UNIVERSITY OF TORONTO

Department of Nutritional Sciences

Mid-Term Examination 2011

November 10, 2011

Advanced Nutrition
NFS 484H1 F/ 1484H1 F

Duration – 2 hours

General Instructions:

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

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

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

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

Introduction

It is widely recognized that environmental changes during fetal development play an important role in determining susceptibility to chronic diseases in later life. Several theoretical models have been proposed to explain this process. The developmental origins of health and disease hypothesis describes that a particular stimulus during critical periods of development induces permanent changes in the fetal structure and metabolism, which may increase the risk of developing diseases in adulthood. In particular, many epidemiological studies have shown that prenatal restriction of early growth (restricting nutrients during pregnancy resulting in poor intrauterine environment) is linked to adult-onset insulin resistance, visceral adiposity and type 2 diabetes in the offspring.

To date, research efforts have focused on events prior to birth as a determinant of health outcome in later life. However, the mechanism by which poor intrauterine growth predisposes the offspring to diseases in adulthood is still unknown. An area of growing interest is in examining the interaction between prenatal growth restriction and postnatal factors (such as diet and exercise) in modulating the risk of disease in later life.

STUDY 1 (Value 13/50)

Study Design

A prospective cohort study was conducted to describe the association between low birth weight (LBW) and glucose regulation and obesity later in life. 163 male children who had been born with LBW and 169 with normal birth weight (NBW; control) were followed for 18 years. Subjects were matched for age and were considered healthy. A baseline capillary blood sample was taken by finger prick to measure glucose and insulin. Percent body fat was determined using body composition analyses by dual-emission x-ray absorptiometry (DEXA) scans. Fasting blood glucose and insulin levels, and percent body fat were measured in all subjects at 2 years and at 18 years of age. Blood glucose and insulin levels and percent body fat were not different between those born with LBW compared to those born with NBW at 2 years of age. Figure 1 shows metabolic profiles at 18 years of age in these male young adults.

Questions

1. Describe the association between birth weight and metabolic phenotype (Figure 1). (Value 4/50)

2. Using all the information given so far, discuss the importance of finding metabolic differences at 18 years of age but not at 2 years in individuals with LBW compared to those with NBW and their risk of developing obesity and type 2 diabetes. What additional measurements would you add in order to understand why there are differences at 18 years of age? (Value 9/50)

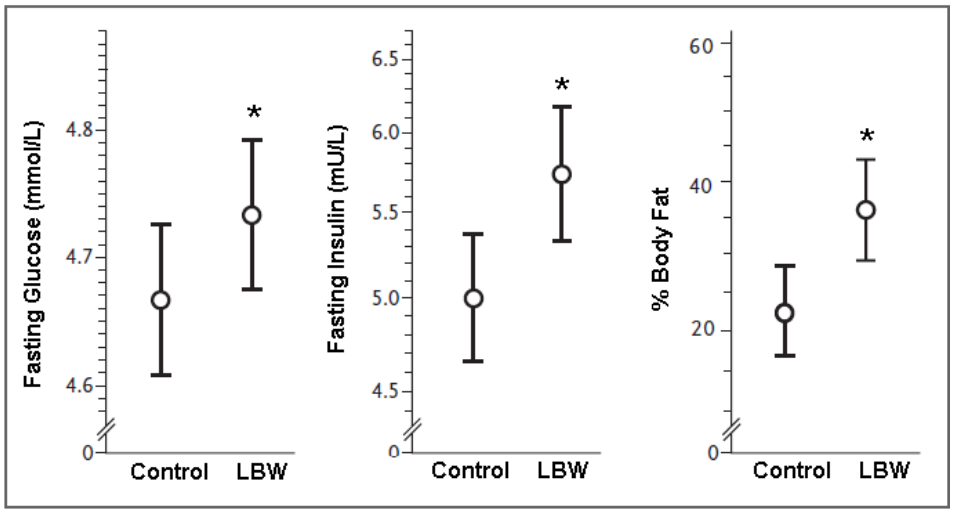

Figure 1. Fasting blood glucose and insulin concentrations and percent body fat measured at 18 years of age in young adults born with low birth weight (LBW) compared to those born with normal birth weight (NBW; control group).
* $P < 0.05$ compared to the control

STUDY 2 (Value 37/50)

Several environmental factors affect birth weight and have potential consequences for development of chronic diseases. Maternal smoking and obesity have been found to be associated with LBW in the offspring. However, the mechanistic basis of the relationship between LBW and subsequent development of obesity and type 2 diabetes is unknown. Intrauterine growth restriction (IUGR) refers to the poor growth of a baby during pregnancy leading to LBW. Rodent models of IUGR are widely used to elucidate the mechanism by which LBW offspring become predisposed to a higher risk of disease at the molecular level. Furthermore, many studies are interested in examining the role of postnatal factors in modulating the effect of early life influences.

