THE EARLY ORIGINS OF OBESITY: THE IMPORTANCE OF PRENATAL VS POSTNATAL ENVIRONMENT

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DECLARATION

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Mini Aprem Vithayathil
BSc. (Honours, First Class)

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COMMONLY USED ABBREVIATIONS

A B C

AA	arachidonic acid
ACC	acetyl-CoA Carboxylase
ACS	acyl-CoA synthetase
ACOD	acyl-CoA oxidase
ad libitum	to any desired extent
ADD-1	adipocyte determination and differentiation-1
ALA	alpha-linolenic acid
ANOVA	analysis of variance
ASP	acylation-stimulating protein
ATP	adenosine triphosphate
ATGL	adipose triglyceride lipase
AUC	area under the curve
BAT	brown adipose tissue
BHT	butylated hydroxyl toluene
BMI	body mass index
C	control
CAF	cafeteria
cDNA	complementary deoxyribonucleic acid
cAMP	cyclic adenosine monophosphate
CART	cocaine- and amphetamine-regulated transcript
C/EBPα	CCAAT/enhancer-binding protein-alpha
C/EBPβ	CCAAT/enhancer-binding protein-beta
C/EBPγ	CCAAT/enhancer-binding protein-gamma
CoA	Coenzyme A

D E F G

D	day(s)
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DOHaD	Developmental Origins of Health and Disease
dsDNA	double stranded deoxyribonucleic acid
DR	diet resistant
EDTA	ethylenediamine tetraacetic acid
EGF	epidermal growth factor
ELISA	enzyme linked immunosorbent assay
EIA	enzyme immunoassay
EPA	eicosapentaenoic acid

ERRα	estrogen related receptor alpha
FABP	fatty acid binding protein
FAME	fatty acid methyl esters
FATP	fatty acid transport protein
FAS	fatty acid synthase
FFA	free fatty acids
FIAF	fasting–induced adipose factor
FID	flame ionisation detector
GDP	guanosine diphosphate
GDM	gestatational diabetes mellitus
GH	growth hormone
G3PDH	glycerol 3-phosphate dehydrogenase
G6PD	glucose-6-phosphate dehydrogenase
GPAT	glycerol-3-phosphate acyltransferase

H I J K L

HRP	horseradish peroxidase
HSL	hormone sensitive lipase
IGFs	insulin-like growth factors
IGF-I	insulin-like growth factor I
IPGTT	Intraperitoneal glucose tolerance tests
IRS	insulin receptor substrate
LA	linoleic acid
LDL-R	lipoprotein receptor
LPL	lipoprotein lipase
LCPUFA	long chain polyunsaturated fatty acids

M N O

ME	malic enzyme
MEFA	methy-N-ethyl-N(β-hydroxyethyl)-aniline
mRNA	messenger ribonucleic acid
min	minute(s)
MGL	monoglyceride lipase
NEFA	non-esterified free fatty acids
n-3	omega-3
n-6	omega-6

P Q R S

PEPCK	phosphoenolpyruvate carboxykinase
POD	peroxidase
PGAR	PPAR-γ angiopoietin related peptide
PI3K	phosphoinositide 3-kinase
6-PG	6-phosphogluconate
PND1	postnatal day 1
PPAR-γ	peroxisome proliferator- activated receptor gamma
PUFA	polyunsaturated fatty acids
RBC	red blood cells
rRNA	ribosomal ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
qRT-PCR	quantitative real time PCR
RXR	retinoid-acid receptor
SC	subcutaneous
SCD-1	stearoyl-CoA desaturase-1
SEM	standard error of the mean
SPSS	statistical package for social sciences
SREBP	sterol regulatory element binding proteins

T U V W X Y Z

T2DM	type 2 diabetes mellitus
TG	triglyceride
TGFα	transforming growth factor-alpha
TGFβ	transforming growth factor-beta
TLC	thin layer chromatography
TMB	Tetramethylbenzidine
TNF-α	tumour necrosis factor-α
UCP-1	uncoupling protein 1
WAT	white adipose tissue
WHO	World Health Organization

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RELATED PUBLICATIONS

1. Gugusheff, JR., **Vithayathil, M**., Ong, ZY., & Muhlhausler, B. S. (2013). The effects of prenatal exposure to a 'junk food'diet on offspring food preferences and fat deposition can be mitigated by improved nutrition during lactation. *Journal of Developmental Origins of Health and Disease*, *4*(05), 348-357.

