ARTICLE 1 - Orally Administered Methylphenidate Increases Resting and Post-prandial Energy Expenditure in Healthy Adults

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ABSTRACT

Objective: This study attempts to clarify the impact of methylphenidate hydrochloride (MPH) on key components involved in energy metabolism, specifically resting and postprandial energy expenditure and substrate oxidation.

Design: A double-blind, randomized, placebo-controlled, cross-over study. MPH (0.5 mg/kg) or placebo (PLAC) was administered orally in the fasting state, 60 minutes prior to a resting energy expenditure (REE) measurement, and 90 minutes prior to a standardized breakfast of approximately 650 kcal.

Subjects: Seven healthy males (age: 19-37y, BMI: 19.8-30.5 kg/m^2, body fat: 8.1-23.6%) and 7 healthy females (age: 20-26y, BMI: 20.6-32.4 kg/m^2, body fat: 18.8-42.1%).

Measurements: Resting energy expenditure (REE), post-prandial energy expenditure (PEE) and respiratory exchange ratio (RER) were obtained from indirect calorimetry. Body composition was measured with DEXA. The thermic effect of food (TEF) was measured over a 3-hour period. Vital signs (BP and HR) were assessed pre- and post-administration of MPH or placebo in every session.

Results: During the MPH condition, REE increased over values obtained during the placebo session (1727.4 ± SDkcal/24h vs. 1612.3± SD kcal/24h, $p<0.001$). No changes in fasting RER were noted; however, significant decreases in post-prandial RER were found during the 30- to 90-min time interval ($p<0.01$). Although PEE continually decreased with time as expected, MPH treatment resulted in significantly greater PEE values at 90-min (MPH: 1946.9 kcal/24h ± 290.0 vs. placebo: 1856.5 kcal/24h ± 260.3, $p<0.005$). No significant effects of MPH were found for vital signs (HR, SBP, DBP).

Conclusion: MPH causes a significant increase in both resting and postprandial energy expenditure without significant changes in heart rate and blood pressure commonly associated with psychostimulant use.

Keywords: *methylphenidate hydrochloride, postprandial energy expenditure, substrate oxidation, placebo-controlled, resting energy expenditure, respiratory exchange ratio*

Introduction

Recent trials have targeted serotonergic neurotransmission with some success (Jordan et al., 2005; Walsh et al., 1999). Anti-obesity agents targeting dopamine (DA) metabolism and signalling are less understood; however, recent findings from both animal and human studies suggest that rapid reuptake/metabolism of intrasynaptic DA resulting in reduced brain DA transmission may be related to the development of obesity (Leddy et al., 2004; Wang et al., 2001).

A method of increasing DA levels is with the use of orally-administered methylphenidate hydrochloride (MPH) which slows the reuptake of intrasynaptic DA allowing it to have a prolonged effect (Seeman & Madras, 2002; Volkow et al., 2001; Volkow et al., 2002). For decades, MPH has been used for treating childhood and adult attention deficit/hyperactivity disorder (AD/HD) (Schachter et al., 2001). MPH's most commonly reported subjective side effect is appetite suppression as reported by parents (Efron et al., 1997).

MPH's capability of increasing both central and peripheral levels of DA and norepinephrine (NE) by blocking their respective transporters is relevant to the current research (J. M. Swanson & Volkow, 2003). As a member of the catecholamine family, injected DA induces B-agonist effects. At a rate of 5 and 10 ug min^{-1} kg^{-1}, the introduction of intravenous DA increased REE by 6% and 15%, respectively, in non-obese subjects. Such an effect could be mediated by the release of endogenous norepinephrine (NE) or even mediated by B-adrenoreceptor stimulation (Jequier, Munger, & Felber, 1992).

The current study represents one of the first attempts to clarify the impact of MPH on resting and post-prandial energy expenditure, and substrate oxidation. Based on current knowledge, it is hypothesized that the data obtained from this study will show a trend of increased REE and PEE favouring MPH versus placebo.

Methods

Participants

Seven healthy men (age 25.7 ± 6.0 y; height 175.0 ± 4.8 cm; weight 75.1 ± 12.0 kg; BMI 24.6 ± 3.7 kg/m^2; body fat 16.3 ± 5.3 %, fat-free mass 59.6 ± 7.7 kg, fat mass 12.6 ± 5.9 kg) and seven healthy women (age 21.7 ± 2.2 y; height 165.0 ± 3.1 cm; weight 69.7 ± 14.4 kg; BMI 25.5 ± 4.5 kg/m^2; body fat 32.2 ± 8.0 %, fat-free mass 43.5 ± 5.9 kg, fat mass 23.0 ± 9.4 kg) were recruited by local advertisements (i.e. posters, newspapers). Participants were included if they were between the ages of 18 and 40, had a BMI $\geq$ 30 and body weight $\leq$ 120 kg to accommodate the recommended maximum dosage of MPH of 60 mg/day, non-smokers, their weight did not vary more than 2kg in the previous 6 months. Ethical approval for this study was granted from the University of Ottawa Research Ethics Committee, the Montfort Hospital Research Ethics Board and also received approval as a clinical trial under Health Canada legislation (CTA No. 102138 Ritalin). Written informed consent was obtained from all participants.

Design

A randomized, double-blind, placebo-controlled, crossover laboratory study was conducted. Participants visited the laboratory for one screening visit and four experimental sessions. The order in which participants received medication (MPH or placebo) and underwent experimental test sessions (energy intake and energy expenditure) was counterbalanced by a computerized randomization scheme. The study was conducted within 18-months at the Behavioural Metabolic Research Unit (BMRU) located at the Montfort Hospital.

Procedures

Anthropometric measurements

Body weight, height and body composition were assessed. Dual-energy x-ray absorptiometry (DEXA) was used to measure body composition. For DEXA measurements, participants were asked to remain lying on the apparatus, fully clothed in a hospital gown with all metal objects removed, while a low-intensity x-ray scanned the entire body. Coefficient of variation and correlation for percent body fat measured with the DEXA in the 12 participants tested in our laboratory were 1.8 % and r = 0.99, respectively. Height and waist circumferences were obtained using a conventional measuring tape abiding by CSEP standards (Canadian Society for Exercise Physiology et al., 2003). Weight measurements were conducted using a digital weigh scale (Tanita BWB-800S Digital Scale®).

Experimental sessions

Written informed consent was obtained from all participants during the initial laboratory visit. To fully assess inclusion criteria, a complete demographic, medical, psychological and nutritional history was completed by physical (medical) examination, and questionnaires. The experimental test sessions began at approximately 7:30AM. Once the participant arrived to the testing laboratory by either car or bus, the researchers ensured adherence to a 12-hour overnight fast through use of a questionnaire. Further, intense physical activity was forbidden for at least 24hr prior to each session as instructed. Anthropometric measurements involving height, body weight, and waist circumference recordings were then taken. A drug effects/side effects checklist was completed and vital signs (blood pressure and pulse rate) were observed before and 1-hour following administration of the test dose (0.5 mg/kg). Those who reported or showed severe side effects such as systolic blood pressure exceeding baseline reading by 20 mmHg, diastolic blood

pressure exceeding the baseline reading by 10 mmHg, overall blood pressure > 160/100, or resting pulse rate increased by >20 beats/minute from the baseline reading were asked to re-schedule the test session to another date at least 7 calendar days later. Some subjective side effects were also measured (e.g., headache, nausea, nervousness) by having participants rate the intensity of their symptoms using the following scale: 1=none, 2=mild, 3=moderate and 4=severe.

If no adverse events were noted, then a measurement of REE followed using indirect calorimetry. In order to measure the TEF, a standardized breakfast of approximately 650kcal was provided and participants were asked to consume all the contents of the breakfast. The breakfast contained: 250ml of 2% milk, 114ml of orange juice, 8g of butter, 13g of raspberry jam, 18g of smooth peanut butter, 21g of cheddar cheese (32% M.F, 39% moisture), and 2 slices of whole wheat toast (approximately 58g). The PEE was evaluated by indirect calorimetry every 60 minutes during a period of three hours (i.e. 10h30-11h00, 11h30-12h00, 12h30-13h00) following the end of the breakfast. The first and last 5 minutes of each collection stage were ommitted and the obtained average values were used to extrapolate PEE over a 1-hour period.

Statistics

All statistical analyses were performed using Statistical Product and Service Solutions software, version 12.0 (SPSS Inc., Chicago, IL). Differences between MPH and placebo in fasting REE and RER were analyzed using paired-samples t-tests. Changes in vital signs (BP & HR) were evaluated using a 2 (condition: MPH vs. PLAC) x 2 (time: pre- and post-administration of dose) repeated measures ANOVA. Finally, a 2 (condition: MPH vs. PLAC) x 3 (time: 30-, 90-, 150-min) repeated measures ANOVA was conducted to assess changes in post-prandial energy expenditure and RER. Effects were considered significant at $P < 0.05$ and data are presented as means ± SD except where otherwise specified.

Energy expenditure and respiratory quotient were measured by a ventilated hood gas analyser system (Deltatrac II, SensorMedics, Yorba Linda, CA), which was calibrated with a precision gas mixture prior to each experimental test session. The post-prandial period began upon completion of the standardized breakfast with 30-min energy expenditure measurements occurring every 60 minutes for 3 hours thereafter. Energy expenditure was calculated according to the Weir equation (Weir, 1949) and expressed as kcal/24h. The Ferranini equation (Ferrannini, 1988) was used to determine substrate oxidation rates for carbohydrates and lipids and displayed in mg/min.

Results

Resting Energy Expenditure (REE) and Post-prandial Energy Expenditure (PEE)

As depicted in Figure 1, a paired samples t-test demonstrated that for REE, treatment with MPH (1.20 ± 0.18 kcal/min OR 1727.4 ± 255.9 kcal/24h) was significantly higher than placebo (1.12 kcal·min^{-1} ± 0.18 OR 1612.3 kcal/24h ± 252.5, $p<0.001$).

A 2(dose: MPH vs. placebo) x 3 (time: 30-, 90-, 150-min) repeated measures ANOVA showed a significant main effect for time ($p<0.005$), and a significant MPH by time interaction ($p<0.05$) for PEE. As expected, a paired-samples t-test on the time main effect showed that PEE continuously decreased over time (30-min: 1956.5 kcal/24h ± 286.3 vs. 90-min: 1901.7 kcal/24h ± 272.0, $p<0.005$) and (1901.7 kcal/24h ± 272.0) to 150-min (1844.7 kcal/min ± 270.3, $p=0.077$) during the post-prandial period as demonstrated in Figure 2. Paired-sample t-tests also demonstrated that PEE values during MPH treatment were significantly higher at 90-min in comparison to placebo treatment (MPH: 1946.9 kcal/24h ± 290.0 vs. 1856.5 kcal/24h ± 260.3, $p<0.005$).

Paired-sample t-tests were used to analyse the changes in TEF – the difference between PEE and REE. As demonstrated in Figure 3, TEF declined steadily during the post-prandial period (30-

min: 306.4 kcal/24h ± 124.9 vs. 90-min: 277.0 kcal/24h ± 126.0, p=0.054) and continued to decline (90-min: 277.0 kcal/24h ± 126.0 vs. (150-min: 172.1 kcal/24h ± 98.1, p<0.005). In order to accurately understand the effects of MPH on TEF, REE during placebo treatment was subtracted from both PEE during MPH treatment and placebo treatment. The mean differences were then compared. Paired-sample t-tests demonstrated that TEF values during MPH treatment were significantly greater at 30-min (MPH: 368.0 kcal/24h ± 153.8 vs. 314.0 kcal/24h ± 99.9, p<0.05) and at 90-min (MPH: 334.6 kcal/24h ± 136.4 vs. 244.2 kcal/24h ± 108.4, p<0.005) in comparison to placebo treatment.

Fasting and Post-prandial respiratory exchange ratio (RER)

Although not significant, fasting RER (Figure 4) seemed to be higher during MPH treatment (0.863 ± 0.07 vs. 0.844 ± 0.06, p>0.05) when compared to placebo.

A 2 (dose: MPH vs. placebo) x 3 (time: 30-, 90-, 150-min) repeated measures ANOVA showed a significant main effect for time (p<0.05). Follow-up paired-sample t-test on the time main effect showed that post-prandial RER significantly decreased during the 30- to 90-minute time period (30-min: 0.92 ± 0.03 vs. 90-min: 0.88 ± 0.03, p<0.005), as demonstrated in Figure 5. No changes in post-prandial RER occurred during the 90- to 150-min interval (90-min: 0.88 ± 0.03 vs. 150-min: 0.89 ± 0.04, p>0.05).

Fasting and Post-prandial substrate oxidation rates

Following suit with RER values, carbohydrate oxidation rates (Figure 16) were insignificantly higher during MPH (Fasting: 3.12 mg/min ± 1.43, 30-min: 5.22 mg/min ± 1.10, 90-min: 4.23 mg/min ± 0.90, 150-min: 3.78 mg/min ± 1.13) treatment when compared to placebo (Fasting: 2.59 mg/min ± 1.38, 30-min: 4.28 mg/min ± 1.51, 90-min: 3.58 mg/min ± 1.23, 150-min: 4.09 mg/min ± 1.42). This equates to a 20%, 22%, 18% and –8% increase in carbohydrate

oxidation respectively. Lipid oxidation seemed to be unchanged (MPH Fasting: 1.20 mg/min ± 0.65, 30-min: 0.69 mg/min ± 0.46, 90-min: 1.05 mg/min ± 0.42, 150-min: 3.78 mg/min ± 1.13 vs Placebo Fasting 1.26 mg/min ± 0.52, 30-min: 0.81 mg/min ± 0.55, 90-min: 1.18 mg/min ± 0.44, 150-min: 0.96 mg/min ± 0.52).

A 2 (dose: MPH vs. placebo) x 4 (time: fasting, 30-, 90-, 150-min) repeated measures ANOVA showed a significant main effect for time ($p<0.05$). No dose related changes were noted during any time period.

Reaction of vital signs (BP & HR) during EE sessions

A 2(dose: MPH vs. placebo) x 2(time: pre-, post-dose administration) repeated measures ANOVA was conducted for SBP, DBP and HR. Results showed a significant main effect for time on all 3 variables ($p<0.001$, $p<0.001$, $p<0.05$), respectively. Follow-up paired-samples t-tests on the time main effect showed that SBP (pre: 113.6 mmHg ± 5.5 vs. post: 120.1 mmHg ± 6.8, $p<0.001$), DBP (pre: 72.4 mmHg ± 5.9 vs. post: 76.3 mmHg ± 6.4, $p<0.001$) and HR (pre: 60.1 bpm ± 8.7 vs. post: 64.8 bpm ± 11.6, $p<0.05$) significantly increased from pre- to post-dose administration regardless of sex or treatment. These findings are depicted in Figure 6.

Discussion

MPH influences energy expenditure

Although controversy persists, some thermogenic pharmaceutical drugs, such as sibutramine, have been approved in an attempt to treat obesity (Bray, 2000). Seeing as energy expenditure is a crucial component of energy balance, finding a safe and efficient method of increasing resting energy expenditure (REE) would be beneficial. The REE accounts for approximately 70% of the total daily energy expended by an otherwise sedentary individual while the thermic effect of food (TEF) accounts for approximately 10% of the total (Ravussin &

Bogardus, 1992). When the sympathetic nervous system (SNS) is stimulated by catecholamines such as dopamine (DA) or norepinephrine, various types of adrenoreceptors are activated (Jequier et al., 1992). This generic activation of adrenoreceptors has been shown to result in increases in both blood pressure and heart rate (Jequier et al., 1992; Volkow et al., 1999; Volkow et al., 2003). In this study, short-acting methylphenidate hydrochloride (MPH) seemed to have had marked effects on energy expenditure variables. Resting energy expenditure (kcal/24h) increased significantly by approximately 7% over values observed during the placebo session (Figure 1). This increase in REE seems to correspond with previous studies using intravenous DA infusion (Nakagawa et al., 1994; Ruttimann et al., 1991). Although not clearly understood, MPH-induced DAT blockade increases in REE may be partly mediated by higher levels of circulating peripheral epinephrine (Kuczenski & Segal, 1997). MPH's ability to increase peripheral epinephrine levels suggests a robust relationship linking the CNS and SNS to adrenal stimulation (Volkow et al., 2003).

It has been well documented that food consumption generally induces increases in energy metabolism (Brondel, Fricker, & Fantino, 1999; Ravussin & Bogardus, 1992; Tappy, 1996). This additional energy is required for the digestion and absorption of the nutrients contained in consumed food (Brondel et al., 1999). The rise in PEE usually reflects between 10-30% of the energy contained in the meal depending on the contents of the ingested meal (Ravussin & Bogardus, 1992). Additionally, PEE during MPH treatment increased by 23%, 21% and 14% throughout the 30-, 90-, 150-min post-prandial period respectively (Figure 2). MPH had a profound effect on PEE in that it was consistently higher than values obtained with placebo treatment throughout the 3-hour post-prandial period. In fact, the MPH curve closely coincided

with peak uptake of quick-release MPH that occurs approximately 90-120 minutes after administration (Volkow et al., 2001; Volkow et al., 1998).

Respiratory Exchange Ratio (RER), Substrate Oxidation and MPH

To our knowledge, no studies have investigated the effects of MPH treatment on substrate oxidation. The RER with MPH and placebo treatments showed no significant changes during the 30- to 90-min post-prandial time interval. Interestingly, the RER during MPH treatment continued to decrease in the 90- to 150-min post-prandial time interval whereas an increase was observed during the placebo treatment.

Although no significant changes in carbohydrate and lipid oxidation rates were found, MPH seemed to show a trend of increasing carbohydrate oxidation. This would tend to show that MPH treatment resulted in an increase in carbohydrate mobilisation with virtually no change in lipid oxidation. Further investigation is necessary to determine how much of this difference can be attributed to MPH.

Possible sex differences in DA metabolism

No sex differences upon MPH exposure were noted in this study. Nonetheless, it should be mentioned that sex differences in DA metabolism have been observed. Notably, women seem to have a more efficient DAT binding capacity (DA is then metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC) or repackaged into synaptic vesicles) resulting in a higher synaptic concentration of DA in the striatum (Bhatt & Dluzen, 2005; Laakso et al., 2002). This may be reflected in the fact that issues with substance abuse are three to five times more prevalent in men than in women (Laakso et al., 2002). Given these demonstrated sex differences found in other studies, it may have been expected to incur discrepancies in eating behaviour between men

and women as well. It is possible that the degree of variation in the level of striatal DA in men and women is not enough to exacerbate the expression of behavioural differences.

Effect of MPH on vital signs and adverse events

Interestingly, both pulse rate and blood pressure rose consistently, yet seemed to be unaffected by MPH yet dependent on time. Although not completely understood, a "placebo effect" might explain the increases observed during the placebo sessions as noted in a study conducted on hypertensive patients (Asmar et al., 2001). Nonetheless, blood pressure and heart rate slightly increased as might be expected with SNS stimulation and perhaps some PNS inhibition resulting from DAT blockade and induced by MPH (Hirsch, Mackintosh, & Aronne, 2000). Similarly, recent studies on the effectiveness of sibutramine (a serotonin reuptake inhibitor used to induce weight loss) have noted little to no effect on vital signs in comparison to the placebo groups (Jordan et al., 2005; Lechin et al., 2006).

