Developmental programming – therapies to reverse metabolic disturbances

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Introduction

- well-established that alterations in the early life environment increase risk for obesity and metabolic and cardiovascular disorders in offspring

- not a single cause but complex multifactorial process

- while the underlying mechanisms are being elucidated, little is known about interventions early in life to diminish the incidence and severity of later disease

- Most evidence to date is derived from experimental models with limited translation
What interventions?

- **Dietary**
  - lipids, pre-/probiotics, taurine, vitamins, polyphenols, methyl donors etc...

- **Pharmacologic**
  - Leptin, growth hormone, melatonin, GLP-1 analogs, nuclear receptor agonists etc...

- **Behavioral/lifestyle**
  - Exercise, counselling etc...

When to intervene?

- Pre-conception, pregnancy, lactation, early infancy/childhood
The importance of the early life period

*Life course view of NCD*

- The earlier the intervention the bigger the effect on later risk reduction

From Godfrey *et al.*, TEM, 2010
Critical windows of opportunity?

Developmental Plasticity

Genotype

Environment

Adult Phenotype

Environment
Maternal nutrition – a “U”-shaped curved

Grattan D R Endocrinology 2008;149:5345-5347
Interventions in programming: 
Evidence from pre-clinical models
Pre-clinical models of early life nutritional manipulation

- Control
- Undernutrition
- Supplements e.g. Folic acid
- High fat
- High salt
- Low protein
- High sugar

Control Supplements e.g. Folic acid Low protein High fat High salt Low protein High sugar
Pre-clinical models of early life nutritional manipulation

- Undernutrition
- Low protein
- High fat
- High salt
- Low protein
- High sugar

- Obesity
- Type 2 Diabetes
- Heart Disease
- Altered appetite
- Inflammation
- Reproductive Disorders
Diet Counselling
Role of Leptin

- Neonatal leptin treatment of *ob/ob* mice rescues neural projection pathways from the hypothalamus.
- *Post-weaning* treatment has no effect.

Leptin as an intervention?

Neonatal Leptin Treatment Reverses Developmental Programming


- The effects appeared permanent and were specific to offspring of maternally undernourished offspring
  - has been repeated in numerous other models/species including effects on hypothalamic neuropeptides
  - Of note, leptin is present in breast milk but is not in infant formula
- we know that the effects of neonatal leptin treatment are **dependent upon prior maternal nutritional status and gender**

- leptin treatment to male neonates of normal pregnancies can elicit an adverse metabolic phenotype in later life

Maternal diet and leptin treatment interactions in offspring

- changes in PPAR-α and 11β-HSD2 methylation status is directionally dependent upon prior maternal nutritional status

Gluckman et al., PNAS, 2007
Maternal Leptin Treatment

- placental 11β-HSD2 activity is reduced by a low-protein diet; this reduction is prevented by maternal leptin treatment
- Offspring partially protected against HF-diet induced weight gain
- in this study, leptin was not given to control mothers

* p<0.05 normal protein saline versus low protein saline

Stocker et al.  
**Neonatal Exendin 4**

- Exendin 4 (GLP-1 analog)
- normalisation of β-cell mass and proliferation
- reverses epigenetic modifications to pancreatic and duodenal homeobox 1 (Pdx1)

Stoffers et al, Diabetes, 52: 737
Maternal Taurine Supplementation

- Taurine concentrations are low in diabetic and pre-diabetic states
- physiological plasma taurine levels are important for adequate β-cell function and insulin action
- Taurine has protective effects in the setting of maternal hepatic cholestasis
- Confers long term beneficial effects in offspring
Maternal Taurine Supplementation

**Fructose-fed mothers**

- fructose supplemented mothers are hyperinsulinemic compared to control mothers with increases in inflammatory markers
- these effects are normalised with maternal taurine supplementation

Maternal Taurine Supplementation

Offspring at birth

- maternal obesity results in increases in markers of inflammation in offspring at birth
- effects are reversed with maternal taurine supplementation

Neonatal GH treatment and adipocyte size in adulthood

- Offspring of undernourished mothers display adipocyte hypertrophy in adult life.
- Adipocyte size is normalised in UN offspring treated with GH as neonates.