2. Muhlhausler, BS., Gugusheff, JR., Ong, ZY., & **Vithayathil, M. A**. (2013). Pregnancy, obesity and insulin resistance: maternal overnutrition and the target windows of fetal development. *Hormone Molecular Biology and Clinical Investigation*, *15*(1), 25-36.

3. Muhlhausler BS, Gugusheff JR, Ong ZY, **Vithayathil MA**. Nutritional approaches to breaking the intergenerational cycle of obesity. *Canadian Journal of Physiology and Pharmacology.* 2013; 91:421-8.

4. Muhlhausler, B. S, **Vithayathil, M. A.** Imapct of maternal obesity on offspring adipose tissue: lessons for the clinic. Expert Review of *Endocrinology &amp Metabolism* 10/2014; 9(6).

ABSTRACT

There is growing evidence that maternal obesity, maternal hyperglycemia or maternal intake of diets high in fat, sugar or total calories during pregnancy and lactation is associated with an increased risk of obesity and metabolic diseases in the offspring. The majority of studies to date, however, have examined the impact of maternal overnutrition during the entire perinatal period. While a small number of studies have provided clues that the impact of exposure to nutritional excess before birth in comparison to exposure during the early postnatal period may not be equivalent, the results of these studies have been inconsistent. Therefore, the relative contribution of prenatal and postnatal nutritional environment to obesity risk in the offspring remains unclear. The central aim of this thesis was to investigate the separate contributions of exposure to a maternal cafeteria diet during the prenatal and suckling periods on the metabolic outcomes of the offspring, specifically body weight, fat mass and the expression of key adipogenic and lipogenic genes at weaning, in early adolescence and in young adulthood using a cross-fostering approach in a rat model.

The results of this thesis demonstrated that exposure to a maternal cafeteria diet during the suckling period is more important for determining fat mass at weaning than exposure before birth. Importantly, this thesis provided considerable evidence to suggest that exposure to a nutritionally-balanced diet during the suckling period has the capacity to prevent the negative effects of exposure to a high-fat/high-sugar diet before birth. In addition, this thesis has demonstrated that the effects of being exposed to a high-fat/high-sugar diet during the perinatal period on offspring adiposity could be reversed/controlled by consuming a nutritionally-balanced diet post-weaning.

The results of this thesis also demonstrated that the levels of total fat, saturated and trans fats and omega-6 polyunsatured fatty acids (n-6 PUFA) in the dams

milk were directly related to their levels in the maternal diet, and were higher in dams consuming a cafeteria diet. This supported the hypothesis that altered fat content and fatty acid composition of the milk is likely to play an important role in mediating the effects of maternal cafeteria diets on offspring fat mass, and may well account for the higher adiposity at weaning in offspring suckled by cafeteria-diet fed dams. Exposure to a cafeteria diet during the suckling period also resulted in altered expression of key adipogenic and lipogenic genes in visceral and subcutaneous fat depots and an increased susceptibility to diet-induced obesity in females. Importantly, this thesis provided evidence of clear sex-differences in the relative impact of prenatal and postnatal nutritional exposures on adipocyte gene expression and the susceptibility to diet-induced obesity in the offspring, suggesting that the timing of nutritional interventions aimed to re-program the offspring may be different in males and females.

Overall, this thesis identifies the early postnatal period in rodents as a ‘critical window’ for the programming of fat mass and susceptibility to diet-induced obesity in the offspring, and has provided important insights into the mechanisms underlying the early origins of obesity.