No serious adverse events were noted during all the sessions in which participants received MPH. The most common adverse event seemed to be a mild rating of "drowsiness" (2/28 sessions). Feelings of "nervousness" (1/28 sessions) and "agitated/restless" (1/28 sessions) both received a moderate rating. The occurrence of adverse events seemed to be similar or even less frequent than those noted in other studies (Efron et al., 1997; Modi et al., 2000); however, somnolence was a common effect in the MPH group (Modi et al., 2000).

General conclusions

The results obtained in this study seem to support the notion that MPH may be a safe method of increasing energy expenditure without the presumed increases in heart rate and blood pressure commonly associated with psychostimulant use. With that said, MPH seems to fulfill

some criteria of an ideal anti-obesity drug as outlined in Leonhardt and colleagues' paper (Leonhardt, Hrupka, & Langhans, 1999) and further investigation is required.

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ARTICLE 2 - Methylphenidate Reduces Energy Intake and Dietary Fat Intake in Adults: A Mechanism of Reduced Reinforcing Value of Food?

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RUNNING HEAD: Methylphenidate and Energy Intake

Abstract

Background: Dopamine mediates the reinforcing value of food, and low levels of dopamine are related to increased feeding behaviour. Thus administering a drug that increases dopamine may reduce energy intake, possibly by reducing food reinforcement.

Objectives: To test whether short-acting methylphenidate (MPH), a drug that increases the availability of dopamine by blocking its reuptake, reduces energy intake and alters macronutrient preference, and to explore whether these effects are due to a mechanism of reduced hunger and/or reduced food reinforcement.

Design: Fourteen adults were given placebo or short-acting MPH (0.5 mg/kg) in a randomized, double blind, placebo-controlled crossover fashion. One hour after ingestion, hunger and the relative reinforcing value of energy-dense snack food were measured, followed immediately by energy intake and macronutrient preference during a buffet-style lunch.

Results: MPH significantly reduced energy intake by 11% (1099.5 + 469.9 vs 1231.1 + 501.6 kcal; p=0.024) as well as intake (in grams) of fat by 17% (40.9 + 19.2 vs 49.3 + 19.8; p= 0.003) relative to placebo. MPH also reduced pre-meal hunger and the relative reinforcing value of high fat food, and pre-meal hunger and the reinforcing value of high fat food predicted overall food intake and intake in dietary fat, respectively, after MPH administration but not placebo.

Conclusion: MPH reduced overall energy intake with selective reductions in dietary fat, with an apparent mechanism of reduced hunger and/or decreased reinforcing value of high fat foods. Findings are consistent with a reward deficiency model of obesity whereby low brain dopamine is associated with overeating and obesity, and administering agents that increase dopamine results in reduced feeding behaviour by reducing hunger or the reinforcing value of palatable foods.

Keywords: Methylphenidate, dopamine, eating, energy intake, food reinforcement, obesity

Food is very reinforcing (1;2), and there are individual differences in the reinforcing value of food whereby obese persons find food more reinforcing than non-obese persons (3-6) and show a stronger preference for highly palatable foods with a high fat, high-carbohydrate content (7-9). Given food reinforcement predicts food intake (10-12), individual differences in the reinforcing value of food may play a role in the development of positive energy balance leading to obesity.

Dopamine has been implicated in mediating the reinforcing value of food (1;13), which has been noted to be a strong determinant of excessive food intake and obesity (3;4). Recent animal (14-17) and human (18-22) data suggest that low availability of circulating dopamine caused by rapid dopamine transport or reduced brain dopamine signalling may be related to the development of obesity. Ingesting palatable food, especially those high in sugar and simple carbohydrates, stimulates the release of dopamine in the accumbens-shell and results in repeated self-administrative behaviour typically observed in drugs of abuse (23;24). Thus, raising brain dopamine levels should reduce the reinforcing value of food and the motivation to eat, making it easier to reduce energy intake essential for weight loss. Moreover, given that polymorphisms associated with reduced brain dopamine are associated with increased craving (25) and overconsumption of high-fat, high-carbohydrate foods (26), increasing synaptic dopamine may alter macronutrient preference, in addition to reducing caloric intake.

There are several theoretical and clinical reasons to consider Methylphenidate (MPH) as an agent to increase brain dopamine. MPH is a dopamine transport/reuptake inhibitor (27-29) currently indicated for the treatment of childhood and adult attention deficit hyperactivity disorder (ADHD) (30;31). Moreover, a common side effect is reduced hunger and weight loss in children and adults (31;32), especially in those with highest BMI at baseline (31-33).

Recently, Leddy et al. (34) found that a single moderate dose of MPH (0.5 mg/kg) produced a 23% reduction in caloric intake (pizza) compared to placebo in 9 obese adult males, with a 21% decrease in energy intake relative to placebo using a high dose (1.0 mg/kg). Moreover, reported side effects from the single MPH doses were mild, not significantly different from placebo and unrelated to food intake (34). However, this study did not explore putative mechanisms linking MPH and reduced food intake or the effects of MPH on macronutrient preference.

The purposes of this study were: 1) to examine the effects of short-acting MPH on hunger, caloric intake, satiety and macronutrient consumption during a buffet lunch; 2) To evaluate the effects of MPH on food reinforcement, and evaluate the relationship between changes in the reinforcing value of high-fat, high carbohydrate (dessert/snack food) and changes in energy intake of these high-fat, high-carbohydrate foods to elucidate whether food reinforcement may be a mechanism by which MPH reduces energy intake and macronutrient preference.

METHODS

Participants. Approximately 50 people called to inquire about the study. Thirty-one were screened, 17 met inclusion criteria, and 3 participants did not complete testing, leaving 14 young adults (7 male and 7 female) for data analysis. Participants were recruited by posting flyers in local universities and in the community. Inclusion Criteria included males or females between the ages of 18-40 years; BMI $\geq$20 (normal weight or higher) and body weight less than 120 kg to accommodate the recommended maximum dosage of MPH of 60 mg/day; non-smoker or tobacco users; body weight that has not varied more than 2 kg in previous 6 months; no known food allergies; no history of previous MPH use or allergy to MPH; no history of ADHD or current diagnosis of an axis 1 psychiatric disorder (e.g., depressive or anxiety disorders) as measured by

the Wender-Utah Rating Scale (35-37) and Structured Clinical Interview for DSM-IV (SCID-IV) (38); no current use of thyroid medication, or any medication or dietary supplement that could affect appetite; normal blood pressure; no history of cardiac problems or symptoms suggestive of any cardiac condition; no history of diabetes or insulin resistance; no excessive use of alcohol (> 21 drinks/week) or alcoholism, or current addictions to opiates, cocaine or stimulants; no history of glaucoma; no personal or family history of seizure disorders; not currently taking Monoamine oxidase (MAO) inhibitors, pressor agents, coumadin, anticonvulsants, phenylbutazone, or tricyclic antidepressants; no history of thyroid disease; no personal or family history of motor tics or Tourettes's Syndrome; and the ability and willingness to comply with the scheduled appointments and experimental protocol. Descriptive characteristics of the sample are presented in **Table 1**. This study received approval from the Research Ethics Boards at the University of Ottawa and Health Canada.

Design and Experimental Procedures:

We utilized a randomized, double-blind, placebo-controlled, cross-over laboratory study to test the effects of MPH (0.5 mg/kg) on energy intake and the relative reinforcing value of food over the course of a mixed meal buffet lunch in young men and women. Participants visited our laboratory for one screening session and two testing sessions under drug or placebo, with the order in which participants received medication (MPH or placebo) counterbalanced. The study was conducted between May 2005 and April 2006 at the University of Ottawa. MPH used in this study was manufactured by Novartis Pharmaceuticals Inc. (Montreal, Canada).

Potential participants were screened via telephone to determine if they met basic inclusion criteria, and eligible participants were invited to the laboratory for more thorough screening. During the initial laboratory visit in which participants heard more about the purpose and

93 requirement of the study, written informed consent was obtained from all subjects interested in
94 volunteering for the study, followed by additional screening. Eligible and interested participants
95 underwent a complete demographic, medical, psychological and nutritional history assessment
96 completed by clinical interview, physical (medical) examination, and questionnaires in order to
97 fully assess inclusion criteria. Subjects were screened for current symptoms of ADHD with the
98 Wender-Utah Rating Scale (37), depression using the Beck Depression Inventory (BDI-II)(39),
99 and restrained eating using the Three factor Eating Questionnaire (TFEQ) (40). Eligible
100 participants then rated all of the foods that were used in the standardized *ad libitum* buffet eating
101 portion of the experiment (Appendix 1) using a 5-point scale (41). Those who rated 50% of foods
102 below moderate liking (3 or lower) on the 5-point scale would have been excluded, but no
103 participant met this exclusion criterion. Participants were then given, in single blind fashion, a
104 dose of MPH (0.5 mg/kg) to assess tolerability before undergoing the experimental test sessions.
105 A drug effects/side effects checklist and vital signs (blood pressure and heart rate) were completed
106 before administration of the test dose and 1-hour following administration. Those who reported
107 severe side effects (e.g., extreme nervousness), systolic blood pressure exceeding baseline reading
108 by 20 mm Hg, diastolic blood pressure exceeding the baseline reading by 10 mm Hg,
109 BP>160/100, or resting heart rate increased by >20 beats/minute from the baseline reading were
110 excluded from the study. However, no participant was excluded for these reasons. Subjective side
111 effects were measured for 19 potential adverse consequences (e.g., headache, nausea, nervousness,
112 etc.) by having participants rate the intensity of their symptoms using the following scale: 1=none,
113 2=mild, 3=moderate and 4=severe. No participants were excluded because of adverse drug
114 effects. Although subjects were informed about the potential side effects of the medication, they
115 were not told about any potential actions of the medications. Eligible participants were then

scheduled for two half-day experimental (test) sessions scheduled one week apart; one day each for evaluating energy intake under drug or placebo conditions. Women were always tested during days 1 to 5 of the follicular phase of the menstrual cycle to control for monthly hormonal effects on appetite and energy intake.

On testing days, subjects arrived at the laboratory at 9:30 am. Upon arrival, they completed a visual analog scale (VAS) to assess hunger and a 24-hour food intake recall (42) to ensure adherence to a 12 hour overnight fast, as instructed, including abstinence from alcohol and caffeine. Subjects were also told to abstain from vigorous physical activity 24 hours preceding testing, and were required to self-report this information upon visiting the lab. All participants adhered to these pre-experimental conditions except for 3 participants who required rescheduling because of excessive exercise within 24-hours of testing and two subjects exhibited symptoms of the common cold. Subjects who had upper respiratory ailments were rescheduled because these conditions hinder gustatory and olfactory sensations and may interfere with food hedonics or food intake (43).

At 9:45 am subjects were then evaluated for height, weight, waist circumference and body composition using Dual X-Ray Absorptiometry (DEXA), followed by rest in a supine position. At 10:10 am subjects then completed an assessment of hunger using a VAS and completion of side effects checklist and vital signs. This was immediately followed by administration of MPH (0.5 mg/kg) or placebo in a double-blind fashion, counterbalanced by order, followed by 60 minutes of leisure time activities and evaluation of hunger using VAS, side effect checklist and vital signs at 11:10 am, as well as the reinforcing value of high-fat dessert food using a questionnaire developed and validated by Goldfield et al (44). We chose a therapeutic dose of 0.5 mg/kg of MPH based on previous research showing that 7 of 9 obese subjects responded to this dose, with no greater

reductions in energy intake associated with an increased dose of 1.0 mg/kg,(34) indicating that this dose was the minimal effective dose. At 11:15 am, approximately one hour following administration of drug or placebo, total food intake, macronutrient preference and satiation was assessed by evaluating energy intake from a standardized mixed meal buffet-style eating methodology (45), with hunger re-evaluated every 30 minutes for three hours following completion of the meal to assess satiety. We chose a lag period between drug administration and meal initiation of 60-minutes because oral MPH takes this long to reach peak brain concentration in adults (28). Subjects were told they were free to eat as much as they wanted in a 30-minute period. *Ad libitum* cooled water consumption was measured during buffet eating sessions. At the end of the final session, subjects completed a treatment completion questionnaire (see below), and were phoned at home four hours after completing the protocol to reassess side effects to ensure they did not need medical assistance due to any delayed drug effects.

Measurement

Anthropometric measurements. Dual-photon x-ray absorptiometry (DEXA) was used to measure body composition (Lunar Prodigy, GE Medical Systems). Briefly, participants lay on an examination table, fully clothed, while a low intensity x-ray scanned their entire body. The measurement takes 15 minutes. Height and body weight were measured (HR-100 Height Rod and BWB-800AS Digital Scale from Tanita Corporation of America, Inc. Arlington Heights, Illinois, USA). Waist circumference was measured using a standard tape measure and placing the measuring tape horizontally mid-way between the bottom of the rib cage and the iliac crest and recording the measurement at the end of a normal expiration (46). Coefficients of variation and correlation for percent fat measured with DEXA in 12 subjects tested in our laboratory were 1.8 %

and r = 0.99, respectively when compared to underwater weighing. On the basis of height and weight data, BMI was calculated according to the following formula: BMI = kg/m^2

Vital Signs. Blood pressure (BP) was measured by a physician with a standard mercury sphygmomanometer and a large size cuff. Resting heart rate was measured by a heart rate monitor. (Polar® CIC, Port Washington, NY).

Food Record. Twenty-four hour food records were administered to participants to calculate energy intake the day before testing and to evaluate adherence to overnight fast instructions.

Energy Intake. Regarding the buffet-style meal, food intake was measured during an *ad libitum* meal offered to subjects at lunch time. The reproducibility of this measurement has been recently reported (45). Briefly, this meal consisted of a variety of foods of differing macronutrient composition. These foods were offered in large amounts and the subject was instructed to eat until satiation was achieved. More food was made available to the subjects in the event that they consumed all that was laid out at the beginning of the measurement. The subject was given 30 minutes for this meal and it was performed in a controlled environment. All foods were weighed to the nearest 0.1g before and after ingestion. Subjects were blinded to this procedure. Energy and macronutrient contents were assessed using Food Processor SQL from ESHA Research, Inc. Participants were asked to rate all of the foods that were used in the *ad libitum* buffet eating using a 1-5 rating scale (Appendix 1) to ensure that foods consumed were liked and foods not consumed were not due to taste aversions.

Hunger Visual Analogue Scale **(VAS).** Desire to eat, hunger, fullness and prospective food consumption was rated immediately before (after a 12 h overnight fast) and after drug or placebo administration, and at 30, 60, 90, 120, 150 and 180 min after completion of the standardized test meal using a 150-mm VAS, anchored by "not at all" to very much". This VAS

was adapted from Hill and Blundell (41). The VAS measurements were always performed in the same environment, using the same table with the same lighting in the same room which was kept free of odours and sounds as well as other factors that might contaminate this measurement (visual stimuli, individuals in the room, etc.). Under these conditions, VAS measurements in our laboratory (47) and others (48) have been shown to be highly reliable before and in response to meals.

Eating Behaviour. In order to assess attitude towards food and dietary restraint, the TFEQ was utilized (40). This 54-item inventory measures cognitive aspects of dietary restraint, dis-inhibition, and hunger. Thus subscale of interest in this study was dietary restraint. Item responses include true/false, frequency of symptoms reported (rarely to always), and Likert type scale responses of "not like me" to "describes me perfectly". The psychometric properties of this instrument are well established in adults and adolescents (49;50).

Wender-Utah Rating Scale. This is a 61-item self-report scale designed to screen for retrospective childhood onset attention deficit hyperactivity disorder (ADHD). It has shown to be a sensitive and valid tool in identifying ADHD in adults (35-37). Research has show that scores above 46 on this rating scale are indicative of ADHD, thus subjects who scored above this clinical cut-off were excluded from the study (35).

Beck Depression Inventory-II. This is a widely used and validated 21 item inventory that assesses cognitive, behavioural and vegetative symptoms of depression (39). Subjects scoring 30 or above, indicative of severe clinical depression, were excluded from the study.

Side effects Checklist. Nineteen subjective responses of potential side effects (headache, nausea, anxiety etc.) were measured by having subjects rate the intensity of their symptoms according to the following scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe. The checklist was

based on the most common side effects listed in the Compendium of Pharmaceuticals and Specialties reference guide, as well as one used by Leddy et al (34) in order to compare side effects profiles of MPH between studies.

Treatment completion Questionnaire. Participants were asked to identify the substance they received at each session (MPH or placebo) and rate how much they liked its effects using a 100mm VAS anchored by "not at all" to "very much."

Analytic Plan

The degree to which MPH influenced overall food intake, macronutrient consumption, food reinforcement, drug effects and vital signs were assessed by a repeated measures ANOVA with drug (MPH vs. placebo) as the repeated subjects variable. The effects of drug on pre-meal hunger and satiety response was evaluated using separate 2-way repeated measures ANOVAs. For pre-meal hunger, Drug (MPH vs placebo) and Time (pre-post administration) represented the within (repeated) subject factors. To assess satiety, Drug (MPH vs placebo) and Time (0, 30, 60, 90, 120, 150, 180 minutes post meal hunger ratings) represented the within-subjects repeated measures variables. Corrections for violations of sphericity that typically occur with more than 3 repeated measures with ANOVA were handled by adjusting the p-values based on the Huyn-Feldt tests. Significant findings on repeated measures were followed by paired t-tests to determine the time points in which hunger ratings differed between groups, using alpha set at .05

To explore the extent to which reduced hunger is a mechanism that links MPH with reduced energy intake was first evaluated by a repeated measures analysis of variance with group (MPH vs. placebo) and time (baseline vs. post) as repeated measure factors. Then, Pearson correlations between post MPH/placebo administration on pre-meal hunger and overall energy intake were examined in both MPH and placebo conditions. Similarly, the extent to which the

relative reinforcing value of high fat snack food is a mechanism linking MPH and reduced energy intake or intake from dietary fat, a within-subjects ANOVA was first conducted, with group (drug vs. placebo) as the within subjects factor and relative reinforcing value of high fat snack foods (i.e. button presses for snacks) as the dependent measure. Then, Pearson correlations between post MPH/placebo administration on the relative reinforcing value of high fat snack food and overall energy intake and intake from dietary fat was examined in both MPH and placebo conditions.

Chi-square analyses were conducted to evaluate the accuracy in which participants identified drug or placebo conditions, as well as the frequency of reported side effects in each drug condition. Two-tailed alpha set at 0.05 was used to evaluate statistical significance for all tests. Statistical analyses were conducted using SPSS© software, version 13.0. (Chicago, IL).

RESULTS

As shown in Table 2, ANOVA revealed that MPH produced significant reductions relative to placebo in overall kilocalories consumed ($p=0.023$) as well as intake (in grams) from fat ($p=0.004$), but no differences for intake of carbohydrates ($p=0.17$) or protein ($p=0.11$) were found between MPH and placebo, respectively.