One postnatal factor under investigation is exercise. Obesity manifests from an imbalance between food consumption and energy expenditure. Exercise is known to confer many benefits toward prevention of obesity as it is associated with lower fat deposition and improvement in insulin sensitivity. Whether the introduction of exercise training can modulate the risk of obesity and type 2 diabetes in IUGR offspring is unknown.

Study Design

The aim of the study was to examine the role of exercise in IUGR and its alteration of metabolic pathways. Pregnant rats received standard low-fat chow either *ad libitum* (control offspring) or 50% of *ad libitum* intake (IUGR offspring) throughout pregnancy and lactation. One half of the IUGR and control offspring underwent daily supervised sub-maximal exercise training and another half of the IUGR and control offspring were maintained under sedentary conditions for 4 months. The exercise comprised of running on a motorized treadmill for 15 min/day, spanning 5 days/week.

At 4 months post-weaning, a 5 g glucose load per kilogram of body weight was fed, via gavage (food being placed directly into the stomach), to all rats after 9 hours of overnight fast and blood insulin levels were measured at 0, 15, 30, 45 and 60 min post gavage. The total area under the curve (AUC) was calculated to examine the overall insulin response throughout the observation period. At 4 months post-weaning, plasma free fatty acid (FFA) and fatty acid synthase (FAS) concentrations, and glucose transporter 4 (GLUT4) protein density were measured in the IUGR and control offspring.

Questions

3. Describe the effect of exercise on plasma insulin AUC, and levels of FFA, FAS protein and GLUT4 in the control and IUGR offspring (Figure 2 and Table 1). (Value 6/50)

4. Based on the Study 2 background and results, how would IUGR impact glucose disposal after a glucose load and the risk of type 2 diabetes? Predict the blood glucose response to a glucose load in the IUGR and control offspring under exercise compared to sedentary conditions. {We are looking for the relative differences between groups – IUGR sedentary, IUGR exercise, control sedentary and control exercise – and not absolute responses in the last part of this question.} (Value 8/50)

5. Using all the information given, explain the role of IUGR in fat handling and development of obesity in the offspring, and how exercise modifies these effects. (Value 10/50)

6. Based on all the information given, how would IUGR, relative to control, affect metabolic measurements if the rat offspring were on a high-fat obesogenic diet rather than a healthy low-fat diet? Would the effect of postnatal exercise differ in IUGR and control groups if they were consuming a high-fat diet (i.e. compared to the responses reported for a low-fat diet)? (Value 6/50)

7. Using all the information presented, what dietary and lifestyle recommendations would you give to children born with LBW to prevent development of obesity and type 2 diabetes in subsequent generations? (Value 7/50)

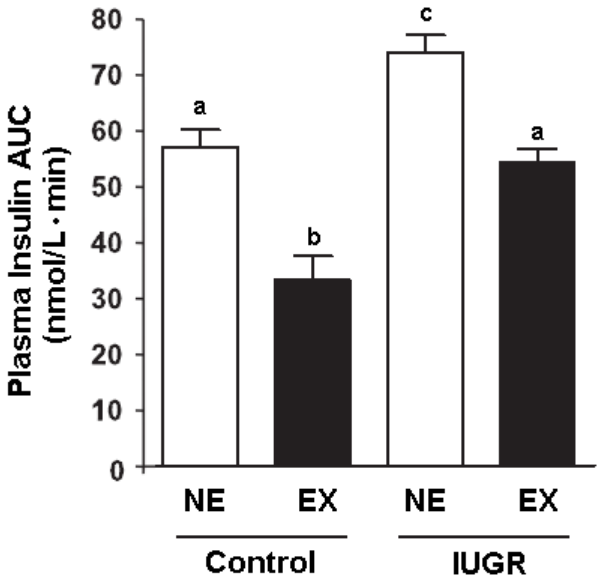

Figure 2. Comparison between exercise (EX) and no exercise (NE) on plasma insulin AUC during oral glucose tolerance test in the intrauterine growth restricted (IUGR) and control offspring.
[abc] Different superscripts are significantly different from each other at $P < 0.05$

Group		FFA (mmol/L)	FAS Protein (nmol/mL)	GLUT4 Protein (membrane density)
Control	NE	0.57 ± 0.09[a]	786 ± 84[a]	4980 ± 561[a]
	EX	0.37 ± 0.09[b]	819 ± 98[a]	6038 ± 409[b]
IUGR	NE	0.83 ± 0.06[c]	1273 ± 90[b]	1866 ± 528[c]
	EX	0.47 ± 0.07[a]	1179 ± 99[b]	4682 ± 637[a]

Table 1. Comparison between exercise (EX) and no exercise (NE) on plasma free fatty acid (FFA) and fatty acid synthase (FAS) concentrations, and glucose transporter 4 (GLUT4) protein density in the intrauterine growth restricted (IUGR) and control offspring.
[abc] Different superscripts are significantly different from each other, within each column, at $P < 0.05$