

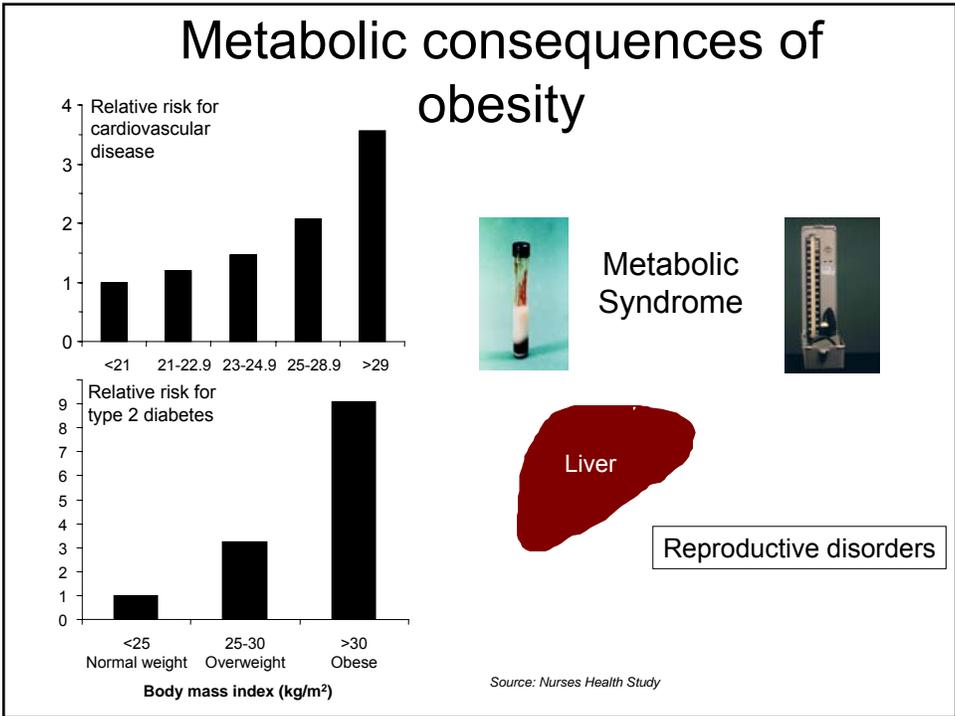


Potential Mechanisms

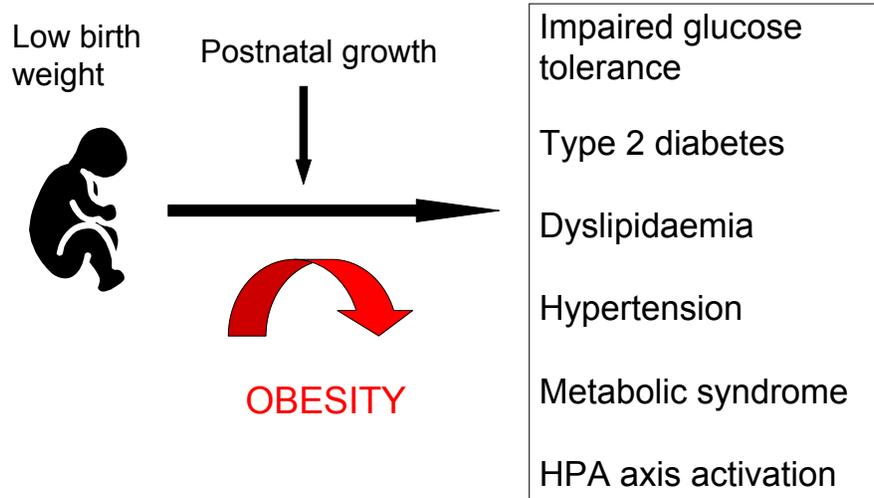
1. **Metabolic syndrome and the early life origins of disease**
2. Mechanisms
 - Tissue level
 - Epigenetic mechanisms
3. Transgenerational effects