Repeated measures ANOVA revealed that MPH (baseline: 34.9 ± 29.7; Post-administration: 11.5 ± 12.2) produced significantly greater reductions in pre-meal hunger compared to placebo which showed increased hunger (Baseline: 50.4 ± 28.8; Post-administration: 83.2 ± 28.4; $p<0.001$) (**see Figure 1**). In addition, there were no significant effects for time ($p=0.35$), on pre-post changes in pre-meal hunger.

There was a non-significant trend favouring MPH over placebo in the reduction of the relative reinforcing value of snack food ($p=0.10$) as shown in Table 2.

The 2-way repeated measures ANOVA indicated that neither the drug nor drug x time interaction was significant on hunger ratings after the buffet lunch. However, a main effect of time on hunger was significant ($p<0.001$), indicating that hunger increased (satiety decreased) over time for all participants.

Pearson correlations showed that reductions in the relative reinforcing value of high-fat snack food was positively correlated with reduced fat intake in the MPH condition ($r=0.41$, $p=0.10$ and food reinforcement and fat intake was negatively correlated, though not significantly, in the placebo condition ($r= -0.38$, $p>0.18$). Similarly, reductions in pre-meal hunger was associated with reductions in overall energy intake after MPH administration ($r=0.49$, $p=0.07$) but showed no relationship to energy intake after placebo administration ($r=0.02$, $p=0.94$).

Drug effects and Vital Signs

ANOVAs showed no significant effects involving differences between MPH and placebo in vital signs such as systolic or diastolic blood pressure, or heart rate in beat per minute. Similarly chi-square tests indicated no differences between MPH and placebo on the drug (side) effects during the screening or test dose. All drug effects reported for both MPH and placebo were in the mild to moderate range, with no symptoms reported for the severe range. Moreover, there were no significant differences in drug liking between MPH and placebo. Sixty four percent of participants correctly identified that they received placebo, which chi-square tests showed not significantly different from chance (i.e. 50%). Similarly, 50% of participants correctly identified that they received MPH, a rate that also did not differ significantly from that expected by chance.

DISCUSSION

Based on a randomized, double blind, placebo-controlled crossover design, which yields the highest quality of evidence in human laboratory studies, our data show that MPH, a drug that

increases brain dopamine by blocking dopamine transporter occupancy (28;51), significantly reduced overall food intake from a mixed-meal buffet style lunch relative to placebo. Interestingly, MPH selectively reduced consumption of high-fat foods but had no significant effects on carbohydrate or protein intake. Moreover, no differences in side effects or vital signs between MPH and placebo were reported, suggesting MPH is well tolerated during acute administration, which is often a period when people experience the most severe side effects from psychotropic medications.

Our data indicate that MPH enhanced satiation by reducing overall energy intake relative to placebo by 11%, which although statistically significant, is below the 23% reduction demonstrated by Leddy et al (34) using the same 0.5mg/kg dose. Several methodological differences between our study and that of Leddy et al (34) may help explain, in part, the discrepancies of drug effects on energy intake. Although differences in characteristics of the samples may contribute to the differences in treatment response, these differences are unlikely to explain much of the variance since these variables were included in the ANOVA models as covariates and identical results were obtained. Perhaps a more important methodological difference between studies relates to the eating paradigms used to assess energy intake. Our study used an all-you-can-eat mixed-meal buffet style eating paradigm whereas Leddy et al (34) used a single-food all-you-can-eat (pizza) model. Given the well documented support for sensory specific satiety (52-54), a phenomenon whereby individuals tend to become sated on one food but continue eating when they are presented with another food with different sensory characteristics (i.e., taste, smell, mouth feel,), these differences in eating paradigms may partially explain differences in caloric reduction observed with MPH. The 20% higher energy intake during placebo and MPH condition observed in our study compared to Leddy et al (34), despite our sample having lower mean BMI values,

298 supports this interpretation that sensory specific characteristics may partially explain the
299 differences in drug response. Alternatively, there is wide variability within and between
300 individuals in serum levels of weight standardized doses of MPH and these unmeasured
301 differences could explain the different treatment effects. Of course, it is quite possible that the
302 obese sample studied by Leddy et al. (34) are simply more responsive to MPH than our
303 predominantly lean sample. This interpretation is consistent with the reward deficiency syndrome
304 of obesity, which states that low levels of dopamine may motivate one to overeat (and become
305 obese) as a means of compensating for a dysregulated reward circuitry (10;20;55-57), thus
306 increasing brain dopamine should theoretically result in a greater reduction in the reinforcing
307 value of food, motivation to eat and reduced intake in obese compared to lean persons (15-17;19-
308 22).

309 Because MPH acts on brain dopamine, and dopamine mediates the reinforcing value of
310 appetitive behaviours such as eating (1;13), and that animal and human models show stronger
311 craving and reward value for snack foods high in fat and simple carbohydrate (23), we
312 hypothesized that MPH could have selective effects on fat and/or carbohydrate intake. Our data
313 show that MPH did in fact selectively reduce, relative to placebo, intake of dietary fat by 17% but
314 had no significant effects on carbohydrate or protein intake during the buffet lunch. Interestingly,
315 MPH also produced a corresponding reduction in the reinforcing value of high-fat snack food by
316 29%, which while only a non-significant trend rather than significant difference, appears to be
317 clinically significant given food reinforcement is a strong determinant of food intake (58). To our
318 knowledge, this is the first study to document that MPH impacts macronutrient preference, and
319 may reduce intake of dietary fat by reducing the reinforcing value of these palatable foods.
320 Although the role that dietary fat intake plays in the aetiology and nutritional intervention of

obesity has recently come under scrutiny with the proliferation of low carbohydrate diets (59), nutritional guidelines from the American Dietetic Association, derived from evidence-based systematic reviews using meta-analysis (60), recommend a low-fat (<30%) diet for the treatment and prevention of obesity and its co-morbidities. Moreover, very low-fat diets have been shown to reverse heart disease processes (61), providing evidence that adherence to low-fat diets is critical to attenuate obesity-related co-morbidities. It is important to note that the current findings were obtained in sample predominantly comprised of non-obese adults, and future research is needed to determine if MPH selectively reduces fat intake in obese persons.

MPH administration produced a greater reduction in pre-meal hunger compared to placebo, and changes in hunger predicted overall change in energy intake in the MPH condition but not placebo. These findings support the notion that reduced hunger is another well-documented mechanism of action linking MPH and weight loss. Our study was designed to assess the effects of MPH on satiation, but it is important to note that even though MPH improved satiation by reducing energy intake relative to placebo, the pattern of hunger ratings over a 3-hour post-prandial period did not differ by condition, and there was even a trend for less hunger at 3 hours post-prandial reported by MPH compared to placebo. This suggests that in addition to reduced hunger and reduced reinforcing value of high-fat foods, future research that measures food intake over a 24 or 48 hour period should investigate the relative importance of satiety as a mechanism of action of the hypophagic effects of MPH.

In summary, our data show that administering a single dose of short-acting MPH at 0.5 mg/kg produced a significant reduction in energy intake, with selective reduction in macronutrient preference for high fat foods. MPH had no impact on liking or hedonics for food, consistent with the incentive salience model which has shown that liking and food reinforcement are related but

conceptually distinct constructs (62;63), and food reinforcement may be a stronger predictor of food intake than liking (58). Although not conclusive, the data suggest that potential mechanisms of the hypophagic response to MPH are reduced hunger and/or reduced reinforcing value of high fat foods. The latter mechanism makes theoretical sense since food is a primary reinforcer and dopamine transport and synthesis mediates the reinforcing value of food (1;13;38). These findings are consistent with the neurobiological "reward deficiency" hypothesis that the dopaminergic system plays an important role in regulating the reinforcing value and consumption of appetitive behaviours such as eating and smoking. Consistent with the reward deficiency model of obesity, (20;56;57) our data suggest that increasing brain dopamine results in reduced energy intake, while other studies indicate that decreasing brain dopamine through administration of antipsychotic mediations results in overeating and weight gain (64). As such, our data along with previous laboratory data of MPH on eating in obese men (34), suggest that MPH and possibly other agents that increase brain dopamine by blocking its reuptake and synthesis warrant further study as methods of inhibiting eating behaviour. With regards to future research on MPH, identifying optimal dose and timing of dose, as well as examining the safety, tolerability, and possible abuse potential of sustained use of MPH in obese males and females is needed before it can be considered for testing as a pharmacological agent in the treatment of obesity.

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Table 1. Mean and (standard deviation) of sample characteristics (n=14)

Variable	Mean (SD)
Age (years)	23.7 (4.8)
Height (cm)	170.0 (6.5)
Weight (kg)	72.4 (13.0)
BMI (kg/m^2)	25.0 (4.0)
Percent obese (BMI >30)	21.4
Waist Circumference (cm)	85.0 (10.9)
Percent body fat	24.2 (10.5)
Dietary restraint	17.8 (9.3)
Depression	2.5 (3.5)
ADHD symptoms	13.1 (9.3)

Table 2. Effects of MPH or Placebo on mean and standard deviations for energy intake, hedonics, food reinforcement, and hunger

Variable	MPH (n=14)	Placebo (n=14)	p-value=
Water Intake (g)	199.2 ± 290.8	128.3 ± 203.9	.302
Energy intake (Kcal)	1099.5 ± 469.9	1231.1 ± 501.6	.024
Fat intake (g)	40.9 ± 19.2	49.3 ± 19.8	.003
Carbohydrate intake (g)	140.5 ± 58.1	151.2 ± 62.7	.170
Protein Intake (g)	45.1 ± 19.9	48.7 ± 23.6	.105
Liking of buffet foods	70.7 ± 20.2	65.6 ± 19.2	.385
Food Reinforcement (button presses)	95.7 ± 58.8	134.3 ± 82.4	.100
Drug Liking (mm)	70.7 ± 20.2	65.6 ± 19.2	.381
Hunger at arrival at lab (mm)	34.9 ± 29.7	50.4 ± 28.8	.061
Hunger 60-min post admin, Pre-meal (mm)	11.5± 12.2	83.2 ± 28.4	.001
Hunger 30 min. post meal (mm)	29.8 ± 27.4	20.5 ± 12.8	.234
Hunger 60 min post-meal (mm)	29.8 ± 19.2	27.0 ± 20.0	.704
Hunger 90 min post-meal (mm)	35.1 ± 25.6	39.6 ± 25.0	.589
Hunger 120 min. post-meal (mm)	46.0 ± 29.4	45.5 ± 25.2	.967
Hunger 150 min post-meal (mm)	48.9 ± 29.8	55.9 ± 22.9	.497
Hunger 180 min post-meal (mm)	53.3 ± 31.8	68.3 ± 26.9	.258

Effects of drug on each outcome measure was analyzed by repeated measures ANOVA. For Hunger, data are presented at each time point but the analysis involved a repeated measures ANOVA to assess the effects of drug (Methylphenidate vs placebo) on hunger at (baseline, pre-meal, 30, 60, 90, 120, 150, 180 minutes post-meal), which was significant. All tests were conducted using two-tailed alpha set at .05.

Figure Legends

Figure 1: Effects of repeated measures ANOVA testing the effects of Methylphenidate and Placebo on pre-post administration changes in hunger, with SEM bars. The drug x time interaction was significant, $p<.001$

Appendix 1: Food Item Selection and Quantity of Food offered in Buffet Lunch. Total weight (in grams) of consumed was calculated by subtracting weight of each food remaining after eating from the weight of each food as presented before eating.

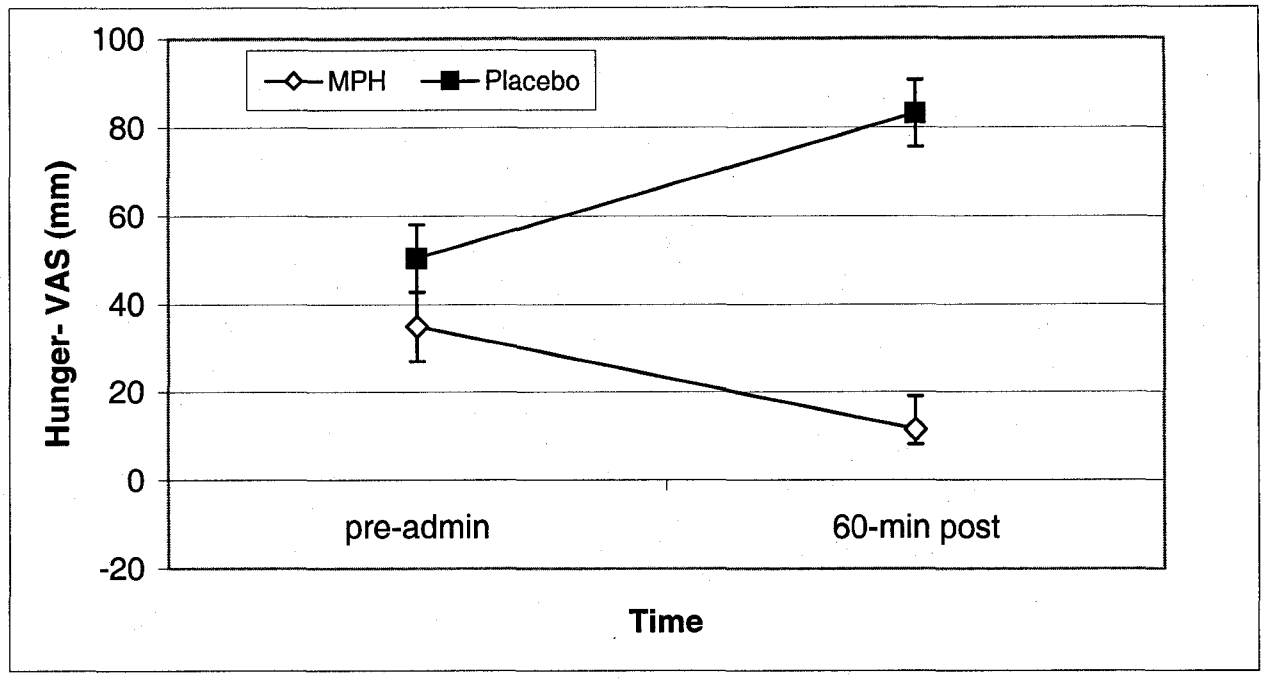

Figure 1.

Appendix 1.

BUFFET MEAL			
Foods	**Weight before (grams)**	**Weight after (grams)**	**Total weight consumed (grams)**
1- Turkey breast slices*	130		
2- Liver Pâté***	70		
3- Brie cheese double cream***	100		
4- Mozzarella cheese**	100		
5- Cottage cheese*	100		
6- Butter***	40		
7- Mayonnaise***	60		
8- Italian dressing**	60		
9- Ranch dressing**	60		
10- Mustard*	30		
11- Ketchup**	40		
12- White bread**	150		
13- Whole-wheat bread*	150		
14- Soda crackers*	100		
15- Lettuce*	60		
16- Tomatoes*	100		
17- Baby carrots*	150		
18- Apple quarters*	100		
19- Chocolate chip cookies (Chips Ahoy!)***	100		
20- Chocolate cake***	200		
21- Fruit yogurt*	250		
22- Skimmed milk (0%)*	1000		
23- Partly-skimmed milk (2%)**	1000		
24- Whole-fat milk (2%)***	1000		
25- Orange juice*	1000		
26- Coca-Cola***	355		
27- 7-up***	355		
28- Regular chips***	60		
29- Water*	1000		

*, low-fat and low-sucrose (12 items) ; ** medium fat and/or medium sucrose (6 items); *** high-fat and/or high-sucrose (11 items). All subjects reported moderate liking or higher for foods.

Matters of Controversy

Tolerance to MPH

To date, there is no evidence of the development of tolerance to MPH (Izenwasser et al., 1999; Solanto, 2000). The effects of acute and chronic treatment of MPH appear to be similar. In addition, there is no long-term remedial effect of the drugs on behaviour (i.e. the symptoms return when the drug is discontinued) (Izenwasser et al., 1999; Solanto, 2000). If tolerance does develop, MPH would be expected to lose its effectiveness and patients would require increased amounts - neither of which seems to occur (Bray, 2000). On the other hand, a recent study found results suggesting that shortly after exposure to high concentrations of MPH, efficacy is reduced (J. Swanson et al., 1999). The authors of the study concluded that acute tolerance to MPH appears to exist (J. Swanson et al., 1999).

Abuse Potential of MPH

Methylphenidate, unlike cocaine, does not appear to have a high abuse potential. A major difference between MPH and cocaine is that MPH lacks affinity for the serotonin transporter (Izenwasser et al., 1999). Hence, it is possible that the inhibition of serotonin uptake contributes to the sensitization observed in cocaine studies and potentially to the abuse potential associated with the drug. Another possibility is that the distinct pharmacokinetic differences between cocaine and MPH contribute to the observed behavioural changes. In humans, intravenously administered MPH and cocaine rapidly enter the brain (6-10 min for MPH and 2–4 min for cocaine) (Modi et al., 2000; Volkow et al., 1999; Volkow et al., 1998). However, the half-life is approximately 20 min for cocaine and 90 min for MPH (Modi et al., 2000; Volkow et al., 1999; Volkow et al., 1997). It is unlikely that the changes in behaviour are solely due to the slightly longer half-life of MPH as compared to cocaine, but it is a notable difference. Nonetheless, the

abuse potential of MPH in special populations such as in the obese remains unknown hence further research is warranted.

The dopamine transporter gene

When DAT density was measured in animals' brains that had been injected with MPH, a small but significant decrease in density was observed in the caudate putamen and no significant change was seen in the NAC (Izenwasser et al., 1999; Madras, Miller, & Fischman, 2002; Trinh, Nehrenberg, Jacobsen, Caron, & Wetsel, 2003). It is not clear whether this decrease in transporter density in the caudate putamen is responsible for the partial tolerance to MPH (Izenwasser et al., 1999; Madras et al., 2002; Trinh et al., 2003). This finding is again opposing to cocaine, which produces no changes in the density or affinity of DATs (Izenwasser et al., 1999; Reith et al., 1997; Trinh et al., 2003; Volkow et al., 1999). These studies show that a sensitized response to MPH does not occur with repeated administration, unlike cocaine (Comings & Blum, 2000; Izenwasser et al., 1999; Reith et al., 1997; Trinh et al., 2003; Volkow et al., 1999; Volkow et al., 1998). In contrast, a partial tolerance to the behavioural effects of MPH occurs (Izenwasser et al., 1999; Ross, Fischhoff, & Davenport, 2002; Solanto, 2000; J. Swanson et al., 1999). These findings suggest that serotonin may play an important role in the adaptive responses to cocaine abuse but not with MPH usage.

The known DAT gene polymorphisms SLC6A3 9-repeat and 10-repeat alleles are of particular importance. The SLC6A3 9-repeat allele has been linked to reduced DAT protein expression resulting in elevated intra-synaptic DA levels and a significant risk allele for externalizing behaviour in children (Heinz et al., 2000; Young et al., 2002). Adversely, evidence suggests that the SLC6A3 10-repeat allele is associated with increased DAT protein expression and thus low levels of intrasynaptic DA (Heinz et al., 2000). Continuing, a recent study found

that the likelihood of obesity in African-American smokers with the SLC6A3 10-repeat allele genotype was 5.16 times greater than that of African-American smokers with the 9-repeat allele (Epstein et al., 2002). Moreover, the SLC6A3 10-repeat allele and various DA receptors have also been linked to other neurological pathologies such as ADHD and Tourette's Syndrome both of which are a result of low intrasynaptic DA availability (Blum et al., 2000; Heinz et al., 2000; Thompson, Comings, Feder, George, & O'Dowd, 1998).