Neonatal GH treatment normalises blood pressure and fat mass in adult life

- Neonatal GH Tx, adults measured at postnatal day 150
- Associated with changes in specific miRNA family (LET-7)
  - Although GH itself is unlikely as a treatment, GH can be modified by diet, exercise, sleep etc

Maternal lipid supplementation

**Conjugated linoleic acid (c9, t11-CLA)**

**Offspring at weaning**

- Offspring from HF mothers had significantly impaired insulin sensitivity and increased gut inflammatory markers, which were reversed in offspring of HFCLA mothers
- Also improved maternal insulin sensitivity

\[ n = 6 \text{ litters/group} ; * \text{HF vs. CON; # HF vs CLA; } + \text{ HF vs HFCLA} \]
Postnatal dietary omega-3 fatty acids prevents programming-induced hyperleptinemia and hypertension at 6 months of age.

*p<0.05 vs all groups, # p<0.05 versus chow
Wyroll et al., Endocrinology 2005
Maternal Vitamin D status

- role in controlling placental inflammation and insulin sensitivity

- pre-pregnancy obesity predicts poor vitamin D status in mothers and their neonates

- Vitamin D deficiency in pregnancy can result in insulin resistance, altered inflammatory profiles and increased risk of early postnatal obesity in offspring\(^1,2\)

- impact of supplements on outcomes related to adiposity are conflicting

\(^1\)Morales E, Int J. Obesity, 2015, \(^2\)Zhang H, Diabetologia, 2014
Dietary methyl donors

Folic acid\textsuperscript{1}

Glycine\textsuperscript{2}

Choline\textsuperscript{3}

Mixed supplements\textsuperscript{4}

Maternal supplementation improves metabolic and cardiovascular outcomes in offspring following both undernutrition and maternal obesity

Maternal Choline Supplementation

- Maternal choline supplementation reduces low-protein induced elevations in systolic blood pressure and fat mass in adult offspring

Exercise/Lifestyle Interventions

- Physical activity has the potential to mitigate against the increased obesity observed in “programmed” offspring during two critical windows:
  - **maternal exercise prior to and during pregnancy**
  - **exercise during childhood for those at risk of “programmed” obesity**

- Recent early feeding practices intervention study reported no change in prevalence of overweight/obesity

Exercise as an intervention

- Early exercise can reduce adiposity in experimental models of both maternal undernutrition and maternal obesity\(^1,2\)
- Effects mediated in part by improved central leptin sensitivity\(^3\)
- Dependent on type and duration - moderate exercise in normal pregnancy can lead to a significant decrease in birth weight\(^4\)

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\(^1\)Miles JL, Endocrinology 2008, \(^2\)Santos M, Am J Phys. 2015
\(^3\)Sun B, Am J Physiol. 2013, \(^4\)Hopkins S, JCEM, 2010
Dietary intervention in obese mothers prior to pregnancy

- dietary intervention in obese mothers reversed metabolic programming in offspring

- effects persisted into adult life but were sex specific

Zambrano et al, J Physiol, 2010
Vega et al, In J Obes., 2013
Catch-up growth

Preventing catch-up growth prevents programmed postnatal obesity?

