1. Metabolic syndrome and the early life origins of disease

2. Mechanisms
   – Tissue level
   – Epigenetic mechanisms

3. Transgenerational effects
Metabolic consequences of obesity

- The most critical factor in the emergence of metabolic disease is obesity.

Source: Nurses Health Study

[Diagram showing relative risk for cardiovascular disease and type 2 diabetes across different body mass index categories]
Birth weight and adult disease

Early life origins of disease – ‘programming’

- Action of a factor at a specific developmental ‘window’ leads to permanent effects on tissue growth and development and predisposition to later disease

- ‘Endocrine disruptors’

- Timing and / or duration of exposure may also be important
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Animal models

Nutrition \[\downarrow\] Low birth weight

Glucocorticoids \[\uparrow\] Glucose intolerance

Obesity

HPA

Hypertension
Where?

Programming of the brain – behaviour

• Maternal undernutrition
  – sedentary behaviour, hyperphagia & obesity (Vickers 2003)
  – Reversible by leptin postnatally (Vickers 2005)

• Prenatal low protein diet alters food preferences in rats
  – Offspring preferred HF (Bellinger 2004)
Programming of the brain – appetite

• SGA infants show increased postnatal weight gain and reduced satiety (Ounsted 1976)

• Prenatal undernutrition in rats associated with rapid catch-up growth and obesity

• Early postnatal malnutrition/ overnutrition in rats induces persistent alterations in hypothalamic appetite regulation (Plagemann)
  – Orexigenic – altered NPY neurone number & decreased response to leptin / insulin
  – Anorexigenic - POMC/α-MSH
Programming of the brain – HPA axis

• GC excess associated with adverse effects on glucose / lipid metabolism and insulin sensitivity

• Obesity associated with abnormalities HPA axis and altered peripheral GC metabolism

• Altered HPA axis/ peripheral GC metabolism may influence fat distribution, increasing risk obesity and metabolic syndrome
Liver

Increased hepatic PEPCK

Increased hepatic GR

Nyirenda et al

- Precocious expression HNF4α in fetus
- Early switch in promoter use to ‘adult’ HNF4α isoform

Nyirenda et al
Muscle

- Increased GR expression in dex-programmed rat – depot specific (Cleasby)

- Increased muscle GR associated with insulin resistance and hypertension in men (Reynolds)

- Programming of lipid composition and remodelling? – increased expression of lipogenic gene SCD1 in obesity correlates with increased muscle TG synthesis (Hulver 2005)

- Prenatal ethanol – alters muscle insulin signalling (Yao)

Adipose tissue

Obesity
Insulin resistance

NEFAs

Adipokines

Adipocyte
Regulation of signalling within adipocytes
e.g. PPARγ/RXR - promoting adipogenesis
In utero exposure to organotins - increased fat pad size and hepatic steatosis (Grun et al)

Programming of Adipokines / cytokines
e.g. leptin, TNFα

Altered GR expression
Decreased fatty acid uptake
Cleasby et al

Effects on pancreas

Normal β-cell
Increased β-cell function
Increased β-cell growth
Normal glucose tolerance
Compensatory hyperinsulinaemia

Susceptible β-cell
β-cell dysfunction
β-cell apoptosis
Type 2 diabetes

Insulin resistance
Glucose
NEFAs
Adipokines
Autonomic N/S
Growth factors

Environment

OBESITY
Effects on pancreas

- Human pancreas half adult β-cell mass by 1yr

- Maternal nutrient restriction associated with reduced β-cell mass\(^1\), increased apoptosis of β-cells\(^2\), decreased insulin content\(^3\), greater age-dependent loss of glucose tolerance\(^4\)
  - Petrik 1999\(^1\), Cherif 1998\(^2\), Blondeau 2001\(^3\), Hales 1996\(^4\)

- Bisphenol A disrupts β-cell function in vivo and induces insulin resistance in mice (Alonso-Magdalena 2006)