Prospective Research

DAT gene studies

There are individuals that are hypersensitive to MPH and require a lower dosage in order to achieve the same effect. This was shown in a recent study that analyzed a particular allele in the DAT gene. The 480 bp VNTR allele was reported to be associated with an over-active transporter protein (SLC6A3) (Barden, 2003). Thus, individuals possessing this allele might be particularly responsive to MPH.

Another explanation for low intrasynaptic DA levels may be as simple as an overly transcribed DAT gene resulting in greater amounts of DAT and thus a greater influence on DA transport. In addition, an individual with higher levels of DAT protein would theoretically have a greater response to MPH.

The fact of the matter is that genetics has a crucial role to play in knowing whether DA levels modulate food intake and thus making individuals more susceptible to obesity. It has been shown that a low intrasynaptic DA level in the NAC of the brain strongly interacts with motivational behaviour. Since seeking and consuming food is considered by many to be a motivational behaviour, the importance of DA in controlling energy balance becomes eminent.

Investigating possible mechanisms by which MPH may peripherally increase EE

With the majority of MPH research focusing on MPH's CNS interactions, further study is needed to pinpoint the peripheral effects MPH had on participants. Blood analyses correlating circulating catecholamine levels along with PET imaging of activated brain regions may help determine possible mechanisms by which MPH can increase EE, while not significantly altering vital signs. This may also lead to further understanding as to the degree of DAT blockade in the periphery.

General Conclusions

The results seem to support the notion that MPH may be a safe method of increasing energy expenditure without accompanied increases in heart rate and blood pressure commonly associated with psychostimulant use. Further, by promoting a net caloric deficit of nearly 250 kcal accompanied with a diminution in dietary lipid intake, MPH seems to fulfill some criteria of an ideal anti-obesity drug as outlined in Leonhardt and colleagues' paper (Leonhardt et al., 1999) and further investigation is required.

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FIGURES

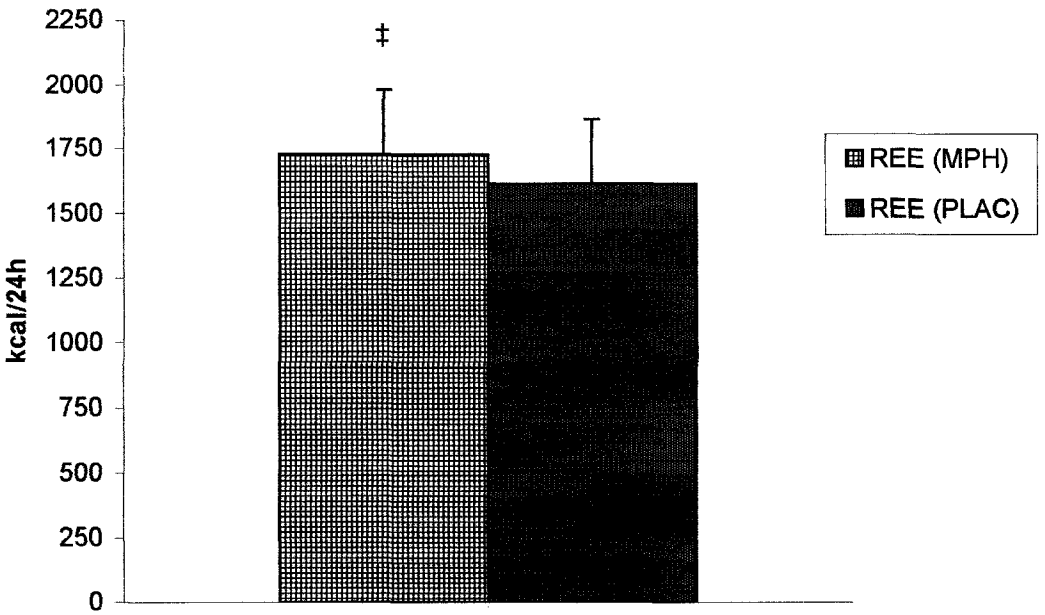


Figure 1 - Comparison (MPH vs. placebo) of mean ± SD resting energy expenditure (REE) during a fasted state. ‡ p <0.001

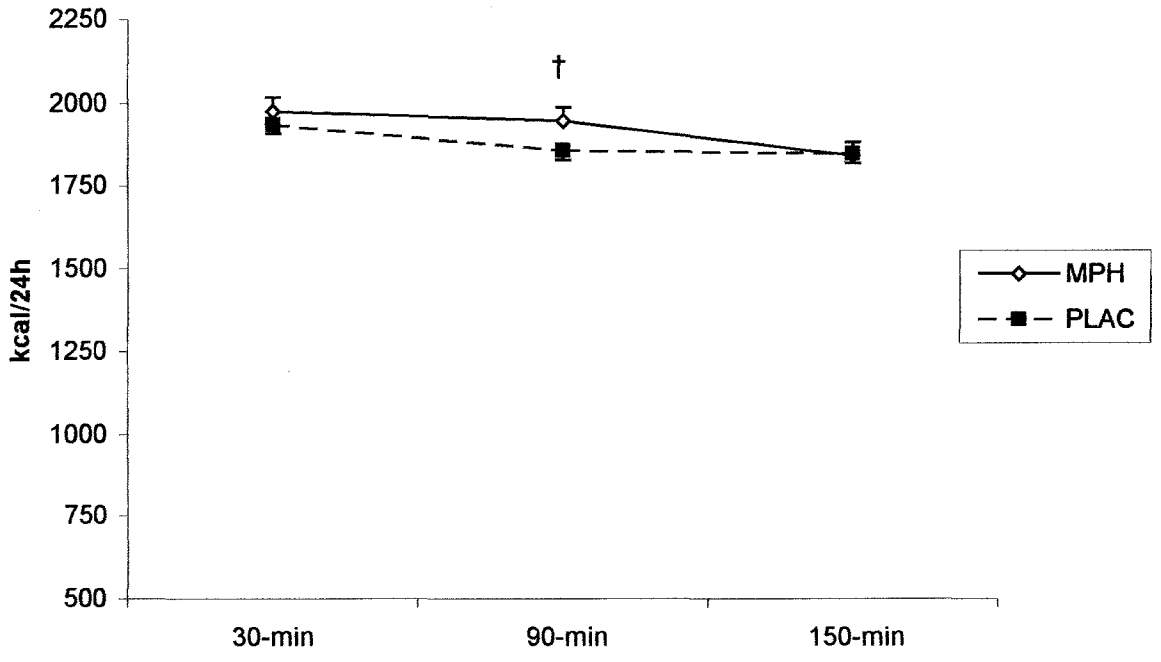


Figure 2 - Mean ± SEM post-prandial energy expenditure (PEE) during MPH vs. PLAC treatment. † p<0.005

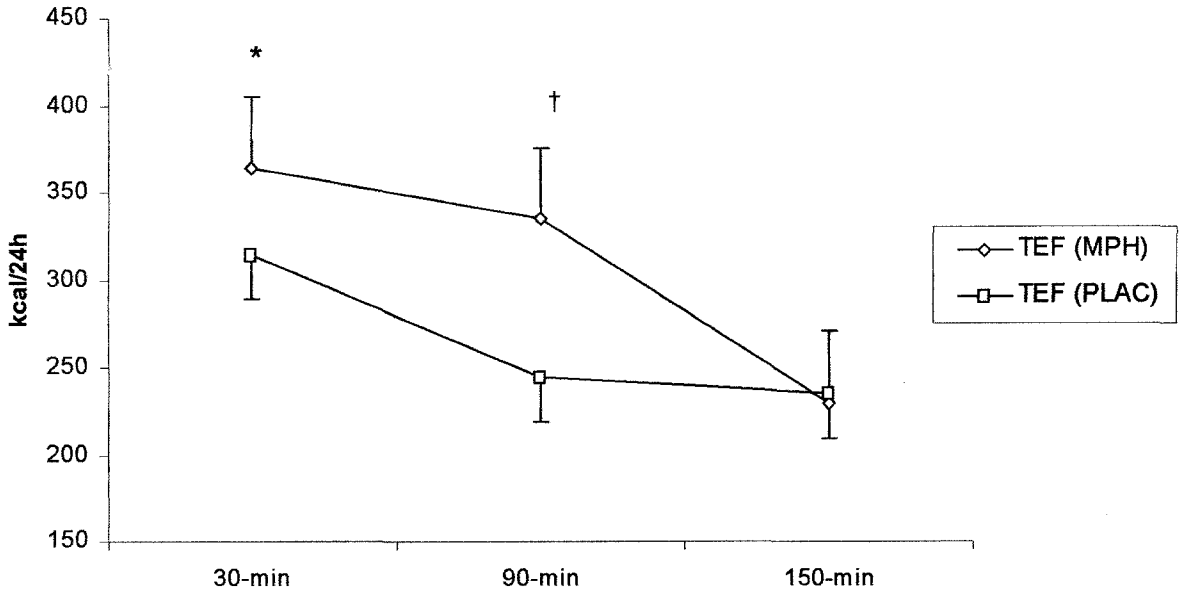


Figure 3 - Mean ± SEM differences in thermic effect of food (TEF) produced by MPH and placebo treatment. * p<0.05, † p<0.005

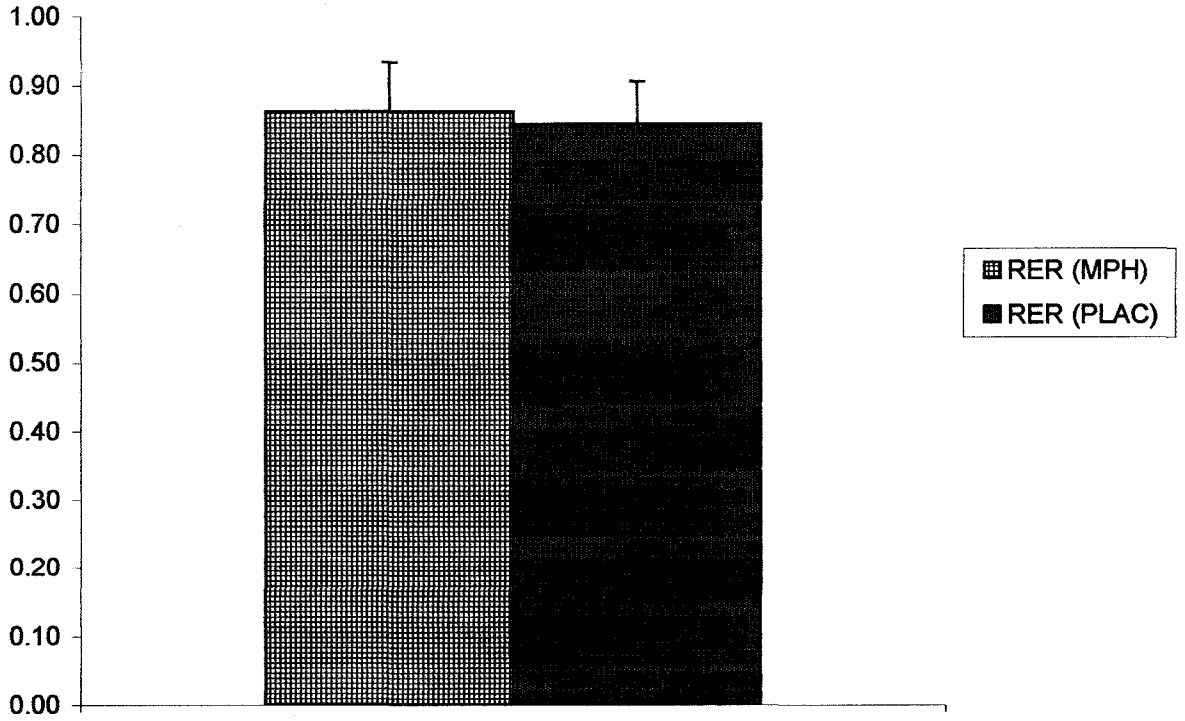


Figure 4 - Mean ± SD values for respiratory exchange ratio (RER) measured during a fasted state.

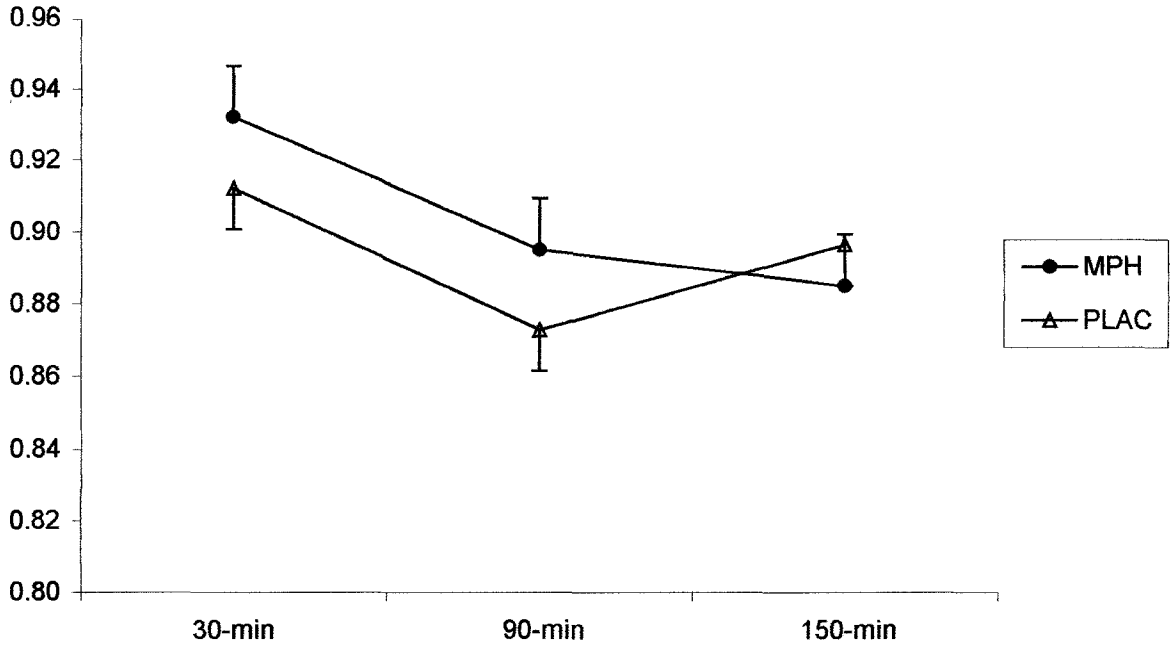


Figure 5 – Comparison of mean ± SEM post-prandial respiratory exchange ratio (RER) during MPH and placebo treatments.

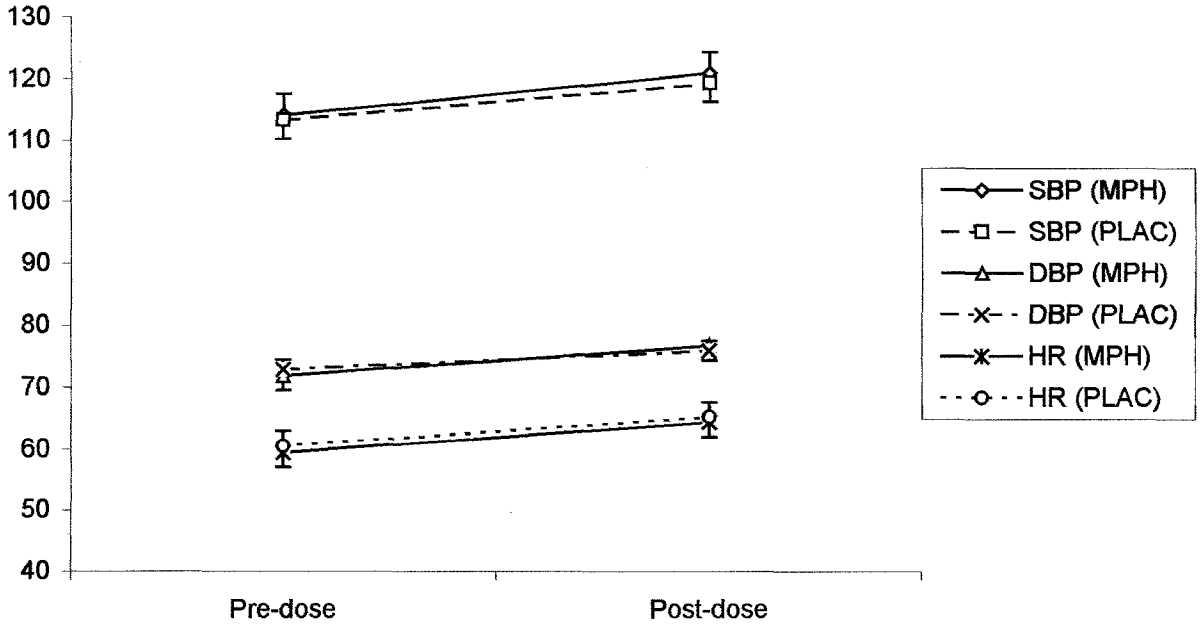


Figure 6 – Comparison (MPH vs. PLAC) of mean ± SEM values obtained for systolic and diastolic blood pressure (mm Hg) and heart rate (beats/min) during energy expenditure sessions.

