Epigenetic Programming of Adolescent Metabolic Phenotypes?

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Overview

- Developmental Origins of Health and Disease hypothesis (DOHaD)
  - Nutritional Programming
- Epigenetics
  - Methylation of DNA
- Methyl Deficient Rat Model

Developmental Origins of Health and Disease

- Adverse event during development
  - Stress, inappropriate nutrition, placental insufficiency
- Adaptation
  - Developing embryo/fetus/neonate compensates to survive
- Timing of insult is important
  - Organs and systems develop at different times
- **Programming**
  - **A permanent change**

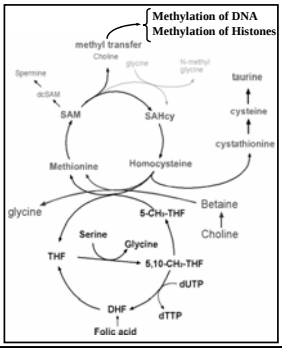
Epigenetics

- A stable change of DNA which alters gene expression without modifying the DNA coding sequence, that can persist into adult life

Methylation of DNA

- Methyl groups are added to cytosine in DNA by methylases which recognise the sequence CG
- Increased methylation reduces gene expression
- Is normal and essential
- During development DNA is actively methylated

Methionine Cycle

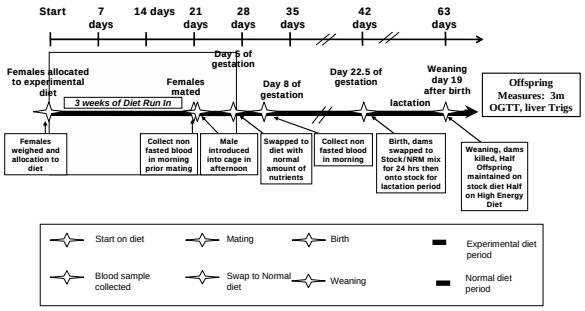


Experimental Diets Used

	CON	MD	NRM
Component	Grams	Grams	Grams
Casein	90	90	180
AA mix minus Methionine	*90*	*90*	
Sucrose	193	193	193
Cellulose Fibre	50	50	50
Cornstarch	425	425	425
Vitamin mix AIN-93 -Folate	10	10	
Vitamin mix AIN-93			10
Mineral mix AIN-93	35	35	35
Maize Oil	100	100	100
L-Methionine	3		1
L-Methionine*	2.3		
Folic acid/sucrose mix	0.2		
Powdered sucrose		0.2	
Choline chloride	2	0.5	2
KH2PO4	2.8	2.8	
Total	1003.3	996.5	994
	CON	MD	NRM

*** Methionine content of 90g of casein**

MD Rat Model Design



MD Rat Model Study design

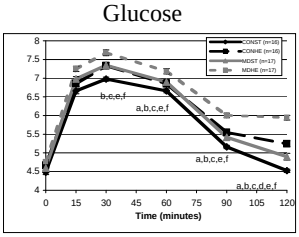
- Feed Female Wistar Rats diets poor in methyl groups
  - 3 week run-in, 1st 5 days of gestation
- Challenge offspring with an obesogenic diet (a high fat, energy dense diet)
- Phenotype offspring for diabetes and obesity at 3 months of age

Maternal Characteristics

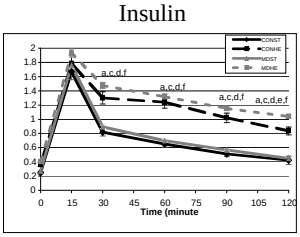
- After 3 week on MD diet
  - Plasma Homocysteine was elevated ~5 fold
  - Plasma Folate was reduced ~3 fold
  - Growth was reduced by ~5%
- By day 8 of gestation
  - Homocysteine was 20% higher than CON group
  - Folate was returning to CON group levels
  - Growth rate was increasing

3M Male Offspring OGTT Results

Glucose

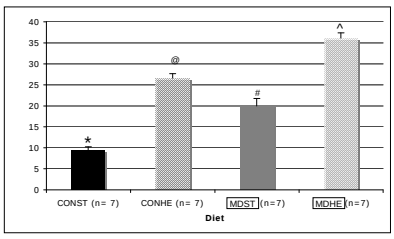


Insulin



Data are means ± SEM. Each letter (a, b, c, d, e, f) indicates a significant difference (p value of < 0.05) between groups: a: CONST vs CONHE, b: CONST vs HYST, c: CONST vs HYPHE, d: CONHE vs HYPST, e: CONHE vs HYPHE, f: HYPST vs HYPHE.

3M Male Offspring Liver Triglycerides



Data are means ± SEM.
Groups with the same symbol are not significantly different (p > 0.05)

Males at 3 months of age

- Methyl deficient (MD) offspring were glucose intolerant
- MD/ High fat diet challenge offspring are glucose intolerant, insulin resistant with a fatty liver
- Pre-natal and Post-natal effects interact to give a larger affect

Conclusion

- The pre and peri conception periods are critical periods of development for insulin/glucose metabolism
- A maternal diet which has a reduced methylation potential can predispose the offspring to develop insulin resistance and glucose intolerance later in life

Acknowledgements

Deepika Velampati
Jenny Phyual
Dr Bill Rees
Prof Ian Caterson

The University of Sydney

Institute of Obesity, Nutrition & Exercise

ROWETT research institute

Sydney University Nutrition Research Foundation