Epigenetic effects

- Modifications which influence gene expression without changing the DNA sequence

- DNA methylation, modification of histones, expression of non-coding RNAs

- Influence transcriptional activity
• Low protein diet in rats (Lillycrop et al)
  – Reduced methylation GR and PPAR α (liver)

• Differences in maternal care associated with altered methylation at hippocampal GR at binding site for NGFIA resulting in increased GR expression (Meaney)

• Epigenetic modifications at some alleles
  – May be modified by ‘environmental factors’

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**Agouti yellow (A<sup>vy</sup>) mice**

• A<sup>vy</sup> allele - IAP inserted at 5’ end agouti A allele
• Ectopic agouti transcription initiated from cryptic promoter in A<sup>vy</sup> IAP
• CpG methylation varies & correlates inversely with ectopic *agouti* expression

Waterland & Jirtle 2003
F0 dietary (methyl donor) supplements *before and during* pregnancy

Increase $A^v_y$ methylation F1 offspring

Shifted towards pseudoagouti phenotype

**Potential mechanisms**

- Altered cell number
  - Alter cell proliferation / apoptosis

- Altered circulating hormone levels
  - Altered hormone synthesis / metabolism

- Modification of gene expression (tissue specific)
  - Direct receptor stimulation/inhibition
  - Altered gene expression
  - Altered transcription factors
  - Epigenetic modifications
1. Metabolic syndrome and the early life origins of disease

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Intergenerational patterns

- Exposure to maternal type 2 diabetes in fetal life associated with abnormal glucose homeostasis in offspring (increased risk of gestational and type 2 diabetes) (Alcolado, Singh, Meigs etc.)

- Maternal obesity associated with offspring obesity (Lawlor)

- Other factors
  - Maternal hyperinsulinamia
  - Maternal glucocorticoids
  - Reduced maternal size
Paternal effects?

- Human studies suggest also paternal effect on transmission diabetes risk etc.

- Överkalix (Kaati 2002, Pembrey 2006)
  - Excess food during paternal grandfather’s SGP increased diabetes risk in grandchild and increased mortality risk in grandson
  - Excess food during paternal grandmother’s SGP increased mortality RR in granddaughter
  - Poor food supply had opposite effect

\[ \begin{align*}
\text{F1dex}^\odot \times \text{F1 dex}^\delta & \rightarrow \text{F2 dex/dex} \\
\text{F1veh}^\odot \times \text{F1 veh}^\delta & \rightarrow \text{F2 veh/veh}
\end{align*} \]
\[ \begin{align*}
\text{F1dex}^\odot \times \text{F1veh}^\delta & \rightarrow \text{F2 dex/veh} \\
\text{F1veh}^\odot \times \text{F1dex}^\delta & \rightarrow \text{F2 veh/dex}
\end{align*} \]
Paternal influence on birth weight

![Bar chart showing weight distribution across different groups.]

- **F2 veh/veh**
- **F2 dex/dex**
- **F2 dex/veh**
- **F2 veh/dex**

- **n=126**
- **n=116**
- **n=71**
- **n=62**

Paternal influence on hepatic PEPCK activity

![Bar chart showing PEPCK activity across different groups.]

- **F2 veh/veh**
- **F2 dex/dex**
- **F2 dex/veh**
- **F2 veh/dex**

Males at 5 weeks, n=7-8 per group
Second generation effects

• Methyl supplements only during mid-gestation (E8.5-E15.5). No effects on F1 (after somatic epigenotype of $A^{vy}$ set)

• Effects on F2 phenotype - presumably by affecting epigenetic state of $A^{vy}$ in germ line

Summary

• Many mechanisms by which EDs operate to increase susceptibility to metabolic disorders
• Many potential ‘programming’ targets
• May be specific time windows of vulnerability
• Effects may be sex-specific
• Epigenetic effects may be particularly important
• Transgenerational effects may result in further increase in prevalence metabolic disorders
• ‘Toxin’ may have acted in previous generation

Cropley et al 2006