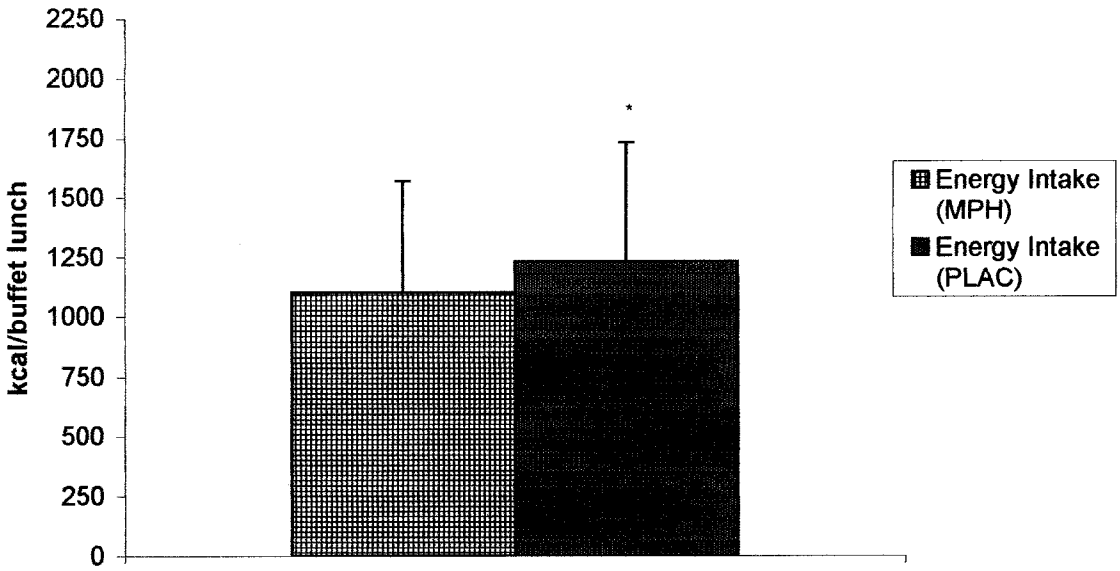


Figure 7 – Presented mean ± SD comparison (MPH vs. PLAC) of energy intake (kcal) during a single *ad-libitum* buffet-style lunch. * p<0.05

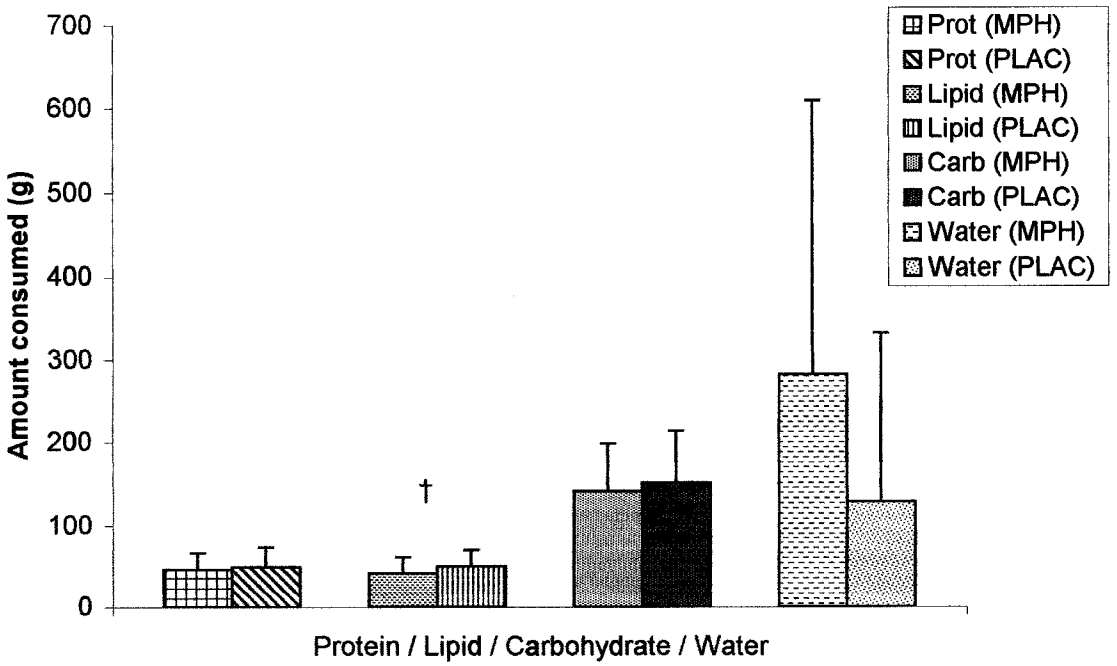


Figure 8 – Differences in mean ± SD macronutrient preference (g) and water consumption (g) observed during MPH treatment and placebo. † p<0.005

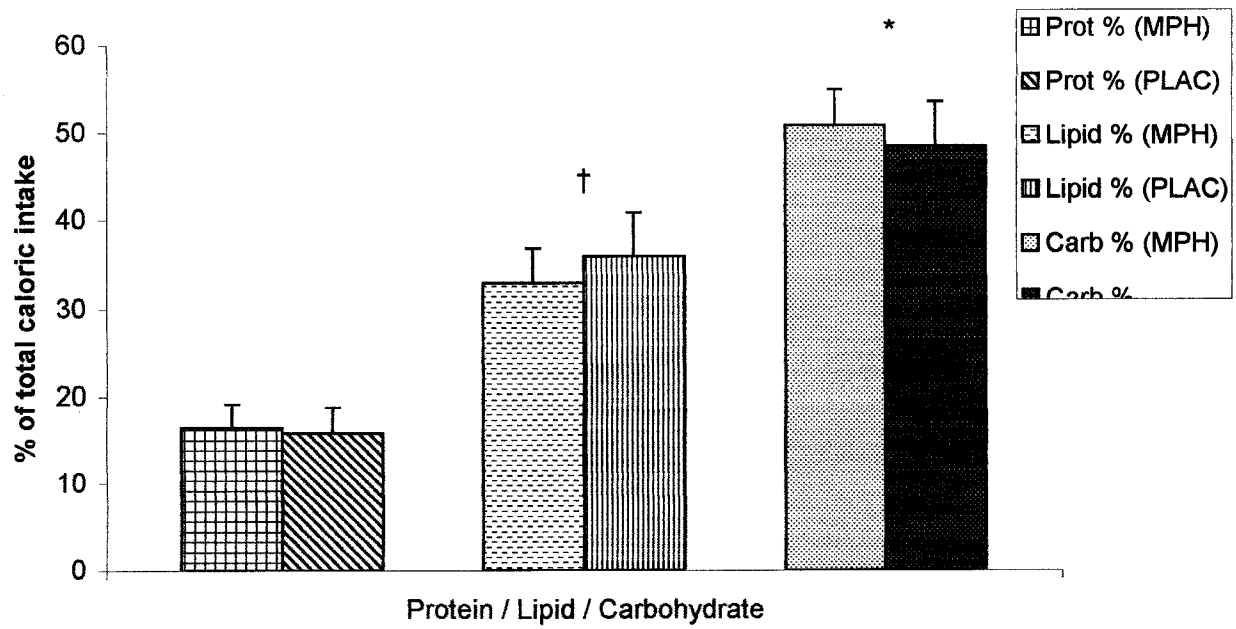


Figure 9 – Differences (MPH vs. PLAC) in mean ± SD macronutrient preference presented as a percentage of total caloric intake during the *ad libitum* buffet-style lunch. * $p<0.05$, † $p<0.005$

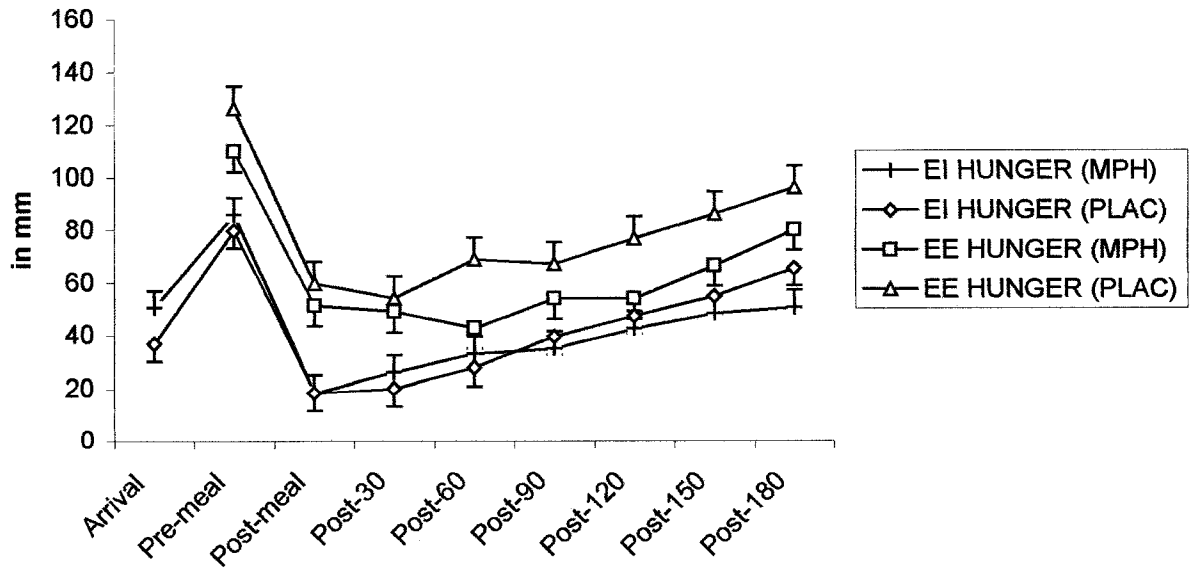


Figure 10 – Results obtained (mean ± SEM) from 150mm visual analogue scale question assessing perceived hunger during both energy intake and energy expenditure sessions.

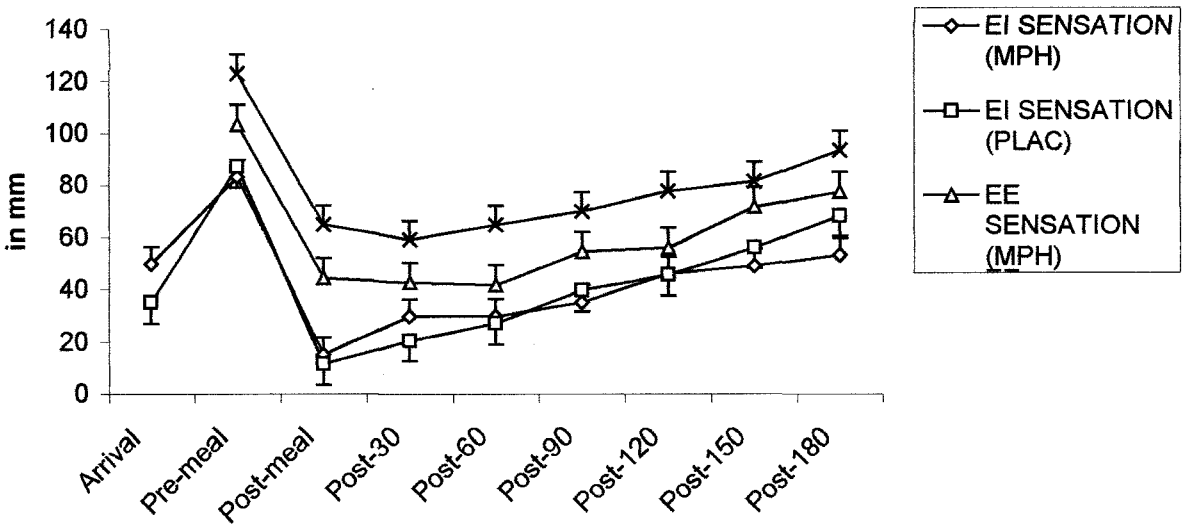


Figure 11 - Results obtained (mean ± SEM) from 150mm visual analogue scale question assessing the sensation of hunger during both energy intake and energy expenditure sessions.

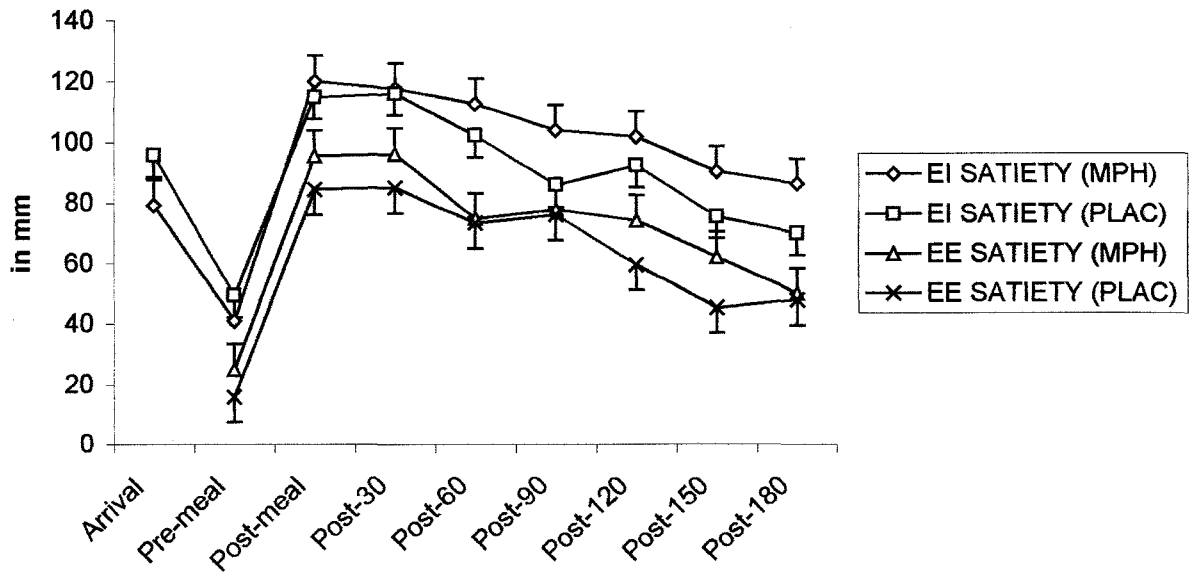


Figure 12 - Results obtained (mean ± SEM) from 150mm visual analogue scale question assessing the level of satiety during both energy intake and energy expenditure sessions.

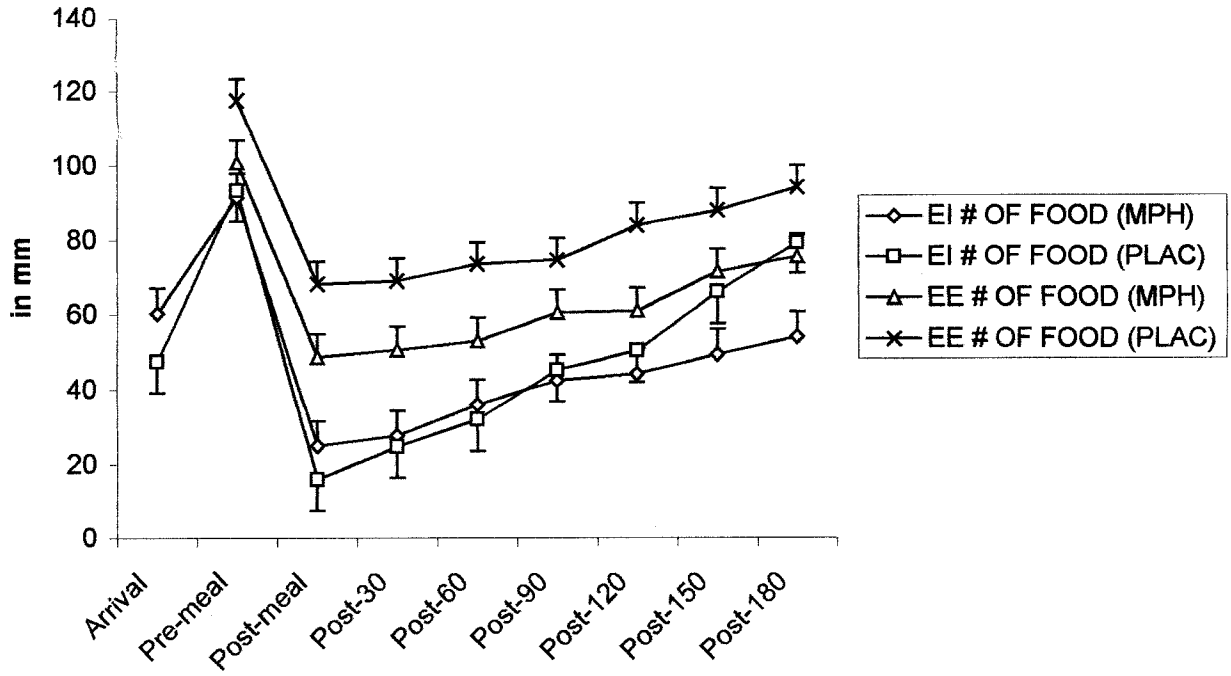


Figure 13 - Results obtained (mean ± SEM) from 150mm visual analogue scale question assessing the perceived amount of food the participant felt they could still consume during both energy intake and energy expenditure sessions.

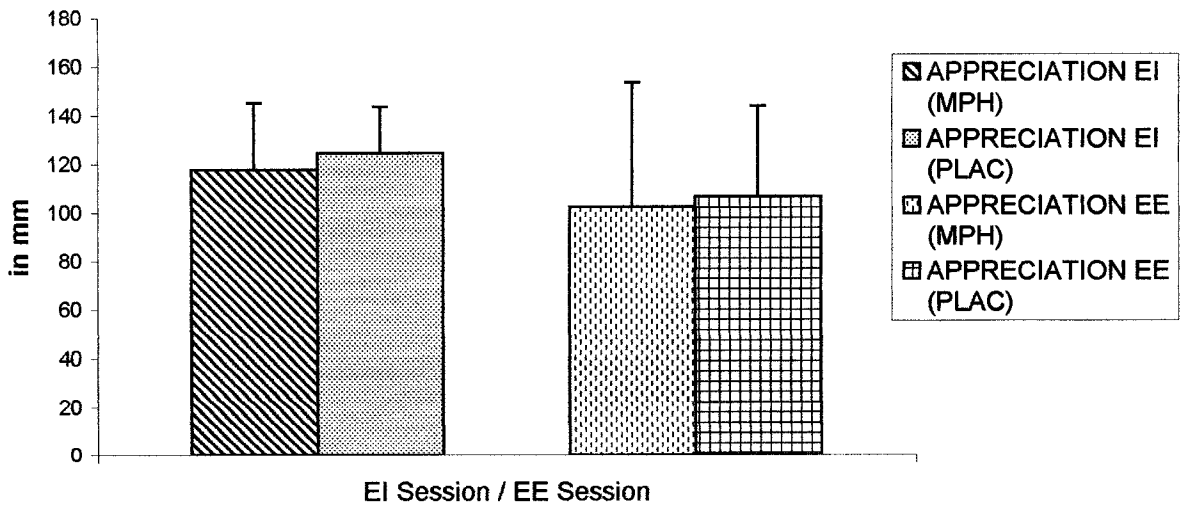


Figure 14 - Results obtained (mean ± SEM) from 150mm visual analogue scale question assessing the appreciation of the *ad-libitum* buffet-style lunch immediately after consumption during both energy intake and energy expenditure sessions.

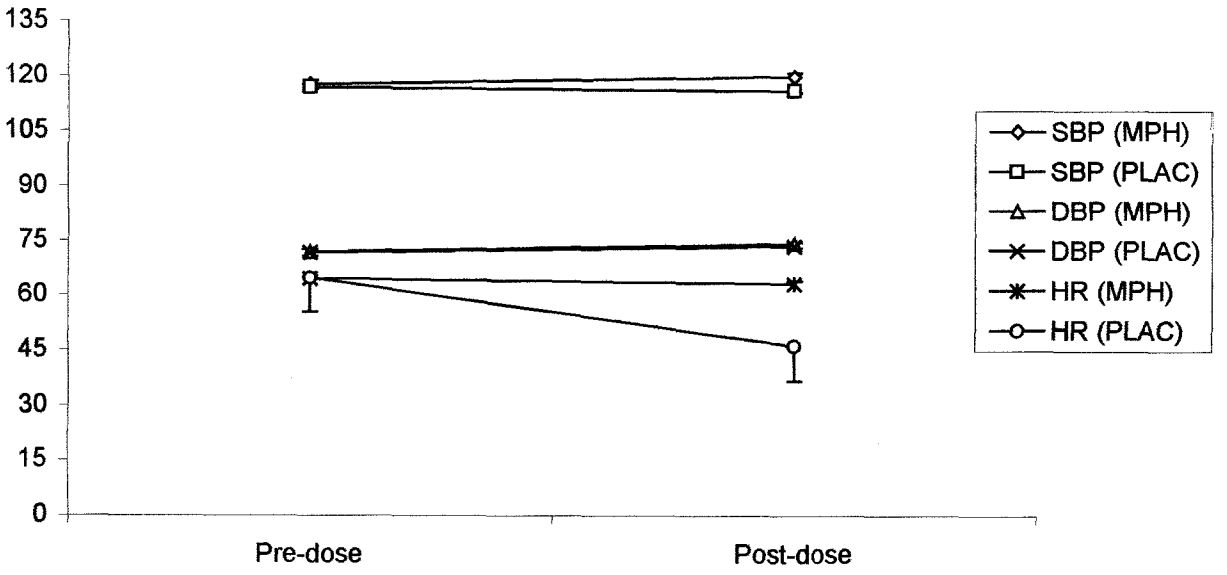


Figure 15 - Comparison (MPH vs. PLAC) of mean ± SEM values obtained for systolic and diastolic blood pressure (mm Hg) and heart rate (beats/min) during energy intake sessions.