Metabolic consequences of obesity

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



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

1. Metabolic syndrome and the early life origins of disease

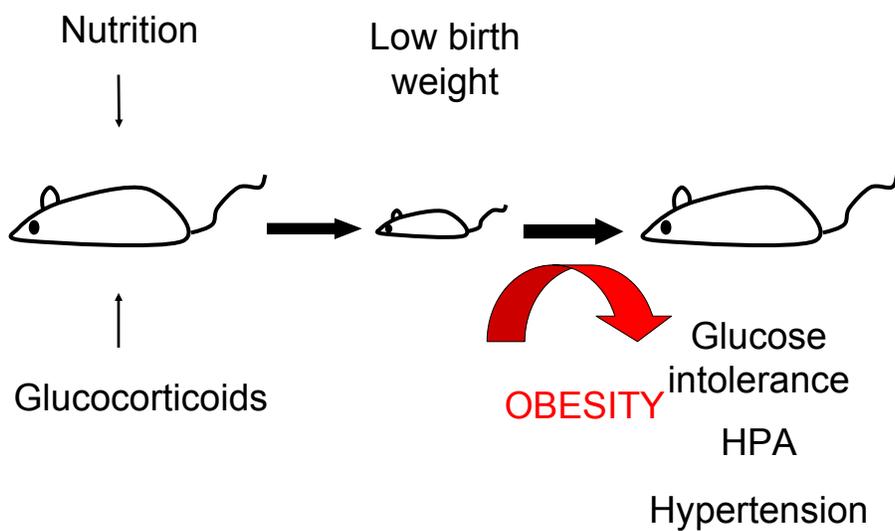
2. Mechanisms

– Tissue level

– Epigenetic mechanisms

3. Transgenerational effects

Animal models



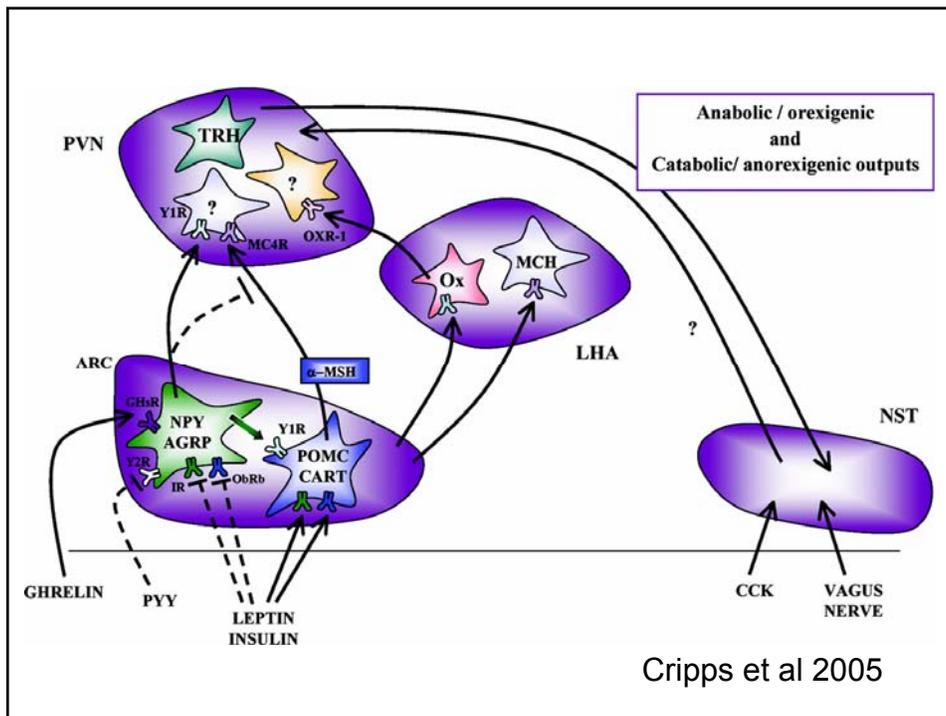
Where?