Howie & Vickers, Br J Nutrition 2012

Low birth weight followed by rapid postnatal weight gain is associated with long-term risks for central obesity and insulin resistance.
Maternal Obesity and Omega-3/DHA

• as an anti-inflammatory - obesity and pregnancy are low-grade inflammatory states that increase the risk of fetal adiposity in the short term and metabolic syndrome in the long term

• maternal-fetal PUFA status is associated with lower infant adiposity - offspring born to mothers with recommended quantity of DHA during pregnancy are 30% less likely to have excessive body fat

• DHA supplementation in women with overweight/obesity results in infants with lower adiposity at birth (Donahue, 2011)

• DHA supplements in last half of pregnancy led to greater gestation length and increased infant size (Carlson et al, Am J Clin Nutr. 2013)

• differences across reported studies may simply relate to doses, sources and potential oxidation of n-3 PUFAs
Pre-/Probiotics

- administration of certain probiotics and/or prebiotics during the perinatal and postnatal period may be a potential prophylactic therapy for obesity and metabolic disease

- early gut microbiota modulation with probiotics may modify the growth pattern of the child by restraining excessive weight gain during the first years of life

- supplementation of infant formula with prebiotic oligosaccharides to compensate for the lack of some of the complex molecules naturally present in human milk?

Thum et al., J Nutr., 2012, 142(11)
Luoto et al., Int J. Obesity, 2010, 34(10)
• potential that interventions in setting of “intact” systems may lead to adverse outcomes

• how best to identify those “at risk” of programmed disorders? – tailored approach, metabolic markers

• sex-specific effects *e.g. maternal methyl-deficient diets can result in metabolic disturbances in male, but not female, rat offspring*
Who and when to target for intervention?

- Predictive biomarkers –
  - Importance of large biobanks
  - E.g. cord blood methylation of RXR-α and later childhood adiposity
  - Predominantly associative

- Biomarkers in populations often have a wide range and within this range, individuals can behave quite differently

- What are the trade-offs? i.e. epimutations that are likely associated with later negative health outcomes
e.g. maternal methyl donor supplementation can lead to a reduction in fatty liver but increased adipose tissue storage in offspring when later exposed to a HF diet
Transgenerational Effects

The effects of a single environmental exposure can be transmitted transgenerationally. An adverse maternal environment ($F_0$) effects not only the development of the fetus ($F_1$) but can also affect the germ cells which form the $F_2$ generation.
What about the father?

- growing evidence re paternal transmission of disease risk
- obesity increases sperm DNA damage
- Can be partially restored via diet/exercise interventions in obese fathers preconception, which improves aspects of sperm DNA integrity

(McPherson, Ann Nutr Metab, 2014)

Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring

Ng et al, Nature, 2010, 467(7318)
Discussion

- the early life period of developmental plasticity offers the most effective avenue for intervention

- although reversal has been shown in a number of experimental models (maternal and neonatal), direct translation to the clinic may prove difficult but will inform on possible intervention strategies

"I'm afraid you're suffering from an increased IL-1β and an aberrant miR843 expression"
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Te Whare Wānanga o Ōtāgo

Te Whare Wānanga o Tāmaki Makaurau
GH and IGFBP2

- Changes in IGFBP2 expression may be a mechanism used by adipocytes to limit further fat gain

Pre-weaning GH treatment normalises the inflammasome in adult offspring

Adipose tissue

C = controls, S = saline, UN = maternal undernutrition, GH = GH treatment

- Although GH itself is unlikely as a treatment, GH can be modified by diet, exercise, sleep etc

* versus all other groups

The Vicious Cycle

Maternal Obesity

Altered fetal/neonatal nutrition

Adult Obesity
Metabolic Syndrome
Type 2 diabetes

Childhood Obesity

Diet, physical activity

Resistance

Diet, physical activity
Maternal lipid supplementation
Conjugated linoleic acid (c9, t11-CLA)

Maternal Effects

- Mothers consuming the HF diet had significantly impaired insulin sensitivity, which was normalised in HFCLA mothers

*HF vs CON; +HFCLA vs HF, n=6 litters/group
Sex-specific Effects

Male placenta

IL-1β (Fold induction)

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TNFα (Fold induction)

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CD68 (Fold induction)

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Female placenta

IL-1β (Fold induction)

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(Gray, Reynolds et al, Biol. Reprod., 2015)