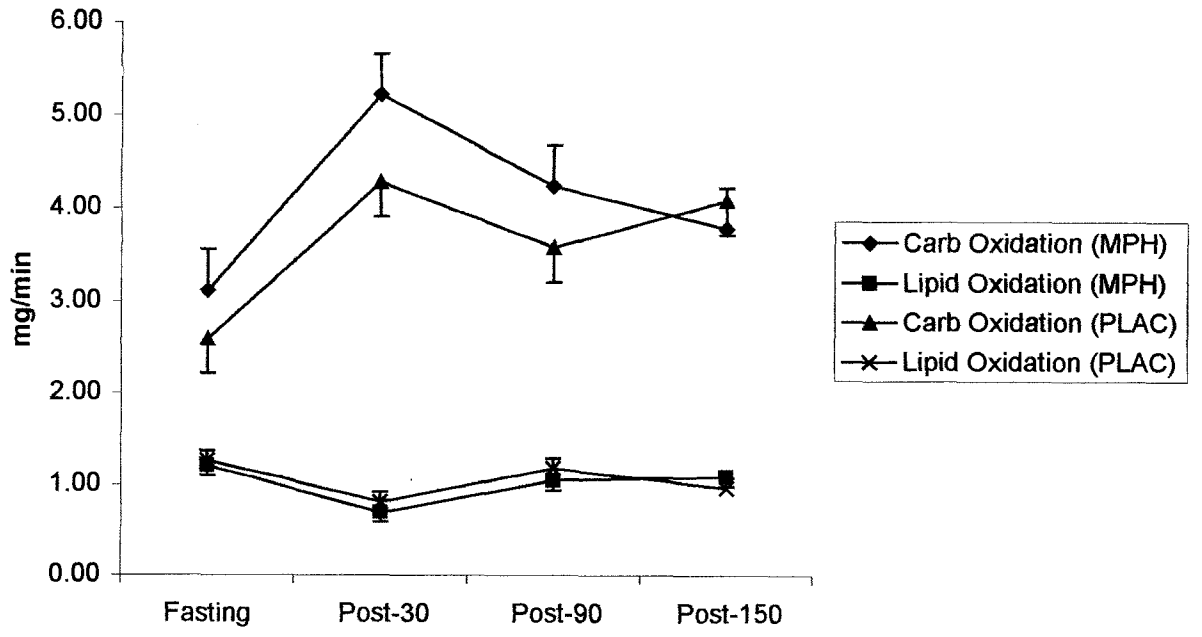


Figure 16 – Substrate oxidation rates (mg/min) calculated using the Ferrannini equation assessing the utilisation of both carbohydrates and lipids during MPH and placebo treatments. Results presented in (mean ± SEM)

TABLES

	Male	Female	Combined
n	7	7	14
Age (y)	25.7 ± 6.0	21.7 ± 2.2	23.7 ± 4.8
Height (cm)	175.0 ± 4.8	165.0 ± 3.1	170.0 ± 6.5
Body weight (kg)	75.1 ± 12.0	69.7 ± 14.4	72.4 ± 13.0
BMI (kg/m^2)	24.6 ± 3.7	25.5 ± 4.5	25.0 ± 4.0
Body fat (%)	16.3 ± 5.3	32.2 ± 8.0	24.2 ± 10.5
Fat mass (kg)	12.6 ± 5.9	23.0 ± 9.4	17.8 ± 9.3
Fat-free mass (kg)	59.6 ± 7.7	43.5 ± 5.9	51.6 ± 10.6

Table 1 - Descriptive statistics (mean ± SD)

APPENDIX A – POSTERS, FORMS & QUESTIONNAIRES

uOttawa
L'Université canadienne
Canada's university

Hôpital Montfort
Montfort Hospital

URCM
BMRU

Want to participate in research?

Looking for individuals to participate in a study on the effects of a commonly used drug on food intake and metabolism

Benefits Include:

- ✓ Accurate measurement of body composition (i.e. body fat %, bone density)
- ✓ Assessment of resting metabolism
- ✓ Nutritional counselling visit with registered dietician

Selection Criteria:

- ✓ Men and women aged 18 to 40 years old
- ✓ No major health problems
- ✓ Non-smokers
- ✓ Stable body weight for the last 6 months (± 2kg)
- ✓ No history of Attention Deficit/Hyperactivity Disorder (ADHD)

For more information, please call Claudio @ 613-263-2353

Behavioural and Metabolic Research Unit (BMRU)
Montfort Hospital - University of Ottawa

2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353 | 2632353

Wender Utah Rating Scale

Attention Deficit Hyperactivity Disorder in Adults, Paul Wender M.D.,1995.

As a Child I Was (or Had):	*Not at all or very slightly*	*Mildly*	*Moder-ately*	*Quite a Bit*	*Very Much*
1.Active, restless, always on the go					
2.Afraid of things					
3.Concentration problems, easily distracted					
4.Anxious, worrying					
5.Nervous, fidgety					
6.Inattentive, daydreaming					
7.Hot or short temp, low boiling point					
8.Shy, sensitive					
9.Temper outbursts, tantrums					
10.Trouble with stick-to-it-tiveness, not following through, failing to finish things started					
11.Stubborn, strong-willed					
12.Sad or blue, depressed, unhappy					
13.Uncautious, dare-devilish, involved in pranks					
14.Not getting a kick out of things, dissatisfied with life					
15.Disobedient with parents, rebellious, sassy					
16.Low opinion of myself					
17.Irritable					
18.Outgoing, friendly, enjoy company of people					
19.Sloppy, disorganized					
20.Moody, have ups + downs					
21.Feel angry					
22.Have friends, popular					
23.Well organized, tidy, neat					
24.Acting without thinking, impulsive					
25.Tend to be immature					
26.Feel guilty, regretful					
27.Lose control of myself					
28.Tend to be or act irrational					
29.Unpopular with other children, didn't keep friends for long, didn't get along with other children					
30.Poorly coordinated, did not participate in sports					
31.Afraid of losing control of self					
32.Well coordinated, picked first in games					
33. (for women only) Tomboyish					
34.Ran away from home					
35.Get in fights					

Appendix 2 – Wender-Utah Rating Scale

As a Child I Was (or Had) cont.:	*Not at all or very slightly*	*Mildly*	*Moder-ately*	*Quite a Bit*	*Very Much*
36.Teased other children					
37.Leader, bossy					
38.Difficulty getting awake					
39.Follower, lead around too much					
40.Trouble seeing things from someone else's point of view					
41.Trouble with authorities, trouble with school, visits to the principal's office					
42.Trouble with the police, booked, convicted					
Medical Problems as a Child:					
43.Headaches					
44.Stomach aches					
45.Constipation					
46.Diarrhea					
47.Food Allergies					
48.Other Allergies					
49.Bedwetting					
As a Child in School:					
50.Overall a good student, fast					
51.Overall a poor student, slow learner					
52.Slow reader					
53.Slow in learning to read					
54.Trouble reversing letters					
55.Trouble with spelling					
56.Trouble with math or numbers					
57.Bad handwriting					
58.Though I could read pretty well, I never really enjoyed reading					
59.Did not achieve up to potential					
60.Repeated grades (which grades?)					
61.Suspended or expelled (which grades?)					

FOOD HABITS QUESTIONNAIRE
(Stunkard et Messick, 1984)

This questionnaire contains a certain number of propositions.

If you agree with the statement or if you feel like it can be applied to you, check the case TRUE who correspond to the statement.

If you disagree with the statement or if you feel like it does not applied to you, check the FALSE case who correspond to the statement.

You have the choice to answer (or not) certain questions.

		TRUE	FALSE
1.	**When I smell a sizzling steak or see a juicy piece of meat, I find it difficult to keep from eating, even if I have just finished a meal.**	❑	❑
2.	**I usually eat too much at social occasions, like parties and picnics.**	❑	❑
3.	**I am actually so hungry that I eat more than 3 times per day.**	❑	❑
4.	**When I have eaten my quota of calories, I am usually good about not eating any more.**	❑	❑
5.	**Dieting is so hard for me because I just get too hungry.**	❑	❑
6.	**I deliberately take small helpings as a means of controlling my weight.**	❑	❑
7.	**Sometimes things just taste so good that I keep on eating even when I am no longer hungry.**	❑	❑
8.	**Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I had enough or that I can have something more to eat.**	❑	❑
9.	**When I feel anxious, I find myself eating.**	❑	❑
10.	**Life is too short to worry about dieting.**	❑	❑
11.	**Since my weight goes up and down, I have gone on reducing diets more than once.**	❑	❑
12.	**I often feel so hungry that I just have to eat something.**	❑	❑

	TRUE	FALSE
13. When I am with someone who is overeating, I usually overeat too.	❑	❑
14. I have a pretty good idea of the number of calories in common food.	❑	❑
15. Sometimes when I start eating, I just can't seem to stop.	❑	❑
16. It is not difficult for me to leave something on my plate.	❑	❑
17. At certain times of the day, I get hungry because I have gotten used to eating them.	❑	❑
18. While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	❑	❑
19. Being with someone who is eating often makes me hungry enough to eat also.	❑	❑
20. When I feel "blue", I often overeat.	❑	❑
21. I enjoy eating too much to spoil it by counting calories or watching my weight.	❑	❑
22. When I see a real delicacy, I often get so hungry that I have to eat right away.	❑	❑
23. I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	❑	❑
24. I get so hungry that my stomach often seems like a bottomless pit.	❑	❑
25. My weight has hardly changed at all in the last 10 years.	❑	❑
26. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	❑	❑
27. When I feel lonely, I console myself by eating.	❑	❑
28. I consciously hold back at meals in order not to gain weight.	❑	❑
29. I sometimes get very hungry late in the evening or at night.	❑	❑

	TRUE	FALSE
30. I eat anything I want, anytime I want.	❑	❑
31. Without even thinking about it, I take a long time to eat.	❑	❑
32. I count calories as a conscious means of controlling weight.	❑	❑
33. I do not eat some foods because they make me fat.	❑	❑
34. I am always hungry enough to eat at any time.	❑	❑
35. I pay a great deal of attention to changes in my figure.	❑	❑
36. While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.	❑	❑

PART 2

Please answer the following questions by circling the number that best corresponds to you.

37. How often are you dieting in a conscious effort to control your weight ?

Rarely	Sometimes	Usually	Always
1	2	3	4

38. Would a weight fluctuation of 5lbs (2 kgs) affect the way you live your life ?

Not at all	Slightly	Moderately	Very much
1	2	3	4

39. How often do you feel hungry ?

Only At mealtimes	Sometimes between meals	Often between meals	Almost always
1	2	3	4

40. Do your feelings of guilt about overeating help you control your food intake ?

Never	Rarely	Often	Always
1	2	3	4

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next 4 hours ?

Easy	Slightly Difficult	Moderately Difficult	Very Difficult
1	2	3	4

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

Not at all	Slightly	Moderately	Extremely
1	2	3	4

43. How frequently do you avoid « stocking up » on tempting foods ?

Almost Never	Seldom	Usually	Almost always
1	2	3	4

44. How likely are you to shop for low calorie foods ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

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

Never	Rarely	Often	Always
1	2	3	4

46. How likely are you to consciously eat slowly in order to cut down on how much you eat ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

47. How frequently do you skip dessert because you are no longer hungry ?

Almost Never	Seldom	At least once per week	Almost every day
1	2	3	4

48. How likely are you to consciously eat less than you want ?

Unlikely	Slightly Unlikely	Moderately likely	Very likely
1	2	3	4

49. Do you go on eating binges though you are not hungry ?

Never	Rarely	Sometimes	At least Once per week
1	2	3	4

50. On a scale of 1 to 5, where :

- 0 (zero) means no restraint in eating (eating whatever you want, whenever you want it) and,
- 5 means total restraint (constantly limiting food intake and never "giving in"),

What number would you give yourself?

- **Eat whatever you want, whenever you want it**
  0
- **Usually eat whatever you want, whenever you want it**
  1
- **Often eat whatever you want, whenever you want it**
  2
- **Often limit food intake, but often "give in"**
  3
- **Usually limit food intake, rarely "give in"**
  4
- **Constantly limiting food intake, never "giving in"**
  5

51. To what extent does this statement describe your eating behaviour?

"I start dieting in the morning, but because of many different things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow"

Not like Me	Little like me	Pretty good description of me	Describes me perfectly
1	2	3	4

APPRECIATION OF CERTAIN FOODS

1- Ask the participant to give their level of appreciation for each of the following foods.

2- Specify that on the appreciation scale, number 1 represents a food that the participant does not like at all and that number 5 represents a food that the participant likes a lot.

Meats	I do not like at all				I like a lot
Sliced turkey	1	2	3	4	5
Liver pate	1	2	3	4	5
Cheeses					
Brie cheese double cream	1	2	3	4	5
Cheddar cheese	1	2	3	4	5
Cottage cheese	1	2	3	4	5
Condiments					
Salted butter	1	2	3	4	5
Mayonnaise / salad dressing	1	2	3	4	5
Italian dressing	1	2	3	4	5
Cesar dressing	1	2	3	4	5
Mustard	1	2	3	4	5
Tomato ketchup	1	2	3	4	5
Breads					
White Kaiser bread	1	2	3	4	5
Whole wheat Kaiser bread	1	2	3	4	5
Soda crackers	1	2	3	4	5

APPRECIATION OF CERTAIN FOODS

Vegetables	I do not like at all				I like a lot
Romaine lettuce	1	2	3	4	5
Raw red tomatoes	1	2	3	4	5
Raw carrots	1	2	3	4	5
Fruits					
Red apple	1	2	3	4	5
Desserts					
Chocolate Brownie bits	1	2	3	4	5
Mixed fruit yogurt	1	2	3	4	5
Chocolate chip cookies	1	2	3	4	5
Beverages					
Whole-fat milk (3.25%)					
Partially skimmed milk (2%)	1	2	3	4	5
Skimmed milk (0%)	1	2	3	4	5
Pulp-free orange juice	1	2	3	4	5
Cola	1	2	3	4	5
7-up	1	2	3	4	5
Others					
Raspberry jam	1	2	3	4	5
Peanut butter	1	2	3	4	5
Plain potato chips	1	2	3	4	5
Water	1	2	3	4	5

Comments : _____

_____

_____

_____

_____

SIDE EFFECTS CHECKLIST

Time: Pre-MPH administration

Side Effect:	*None*	*Mild*	*Moderate*	*Severe*
1. Nervousness				
2. Nausea				
3. Dizziness				
4. Palpitations				
5. Headache				
6. Drowsiness				
7. Abdominal Pain				
8. Agitation/Restlessness				
9. Euphoria/Intense Pleasure				
10. Confusion/Disorientation				
11. Sweating				
12. Flushing				
13. Dryness of Mouth				
14. Blurry Vision				

Additional Comments:

_____

_____

_____

SIDE EFFECTS CHECKLIST

Time: Post 60 min.

Side Effect:	*None*	*Mild*	*Moderate*	*Severe*
1. Nervousness				
2. Nausea				
3. Dizziness				
4. Palpitations				
5. Headache				
6. Drowsiness				
7. Abdominal Pain				
8. Agitation/Restlessness				
9. Euphoria/Intense Pleasure				
10. Confusion/Disorientation				
11. Sweating				
12. Flushing				
13. Dryness of Mouth				
14. Blurry Vision				

Additional Comments:

_____

_____

_____

VITAL SIGNS CHECKLIST

Time: Pre-MPH administration

Those who report or show severe side effects such as **systolic blood pressure exceeding baseline reading by 20 mmHg, diastolic blood pressure exceeding the baseline reading by 10 mmHg, overall blood pressure > 160/100**, or **resting pulse rate increased by >20 beats/minute** from the baseline reading will be excluded from the study.

	Recording
Systolic Blood Pressure (mmHg)	
Diastoilc Blood Pressure (mmHg)	
HR (beats/min)	

Comments/Notes:

VITAL SIGNS CHECKLIST

Time: Post 60 min.

Those who report or show severe side effects such as **systolic blood pressure exceeding baseline reading by 20 mmHg, diastolic blood pressure exceeding the baseline reading by 10 mmHg, overall blood pressure > 160/100**, or **resting pulse rate increased by >20 beats/minute** from the baseline reading will be excluded from the study.

	Recording
Systolic Blood Pressure (mmHg)	
Diastoilc Blood Pressure (mmHg)	
HR (beats/min)	

Comments/Notes:

ANTHROPOMETRIC MEASUREMENTS

Height _____ . _____ cm

BMI _____ . _____ kg/m^2

Weight _____ . _____ kg

1. Do you have symptoms of a cold?	YES	☐	NO	☐
If YES, what symptoms?				
2. What time did you fall asleep last night?				
3. Sleep well?	YES	☐	NO	☐
4. Have you practiced any intense physical activity in the last 48 hours?	YES	☐	NO	☐
5. Have you taken any medicine within the last 12 hours?	YES	☐	NO	☐
If YES, specify?				
6. Have you smoked or had coffee in the last 2 hours?	YES	☐	NO	☐
7. Are you fasted?	YES	☐	NO	☐
If YES, since what time?	_____ . _____			
8. *(**Ask at the end of session)* Do you feel you received the placebo or the MPH?	Placebo	☐	MPH	☐

How much did you like its effects?