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)

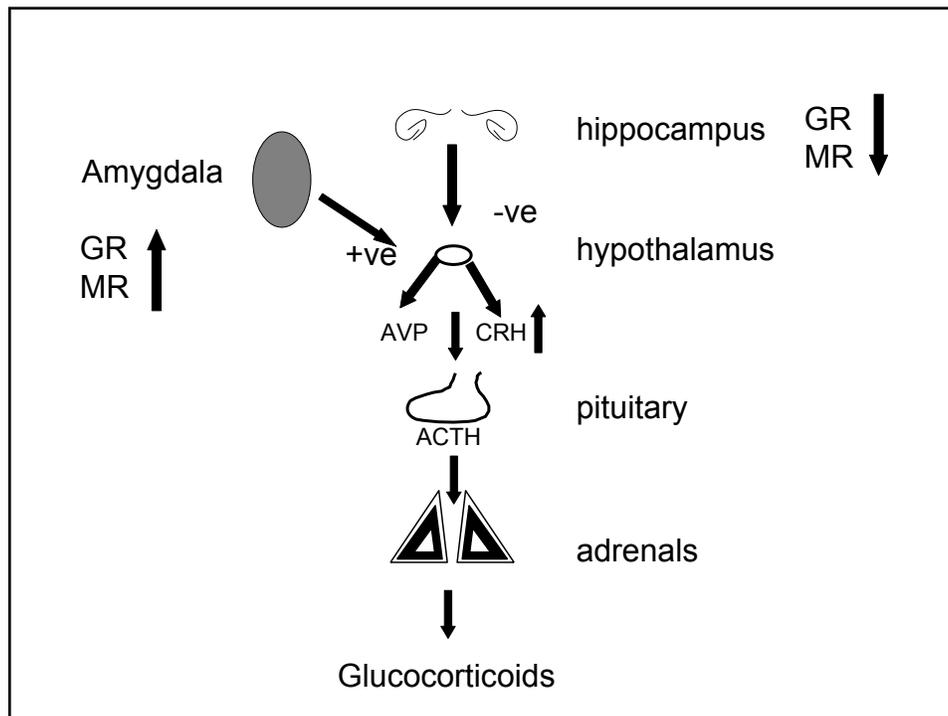
Programming of the brain – appetite

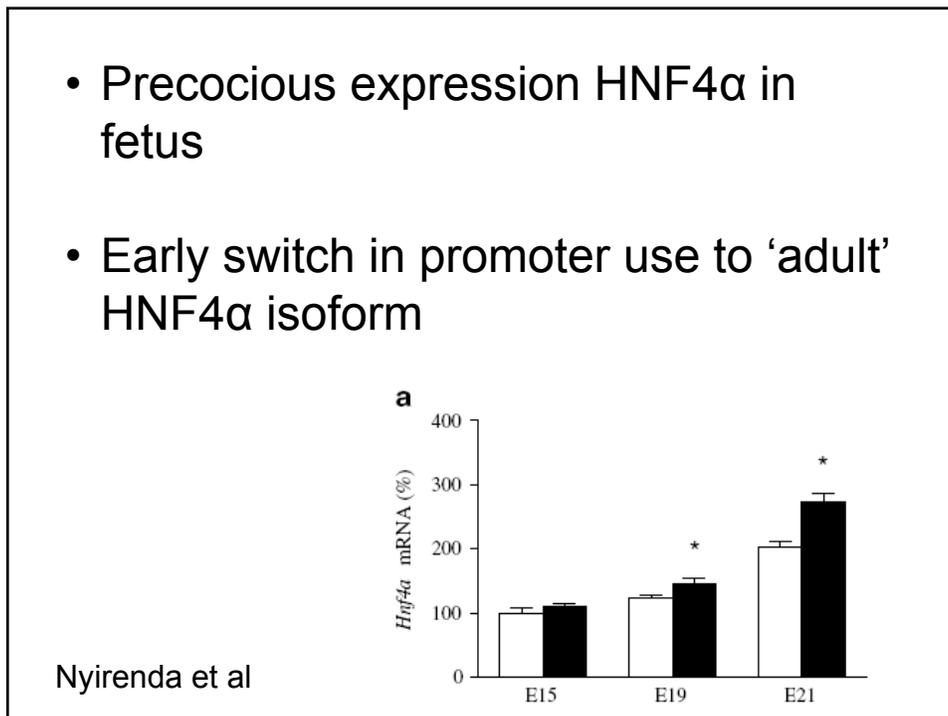
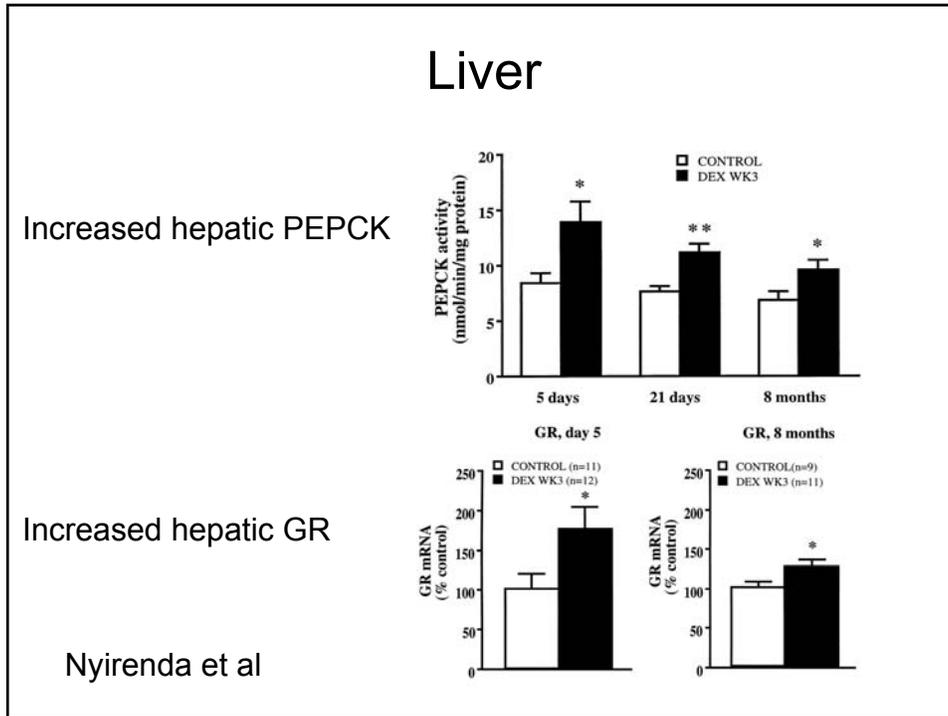
- SGA infants show increased postnatal weight gain and reduced satiety (Ounsted 1976)
- Prenatal undernutrition in rats associated with rapid catch-up growth and obesity
- Early postnatal malnutrition/ overnutrition in rats induces persistent alterations in hypothalamic appetite regulation (Plagemann)
 - 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