I did not like it at all

I liked it a lot

Pre-screening questionnaire for the study entitled:

EFFECTS OF METHYLPHENIDATE ON ENERGY BALANCE IN MEN AND WOMEN

Researcher:
Claudio Lorello
Supervisors :
Eric Doucet (Ph.D)
Faculty of Health Sciences, University of Ottawa
School of Human Kinetics
Gary Goldfield (Ph.D)
Children's Hospital of Eastern Ontario Research Institute

1)	**What is your age?**	_____
2)	**Do you smoke?**	**Yes** ☐ **No** ☐
3)	**Have you maintained a stable body weight (± 2 kg) over the last 6 months?**	**Yes** ☐ **No** ☐
4)	**Do you take medication?** **If so, which ones?**	**Yes** ☐ **No** ☐ _____ _____ _____
5)	**Do you, or have you ever been diagnosed with having ADHD?**	**Yes** ☐ **No** ☐
6)	**Have you ever taken Ritalin?**	**Yes** ☐ **No** ☐
7)	**Do you have any known allergies to Ritalin?**	**Yes** ☐ **No** ☐
8)	**Any personal or family history of motor tics or Tourette's Syndrome**	**Yes** ☐ **No** ☐
9)	**Do you have any other known food allergies?**	**Yes** ☐ **No** ☐
10)	**Do you have diabetes?**	**Yes** ☐ **No** ☐
11)	**Do you have any heart problems?**	**Yes** ☐ **No** ☐
12)	**Do you have high or low blood pressure?**	**Yes** ☐ **No** ☐
13)	**Do you have asthma or any other respiratory problems?**	**Yes** ☐ **No** ☐
14)	**Has your doctor ever diagnosed you with thyroid gland abnormalities?**	**Yes** ☐ **No** ☐
15)	**How many alcoholic beverages do you normally consume in 1 week?**	_____
16)	**Have you ever been diagnosed with glaucoma?**	**Yes** ☐ **No** ☐
17)	**Do you have any other health problems that were not mentioned in this questionnaire?** **If yes, please specify**	**Yes** ☐ **No** ☐ _____ _____

Multiple Choice Questionnaire

For each choice below, circle whether you would prefer to press buttons to earn 100 grams of your preferred snack food or 20-minutes of your preferred sedentary activity. Note that the number of button presses for snack foods increases, whereas the number of button presses to 20-minutes of sedentary activity stays the same for all of the 16 choices. Please take this task seriously even though YOU WILL NOT be rewarded for one of your choices with either snack food or sedentary activity. The choices you make are completely up to you. Please select the option that you prefer since there are no right or wrong answers. **In the shaded area below, please write down your most preferred snack food from the items that you just rated on the previous page (e.g., Chocolate Chip cookies, Potato Chips) above the Snack Food option. Now, please write down your most preferred sedentary activity from the items that you just rated on the previous page (e.g. reading, watching television) above the Sedentary Activity option.** You now have 16 choices to make, with each choice representing a decision to press buttons to get access to 100 grams of your most preferred snack food or 20-minutes of your most preferred sedentary activity. For example, Choice # 3 involves a choice to press a button 60 times to earn 100 grams of snack food or pressing a button only 20 times to earn 20-minutes of your most preferred Sedentary activity. For each of the choices, PLEASE MARK AN "X" IN THE APPROPRIATE PLACE AS IF YOU COULD REALLY EARN YOUR FOOD/ACTIVITY CHOICES.

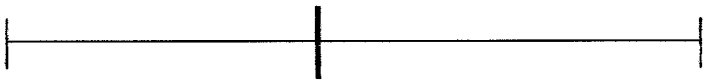
Choice #	**X**	**Preferred Snack Food:**	**Button Presses**		**Preferred Sedentary Activity:**	**Button Presses**	**X**
1		Snack food (100 g)	20	**OR**	Sedentary Activity (20 min)	20	
2		Snack food (100 g)	40	**OR**	Sedentary Activity (20 min)	20	
3		Snack food (100 g)	60	**OR**	Sedentary Activity (20 min)	20	
4		Snack food (100 g)	80	**OR**	Sedentary Activity (20 min)	20	
5		Snack food (100 g)	100	**OR**	Sedentary Activity (20 min)	20	
6		Snack food (100 g)	120	**OR**	Sedentary Activity (20 min)	20	
7		Snack food (100 g)	140	**OR**	Sedentary Activity (20 min)	20	
8		Snack food (100 g)	160	**OR**	Sedentary Activity (20 min)	20	
9		Snack food (100 g)	180	**OR**	Sedentary Activity (20 min)	20	
20		Snack food (100 g)	200	**OR**	Sedentary Activity (20 min)	20	
11		Snack food (100 g)	220	**OR**	Sedentary Activity (20 min)	20	
12		Snack food (100 g)	240	**OR**	Sedentary Activity (20 min)	20	
13		Snack food (100 g)	260	**OR**	Sedentary Activity (20 min)	20	
14		Snack food (100 g)	280	**OR**	Sedentary Activity (20 min)	20	
15		Snack food (100 g)	300	**OR**	Sedentary Activity (20 min)	20	
16		Snack food (100 g)	320	**OR**	Sedentary Activity (20 min)	20	

Pleasantness Visual Analog Scales of Selected Foods

After looking at the example, please draw a short line across the long line to show how much you like or don't like the following foods.

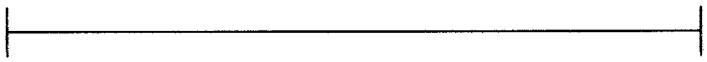
Example:

Water



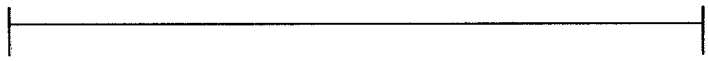
Don't like at all ***Like very much***

Regular Chips



Don't like at all Like very much

Fruit Yogurt



Don't like at all Like very much

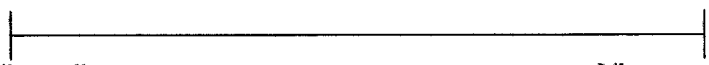
Chocolate Brownies

Don't like at all Like very much

Chocolate Chip Cookies

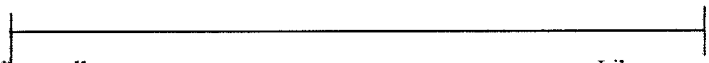
Don't like at all Like very much

White Bread



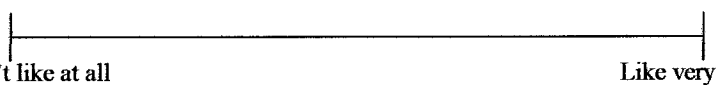
Don't like at all Like very much

Caesar Salad



Don't like at all Like very much

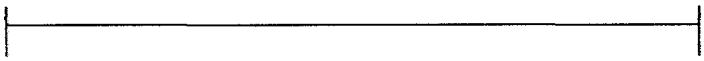
Cottage Cheese



Don't like at all Like very much

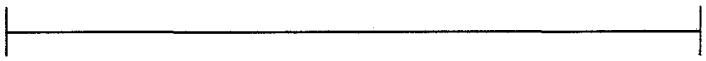
Appendix 9 - Relative Reward (Snack vs Activity)

Brie Cheese



Don't like at all Like very much

Snack Food not Mentioned_____



Don't like at all Like very much

Pleasantness Visual Analog Scales of Selected Activities

After looking at the example, please draw a short line across the long line to show how much vou like or don't like the following activities.

Example:

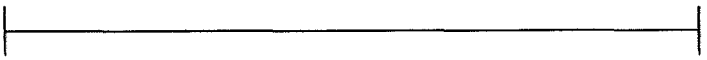
Reading

Don't like at all ***Like very much***

Watching Television

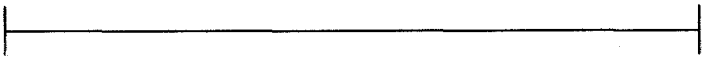
Don't like at all Like very much

Reading



Don't like at all Like very much

Computer Games



Don't like at all Like very much

Listening to Music

Don't like at all Like very much

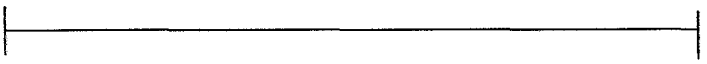
Hand-held Computer games

Don't like at all Like very much

Talking on Telephone

Don't like at all Like very much

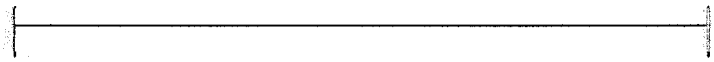
Shopping



Don't like at all Like very much

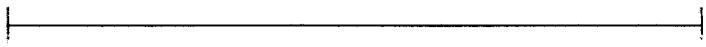
Appendix 9 - Relative Reward (Snack vs Activity)

Board Games/Cards



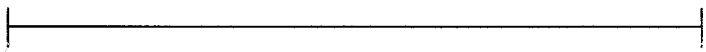
Don't like at all Like very much

Theatre Movies



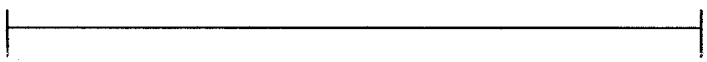
Don't like at all Like very much

Arts & Crafts



Don't like at all Like very much

Sedentary Activity not Mentioned: _____



Don't like at all Like very much

BDI-II

Beck Depression Inventory; Beck, A. T., Steer, R. A. & Brown, G. K., 1996.

1. Sadness

0 I do not feel sad.

1 I feel sad much of the time.

2 I am sad all of the time.

3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.

1 I feel more discouraged about my future than I used to be.

2 I do not expect things to work out for me.

3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.

1 I have failed more than I should have.

2 As I look back, I see a lot of failures.

3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy

1 I don't enjoy things as much as I used to.

2 I get very little pleasure from the things I used to enjoy.

3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.

1 I feel guilty over many things I have done or should have done.

2 I feel quite guilty most of the time.

3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.

1 I feel I may be punished.

2 I expect to be punished.

3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.

1 I have lost confidence in myself.

2 I am disappointed in myself.

3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.

1 I am more critical of myself than I used to be.

2 I criticize myself for all of my faults.

3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.

1 I have thoughts of killing myself, but I would not carry them out.

2 I would like to kill myself.

3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.

1 I cry more than I used to.

2 I cry over every little thing.

3 I feel like crying, but I can't.

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to be.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much work.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Patterns

0 I have not experienced any changes in my sleeping pattern.

1 I sleep somewhat more than usual.

2 I sleep somewhat less than usual.

3 I sleep a lot more than usual.

4 I sleep a lot less than usual.

5 I sleep most of the day.

6 I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any changes in my appetite.

1 My appetite is somewhat less than usual.

2 My appetite is somewhat greater than usual.

3 My appetite is much less than usual.

4 My appetite is much greater than usual.

5 I have no appetite at all.

6 I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

MPH Study
24HR Dietary recall

Objective: To obtain a better understanding of your personal dietary habits, in order to provide an accurate nutritional assessment regarding the quality of your diet.

Instructions:

- We ask that you complete **your entire** food intake **(including water and nutritional supplements (i.e., vitamins & minerals)** for seven full days in the tables provided on the following pages.

- It is very important that you be as specific as possible in your descriptions of food intake and when recording precise quantities of measurement **(ml, tablespoons, teaspoons, grams, ounces, etc...)**. To aid in this process, questions to trigger your memory have been placed on the right hand side of the page for each meal and snack period.

The more precise your dietary recall, the more we will be able to provide an accurate assessment that will best fit your needs.

If you have any questions, please do not hesitate to ask

Claudio Lorello : clore018@uottawa.ca

DAY 1 Week-end? ☐ Yes ☐ No

MEAL	TIME	PLACE	NAME AND DESCRIPTION OF FOOD	QUANTITY	*DID YOU REMEMBER THE FOLLOWING?*
Breakfast					• **Juice?** *Real juice, sugar/no-sugar, dry mix, cocktail* • **Bread?** *white, whole-wheat, cereal* • **Garniture? *Quantity of:*** *peanut butter, margarine, jam, cheese* • **Muffin? 1) Size:** *small,, medium, large* **2) Type:** *homemade or store bought* **3) Contents:** *fruits, chocolate chips, raisins, nuts etc…* • **Crepes?** *Diameter in centimeters or inches* • **Eggs?** *Fried, boiled, poached* • **mg % milk fat ?** *Milk, cheese, yogurt, Cream* • **Sugar, cream and added syrup?** *In coffee, cereals, on crepes,...* • **Added fat to cooking ?** *Quantity of butter, Margarine, or oil* • **Cereal bars?** *Nuts, peanuts, marshmallows, fruits, chocolates,...*
Snack before lunch					

DAY 1 CONTINUED

MEAL	TIME	PLACE	NAME AND DESCRIPTION OF FOOD	QUANTITY	***DID YOU REMEMBER THE FOLLOWING ?***
Lunch					• **Soup?** *homemade, condensed, packaged* • **Salad?** ***1) Contents*** : *quantity of vegetables, cheese, croutons, grains and nuts,...* **2) Vinaigrette** : **a) type** : *cream, Italian,...* **b) quantity** : *ml, tsp, tbsp, gram* • **Sandwich? 1) Pain:** *white, whole-wheat, cereals* **2) Condiments:** *quantity of mayonnaise, butter, mustard,...* • **Meat? 1) Cooked:** *oven, microwave, grill,...* • **Skin?** *Did you eat the skin?* • **Added fat by cooking?** *Quantity of butter, margarine or oil* • **Dessert? 1) Size** : *in centimeters, in inches* **2) Garniture** : *icing, cream, ice cream, syrup, sauce...* • **Cereal bars?** *Nuts, peanuts, marshmallows, fruits, chocolate,...* • **Snacks? 1) Type:** *chips, Pretzels, Salted crackers,...* **2) Quantity** : *in grams or in units*
Afternoon snack					

DAY I (continued)

MEAL	TIME	PLACE	NAME AND DESCRIPTION OF FOOD	QUANTITY	*DID YOU REMEMBER THE FOLLOWING?*
Supper					• **Soup?** *Homemade, condensed, packaged* • **Salad? 1) Contents:** *quantity of vegetables, cheese, croutons, grains and nuts,...* **2) Vinaigrette: a) type** : *cream, Italian,...* **b) Quantity**: *ml, tsp, tbsp, gram* • **Sandwich? 1) Bread:** *white, whole-wheat, multigrain* **2) Condiments:** *quantity of mayonnaise, butter, Mustard,...* • **Meat? 1) Cooked:** *oven, microwave, Frying pan, grill...* • **Skin?** *Did you eat the skin?* • **Added fat from cooking?** *Quantity of butter, margarine or oil* • **Dessert? 1) Size** : *in centimeters, in inches or in fractions* **2) Garniture** : *icing, cream, ice cream, syrup, sauce...* • **Cereal Bars?** *nuts, peanuts, marshmallows, fruits, chocolate,...* • **Snacks? 1) Type** : *chips, pretzels, Salted crackers,...* **2) Quantity** : in grams *or in units*
Evening Snack					

ACTIVITY CATEGORIES – PHYSICAL ACTIVITY RECORD

Activity categories	Activities examples for each category			Approximate energy expenditure (Kcal/kg/15min)
1	**Lying :** -Sleeping	-Resting in bed		0.25
2	**Sitting :** -Listening in class -Listening to radio or watching television -Writing or computer typing	-Taking a bath -Eating -Reading	-Riding in car (passenger) -Driving a car	0.41
3	**Very light activities :** -Taking a shower -Shaving, Combing hair, applying makeup -Fixing bed -Getting dressed	-Cooking -Ironing clothes -Washing dishes -Dusting	-Driving a truck or a bus -Driving a motorcycle -Pool, croquet -Supervising machinery or equipment	0.58
4	**Light activities:** -Taking a leisurely walk -Playing music -Bowling	-Throwing and catching (ball, Frisbee) -Sowing -Nurse		0.71
5	**Light manual work :** -Moderate walking (going to school, to work, shopping, etc.) -Chores (washing windows, sweeping, etc.) -Archery	-Ski-Dooing -Woodworking, painter -Baker	-Electrician, plumber -Gardening, cutting the grass	0.93
6	**Light leisure or sporting activities (recreational):** -Sailing -Kayak* -Golf -Baseball (except pitcher) -Bike ride*	-Aquatic aerobics (Aquafit) -Ping-pong -Horseback riding* -Weight training -Dancing (couple, in line)	-Volleyball*	1.1
7	**Moderate manual work, leisure or sporting activities :** -Labourer (Construction, mine) -Shovelling snow -Loading bags or boxes -Plantation or forestry work* (mechanical sawing and handling wood)		-Skiing -Baseball (pitcher) -Badminton* -Tennis*	1.53
8	-Removing branches from trees -Hand sawing -Briskly walking* -Cycling (rapid biking)* -Skating (ice, rollerblade)*	-Swimming* -Canoeing* -Snowshoeing* -Jogging (light running)	-Trekking -Judo, karate, boxing* -Step Aerobics*	2.0
9	**Very intense manual work, leisure or sporting activities (competitive):** -Cutting trees (working with an axe)* -Climbing* -Soccer* -Handball* -Squash* -Hockey *	-Basketball* -Racquetball* -Cross-country skiing* -Running	-Football, Ultimate Frisbee*	2.4

3-Day Physical Activity Record

DAY 1

Surname : _____

Name : _____

_____

_____

INSTRUCTIONS

Each box located to the right of the time column corresponds to 15 minutes. Hence, one hour is divided into 4, 15-minute periods. Based on the activities listed at the end of this document, write the code that corresponds to the activity you performed during every 15-minute period. If an activity (I.e. sleeping) is performed for an extended length of time, you can draw a continuous horizontal line through the boxes that follow for the duration of the activity. For example, in the adjacent table we notice that the person remained sitting from 12:00AM to 12:45AM, and that she slept from 12:45AM to 9:00AM.

Time	Minutes			
	0-15	16-30	31-45	46-60
0 A.M.				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12 P.M.				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				

Day 2

Surname : _____

Name : _____

Weight : _____

ID _____

INSTRUCTIONS

Each box located to the right of the time column corresponds to 15 minutes. Hence, one hour is divided into 4, 15-minute periods. Based on the activities listed at the end of this document, write the code that corresponds to the activity you performed during every 15-minute period. If an activity (I.e. sleeping) is performed for an extended length of time, you can draw a continuous horizontal line through the boxes that follow for the duration of the activity. For example, in the adjacent table we notice that the person remained sitting from 12:00AM to 12:45AM, and that she slept from 12:45AM to 9:00AM.

Time	Minutes			
	0-15	16-30	31-45	46-60
0 A.M.				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12 P.M.				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				

DAY 3

Surname : _____

Name : _____

Weight : _____

ID _____

INSTRUCTIONS

Each box located to the right of the time column corresponds to 15 minutes. Hence, one hour is divided into 4, 15-minute periods. Based on the activities listed at the end of this document, write the code that corresponds to the activity you performed during every 15-minute period. If an activity (I.e. sleeping) is performed for an extended length of time, you can draw a continuous horizontal line through the boxes that follow for the duration of the activity. For example, in the adjacent table we notice that the person remained sitting from 12:00AM to 12:45AM, and that she slept from 12:45AM to 9:00AM.

Time	Minutes			
	0-15	16-30	31-45	46-60
0 A.M.				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12 P.M.				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				

Present the buffet to the participant and invite them to voluntarily eat until they have reached satiety without overeating. The participant must eat in a calm and quiet environment without any source of distraction during a period of 30 minutes.

MID-DAY BUFFET					
Food item	**# Nutrifiq**	**Wt. wanted (gr)**	**Wt. Before (gr)**	**Wt. After (gr)**	**Wt. consumed (gr)**
1 - Sliced turkey breast*	50220	130			
2 - Liver pâté***	70055	70			
3 - Double cream Brie cheese***	10006	100			
4 - Cheddar cheese**	10027	100			
5 - Cottage cheese*	13015	100			
6 - Butter***	13001	40			
7 - Mayonnaise***	45018	60			
8 - Italian salad dressing**	45114	60			
9 - Caesar salad dressing**	45017	60			
10 - Mustard*	66008	30			
11 - Ketchup**	113935	40			
12 - White bread**	180416	150			
13 - Whole wheat bread*	183075	150			
14 - Soda crackers*	180228	100			
15 - Leaf of lettuce*	110251	60			
16 - Slice of tomato*	113529	100			
17 - Cut baby carrots*	113124	150			
18 - Quarter slice of red apple*	93003	100			
19 - Chocolate chip cookie ***	180158	100			
20 - Chocolate brownies ***	180096	200			
21- Fruit yogurt*	15120	250			
22- Skim milk (0%)*	12085	1000			
23 - Partially skimmed milk (2%)**	10079	1000			
24 - Homogenized milk (3.25%)***					
25 - Orange juice*	93207	1000			
26 - Coca-Cola***	140400	355			
27 - 7-Up***	140145	355			
28 - Regular chips***	196411	60			
29 - Water*	140429	1000			

Has the participant taken 30min to eat? Yes ☐ No ☐

If not, why:_____

* Low in fat and/or sugar (12 items); ** Moderate in fat and/or sugar (6 items); *** High in fat and/or sugar (11 items).

Approximate weight of standardized breakfast food items served to males and females.

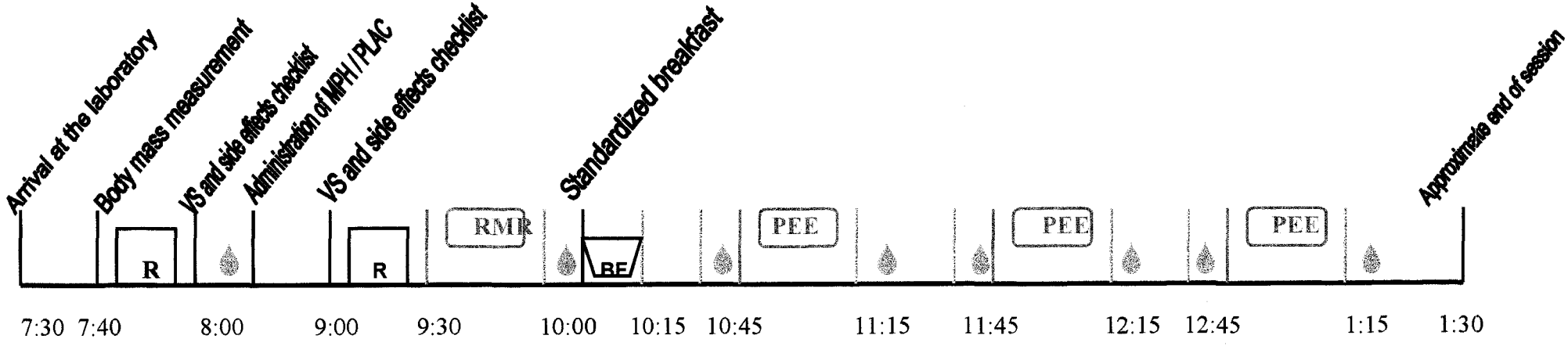
2% milk → 250ml
Orange juice → 114ml
Butter → 8.0g
Raspberry jam → 13.0g
Smooth peanut butter → 18.0g
Cheddar cheese (32% M.F, 39% moisture) → 21.0g
Whole wheat toast → 58.4g

Approximate macronutrient content

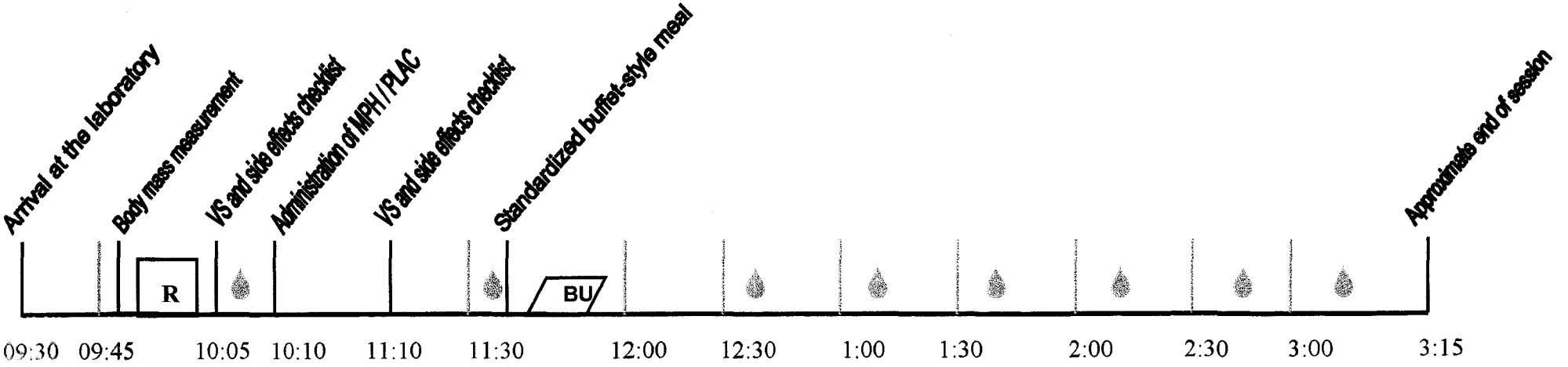
Energy: 638 kcal
Carbohydrates: 71 g (43%)
Fat: 30 g (42%)
Protein: 24 g (15%)

APPENDIX B – STUDY TIMELINE

EE Measurement Session



EI Measurement Session



LEGEND:

———	Visual Analogue Scale	**R**	Rest in the supine position
———	Energy Expenditure Measurement	**BU**	Buffet
🩸	Blood Sample	**BF**	Breakfast

APPENDIX C – CONSENT FORMS

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 Methylphenidate on Energy Balance

Graduate Student:

Claudio Lorello, B.Sc

Investigators/Research Supervisors :

Éric Doucet, Ph.D

Gary Goldfield, Ph.D

School of Human Kinetics

Faculty of Health Sciences, University of Ottawa

CHEO Research Institute

1. INVITATION TO PARTICIPATE

I, _____, agree to participate in the research conducted by Claudio Lorello, a graduate student supervised by Drs Éric Doucet and Gary Goldfield of the School of Human Kinetics at the University of Ottawa and the CHEO research institute, respectively.

2. PURPOSE OF THE RESEARCH

The purpose of this research is to examine the effects of methylphenidate (MPH) "Ritalin" on energy balance. The Canadian Institutes of Health Research and the University of Ottawa Research Fund support this study.

3. BACKGROUND

During this study, data will be collected pertaining to changes in energy input and output. From this experiment, the researchers anticipate further understanding of the influences of dopamine transport on key components of energy balance. This requires investigating mechanisms that could influence appetite, but also examining the effects of methylphenidate on energy expenditure.

4. DESCRIPTION OF THE PROPOSAL

Initial contact and pre-screening visit I (approximately 60 minutes)

During the initial screening visit, I will be required to come to the laboratory so that the consent form and any other questionnaires I may have to complete can be explained to me in detail. I can then bring the consent form home, along with any accompanying questionnaires, so that further reading and understanding of the protocol is possible.

Pre-screening visit II (approximately 4 hours)

After carefully reading the consent form and inquiring about any questions or concerns I may have, I will sign the consent form. I will then take part in a more thorough screening in the laboratory during which some preliminary measurements will be made. A complete demographic, medical, psychological and nutritional history will be completed by a physician through clinical interview, physical (medical) examination, and questionnaires in order to fully assess inclusion criteria. A blood sample either will be taken by a qualified registered nurse in order to test for possible differences in the dopamine transporter gene. With this information, the researchers wish to divide carriers and non-carriers of the dopamine transporter gene mutation into an appropriate group. There are no known dangers associated with this genetic mutation. The researchers are simply interested in further understanding the mutation and learning if it has any implications in obesity. I will then be asked to rate all of the foods that will be used in the

standardized breakfast food and unrestricted buffet-eating portion of the experiment. I will also be asked to rate my like/dislike for all test foods using a scale with a ranking of 1 indicating "I do not like at all" through 5 indicating "I like a lot". Vital signs (blood pressure and pulse) will be completed by the physician before administration of the experimental dose and 1-hour following the administration of the experimental dose. At this time, and under the supervision of a physician, I will be given a single dose (0.5mg/kg) of methylphenidate and will be monitored for the next 60 minutes. Afterwards, a drug effects/side effects checklist will be completed. If I report or show severe side effects (e.g., extreme nervousness) I will be excluded from the study. Subjective side effects will be measured for 19 potential side effects (e.g., headache, nausea, nervousness) by having me rate the intensity of the symptoms I feel using the following scale: 1=none, 2=mild, 3=moderate and 4=severe.

Experimental sessions 1 to 4:
In addition to the screening visits, I will participate in four experimental sessions during which many measurements will be made. Two of the four experimental sessions will involve measurements of energy expenditure and will be performed between 7h30 and 13h15 (approximately five hours), and the two experimental sessions involving measurements of energy intake will be performed between 11h00 and 16h35 (approximately five hours). The four experimental conditions will be randomized and performed on four separate days in no particular order. There will be at least a one-week period between each experimental session. A detailed description of the screening visit as well as the four experimental visits is presented in the following sections.

5. DESCRIPTION OF MEASUREMENTS

Initial contact

9h00- Initial contact An initial brief contact will be required to explain the study. The research coordinator will explain the protocol and any relevant questionnaires and will suggest that I bring the consent form and any other questionnaires home for further reading and understanding of the protocol.
9h30- Estimated end of initial contact visit

Pre-screening visit

8h30- Arrival at the laboratory
8h30-9h30- Further explanation of the procedures I will ask any questions or comments I may have pertaining to any of the aspects of the study. If my questions are answered satisfactorily, I will then agree and give informed consent to participate in the study.
9h30- Blood sample A blood sample will be taken to consider whether I am a carrier or non-carrier of the dopamine-transport mutation as previously mentioned. This analysis will take approximately one week.
10h00- Anthropometric measurements (height, weight, waist circumference, body composition) Body weight, height, and composition will be assessed. A medical exam/questionnaire will also be administered by the physician. A method called dual-energy x-ray absorptiometry (DEXA) will be used to measure percent body fat and percent lean body mass. I will have to lie on an examination table, fully clothed, while a low-intensity x-ray will scan my entire body. The measurement takes approximately 20 minutes to complete. The only risk is a minimal x-ray exposure of less than 0.5 millirem. This is equivalent to less than $1/20^{th}$ of a day's exposure to sunlight. My hip and waist circumferences will also be measured.
11h00- Administration of MPH The MPH will be administered orally by a physician and vital signs will be examined for the next 60 minutes. This is to ensure that I do not react adversely to MPH. I will then be randomized in an appropriate group.
12h00- Estimated end of pre-screening visit

N.B. After this screening visit, I will be notified in approximately 2 weeks of my inclusion or exclusion in the study. If I am excluded, the researchers will offer me a free dietary and nutritional consultation visit at a convenient time.

Overview of the experimental sessions

If my characteristics correspond to all the necessary inclusion criteria and that I accept to participate in this study, I will be subjected to the following conditions:

A. Energy expenditure measurement days

7h30- Arrival at the laboratory

7h40- Vital signs and body mass evaluation: Involves measurement of blood pressure and heart rate, which will be taken by a nurse. Height, body weight, and waist circumference will be assessed by a research assistant.

8h00- Insertion of a catheter and administration of short-acting methylphenidate (MPH) or placebo These two (2) sessions will begin with a registered nurse inserting a catheter in the antecubital vein of my non-dominant arm and administration of short-acting MPH (0.5 mg/kg) or placebo immediately followed by blood sampling. A second blood sample will be drawn after the ingestion of the standardized breakfast as well as one every 30 minutes thereafter. Thus, eight (8) blood samples will be drawn during the energy expenditure sessions, which is equivalent to eight (8) tablespoons (130 ml) of blood. The catheter will be removed immediately after the last energy expenditure measurement. Following the administration of the drug, a drug effect questionnaire and leisure time activity (e.g., reading, school or class work) for 60 minutes will ensue.

9h00- Assessment of vital signs

9h10- Twenty-minute rest period in the supine position

9h30- Measurement of resting metabolic rate After a 20 minute resting period in the supine position (laying down), a measurement of resting energy expenditure will be performed. A Plexiglas hood will be placed over my 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. With this measurement, the researchers will be able to determine the amount of oxygen that is consumed and derive energy expenditure. This test requires me to lie quietly and relaxed in bed for about 30 minutes. There are no risks associated with this procedure.

10h00- Standardized breakfast For every experimental session, I will be required to consume a standardized breakfast consisting of 2 slices of whole wheat toast, 1 tablespoon of smooth peanut butter, 1 tablespoon of jam, 1 cup of orange juice, 1 serving of mozzarella cheese (50g) 31% m.f., 1 teaspoon of butter, and 1 cup of 2% milk. Upon completion of the standardized breakfast, the thermic effect of food will be evaluated by means of indirect calorimetry (parallel to the method required to measure resting metabolic rate, as mentioned above). In addition, re-evaluation of hunger using VAS will be conducted every 30 minutes for three hours.

10h15- Re-evaluation of vital signs

10h30-13h00- Energy expenditure measurement every 30 minutes for 2.5 hours (10h30-11h00, 11h30-12h00, 12h30-13h00)

13h15- Approximated end of experimental session

NB. A snack will be offered to participants before they leave the laboratory.

B. Energy intake measurement days

11h00- Arrival at the laboratory

I will arrive at the laboratory after having consumed the standardized breakfast around 8h00 at home. This will be confirmed by a morning food recall. In addition, a 24-hour food recall will be given to ensure I avoided consumption of the buffet test foods in the previous day, as instructed. I will also be asked to complete a 3-day physical activity record to determine the amount of physical activity completed 3 days prior to the testing session. If I do not adhere to these pre-experimental conditions, the session will be rescheduled to a later date. In addition, because upper respiratory ailments limit taste and smell sensations and may interfere with appetite, participants with upper respiratory conditions will also be rescheduled.

11h15- Assessment of body mass and appetite Using VASs to assess appetite and a medical scale to measure body mass.

11h45- Insertion of catheter These two (2) sessions will also require a registered nurse to insert a catheter in the antecubital vein of my non-dominant arm immediately followed by blood sampling. A second blood sample will be drawn before and a third after the ingestion of the standardized buffet-style meal as well as one every 30

minutes thereafter. Thus, eight (8) blood samples will be drawn during this energy intake session, which is equivalent to eight (8) tablespoons (130 ml) of blood. The catheter will be removed immediately after the last blood sample.

11h45- Administration of methylphenidate or placebo Followed by 60 minutes of leisure time activities and evaluation of side effects and vital signs.

12h45- Standardized buffet-style meal

13h30-16h30- Satiation assessment VASs will be used in order to re-evaluate appetite every 30 minutes for three hours following completion of the meal.

16h30- End of experimental session

** At the end of each test session, I will be asked to identify which substance I think I received (drug or placebo) and rate how much I liked its effects.

6. FORESEEABLE RISKS/DISCOMFORTS

The risks associated to this study are low. The proposed measurements such as DEXA, energy expenditure, anthropometrical assessments and measurements to determine the body's percentage of fat, pose very little risk to my health. Blood sampling also poses minor health risks and will be performed by a qualified nurse. Small bruising may develop where the catheter is inserted and would only persist for a few days. Because the catheter will remain inserted for a few hours, I could feel some degree of discomfort. It is important to note that the risks of infection or phlebitis (inflammation of a vein) are low under sterile laboratory conditions, but nonetheless remain a possibility. It is important to note that a physician will administer the test dose of methylphenidate during the pre-screening visit and an experienced registered nurse will oversee and administer either the methylphenidate or the placebo during all experimental sessions. Those who report or show severe side effects (e.g., extreme nervousness), systolic blood pressure exceeding baseline reading by 20 mm Hg, diastolic blood pressure exceeding the baseline reading by 10 mm Hg, BP>160/100, or resting pulse increased by >20 beats/minute from the baseline reading will be excluded from the study. Subjective side effects will be measured for 19 potential side effects (e.g., headache, nausea, nervousness) by having participants rate the intensity of their symptoms using the following scale: 1=none, 2=mild, 3=moderate and 4=severe. Measurements of food intake present no risk.

7. BENEFITS

I will gather information regarding my body composition and other health markers such as waist circumference and body mass index, for example. Finally, a nutritional and physical activity-counselling visit will be offered to all participants of this study.

8. MONETARY COMPENSATION

The researcher will compensate me by offering $125.00, which will be paid in increments of $25.00 as more amply described hereinafter. This amount compensates for any possible inconveniences the participation in this study may have caused, such as transportation costs or loss of wages. I shall be compensated by increments of $25.00 at the beginning of each session (i.e. screening and 4 Experimental sessions). If I choose not to participate in one or more of the sessions, then I will not receive any compensation for the missed sessions.

9. CONFIDENTIALITY AND ANONYMITY

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

- The names of participants will not appear on any reports. A number code will be used to identify participants on all research documents.
- If there is secondary use of data, only the code of participants will appear on 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.
- The data collected will be kept in the filing room of our laboratory at Montfort. The data will be secured in a locked cabinet in the data storage room which is also locked. Only the researchers, study coordinator, research assistant and the nurse will have

APPENDIX D – ETHICAL APPROVALS

Appendix 17 – Ethics Approval

May 20, 2004

Dr. Eric Doucet
School of Human Kinetics
University of Ottawa
125 Université
Room 353
Ottawa, ON K1N 6N5

Dr. Gary Godlfield
Children's Hospital of Eastern Ontario
Research Institute
401 Smyth Road
Ottawa, ON K1H 8L1

Object: **Effect of Methylphenidate on Energy Balance in Obese Males (file H 11-03-12)**

Dear Researchers,

You will find enclosed the Health Sciences and Science REB ethical clearance for the abovementioned research study.

Please note that it is the responsibility of the Researchers to:

a) Inform the ethics office of any changes in the research project; and
b) Fill out an annual status report to be sent to the Protocol Officer for Ethics in Research. Such report can be found on the ethics web site at:
http://www.uottawa.ca/services/research/rge/rebs/download/rapport_annuel_projets_anglais.doc

A copy of this approval will be sent to Research Services.

If you have any questions, you may contact me at extension 5387.

Sincerely yours,

Rita D'Alessandro
Protocol Officer for Ethics in Research
For Dr. Hugh French, Chair of the Health Sciences and Science REB
cc. Claudio Lorello (via email)

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATE OF ETHICAL APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board has examined the application for ethical approval for the research project entitled **Effect of Methylphenidate on Energy Balance in Obese Males (file H 11-03-12)** submitted by Dr. Eric Doucet and Dr. Gary Goldfield. The Board found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid for one year from the date indicated below.

May 20, 2004
Date

Rita D'Alessandro
Protocol Officer for Ethics in Research
For Dr. Hugh French, Chair of the
Health Sciences and Science REB

APPENDIX E – RANDOMISATION SCHEME

Appendix 19 – Randomisation Scheme