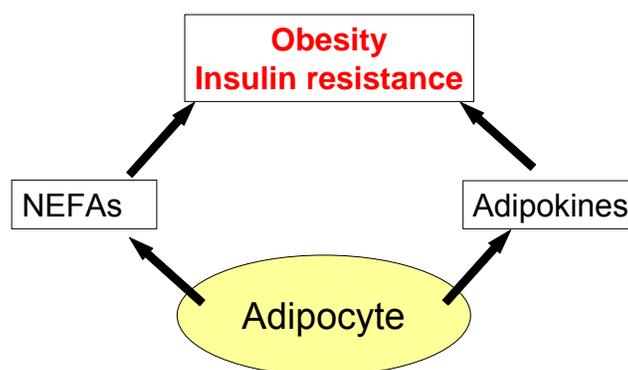


Muscle



- 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



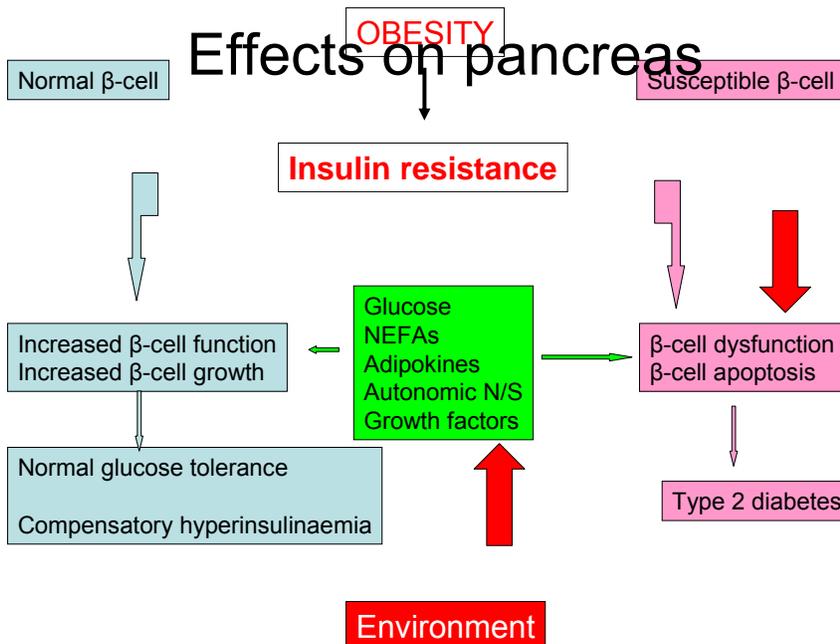
Regulation of signalling within adipocytes
 e.g. PPAR γ /RXR - promoting adipogenesis
 In utero exposure to organotins - increased fat pad
 size and hepatic steatosis (Grun et al)

Programming of
 Adipokines / cytokines
 e.g. leptin, TNF α

Adipocyte

Altered GR expression
 Decreased fatty acid uptake
 Cleasby et al

Effects on pancreas



Effects on pancreas

- Human pancreas half adult β -cell mass by 1yr
- Maternal nutrient restriction associated with reduced β -cell mass¹, increased apoptosis of β -cells², decreased insulin content³, greater age-dependent loss of glucose tolerance⁴
 - Petrik 1999¹, Cherif 1998², Blondeau 2001³, Hales 1996⁴
- 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 (Lillicrop 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’

Agouti yellow (A^{vy}) mice

- A^{vy} allele - IAP inserted at 5' end agouti A allele
- Ectopic agouti transcription initiated from cryptic promoter in A^{vy} IAP
- CpG methylation varies & correlates inversely with ectopic *agouti* expression



Waterland & Jirtle 2003

F0 dietary (methyl donor) supplements
before and during pregnancy



Increase A^{vy} 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

2. Mechanisms

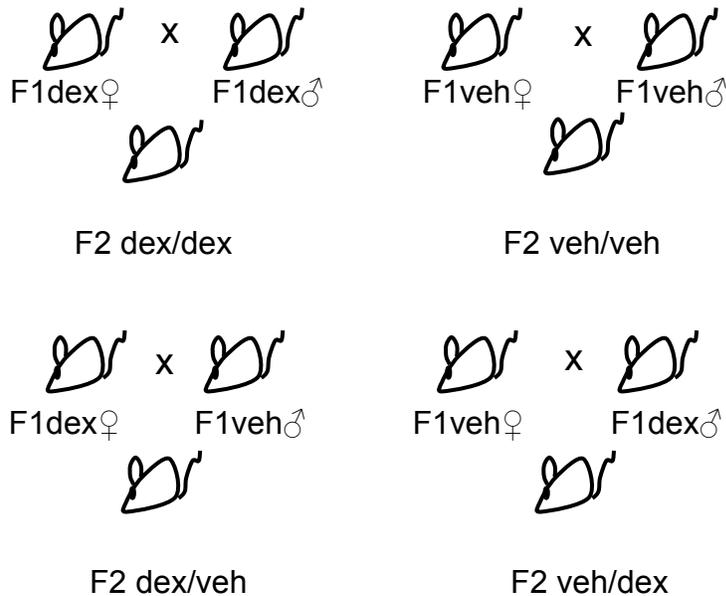
3. Transgenerational effects

Intergenerational patterns

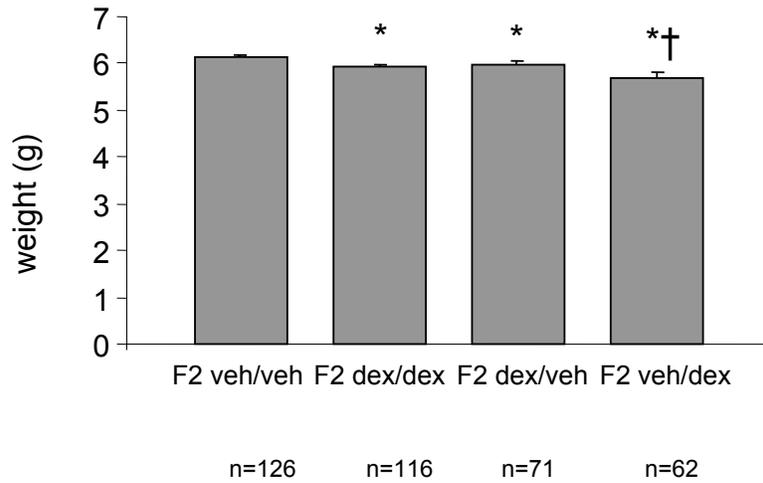
- Exposure to maternal type 2 diabetes in fetal life associated with abnormal glucose homeostasis in offspring (increased risk of gestational and type 2 diabetes) (Alcolado, Singh, Meigs etc.)
- Maternal obesity associated with offspring obesity (Lawlor)
- Other factors
 - Maternal hyperinsulinemia
 - Maternal glucocorticoids
 - Reduced maternal size

Paternal effects?

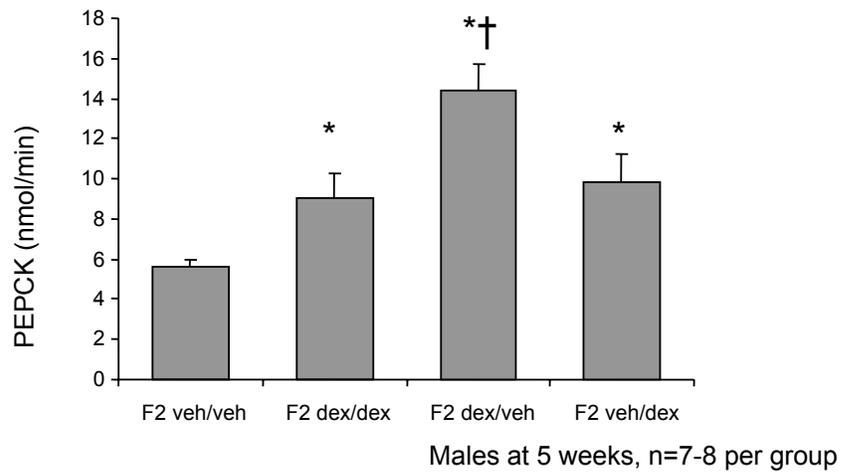
- Human studies suggest also paternal effect on transmission diabetes risk etc.
- Överkalix (Kaati 2002, Pembrey 2006)
 - Excess food during paternal grandfather's SGP increased diabetes risk in grandchild and increased mortality risk in grandson
 - Excess food during paternal grandmother's SGP increased mortality RR in granddaughter
 - Poor food supply had opposite effect



Paternal influence on birth weight



Paternal influence on hepatic PEPCK activity



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

Cropley et al 2006



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

