Metabolic Programming

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Metabolic programming is a phenomenon where nutritional stress/stimuli permanently changes the physiology and metabolism of an organism. The consequence of stress/stimuli are observed much later in life. Early period critical window can lead to organogenesis of target tissues, which is a consequence of metabolic programming.
nutrition during three critical periods

- fetal development during gestation
- birth: fetal-postnatal transition (abrupt)
- postnatal-weaning transition (gradual)

Rapid changes in enzyme activities occur in response to the nature of the available nutrients during these periods under normal development.
“Barker’s hypothesis is the phenomenon of metabolic programming, which refers to the altered development of a somatic structure, resetting of a physiological system and/or an imbalance in normal homeostatic mechanisms in response to a nutritional stimulus or insult experienced during crucial periods of development.”

The ‘thrifty phenotype’ hypothesis —
by Hales and Barker in 1992

insufficient maternal nutrition

impaired fetal growth

placental dysfunction

impaired glucose tolerance
hypertension
central obesity
dyslipidemia

increased risk of developing metabolic syndrome

“...suboptimal early environment, the fetus makes metabolic adaptations to maximise chances of surviving postnatally in conditions of ongoing deprivation...”

it is the accelerated weight gain after birth...

growth restricted during fetal life

after birth grow rapidly and achieve higher body weight

most affected and have the greatest adiposity

programming obesity with early over-nutrition

offspring born to mothers with high BMI or with gestational diabetes are larger at birth, increase adipose tissue and diabetes risk

both ends of the birth-weight spectrum have increased obesity risk as adults

maternal over/under nutrition

rats and mice impaired early growth due to maternal protein restriction → impairments in glucose tolerance with age → reduction in Beta cells and reduced insulin secretion

High-fat feeding during pregnancy and lactation → metabolic syndrome phenotype
Offspring become: hyperinsulimic and hyperglycemic in adulthood; altered pancreatic development and reduction in glucose-stimulated secretion.

the type of fat matters! PUFAs showed a beneficial effect while saturated fats showed pancreatic impairment effects

energy homeostasis regulation

obesity =

energy intake

energy expenditure

leptin
insulin
glucose
gut hormones
recall, central energy balance pathways

- Arcuate N.
- NPY/AgRP
- CART/POMC
- PVN, LHA, DMN
- higher cortical centers
- hindbrain/NTS
- feeding, GIT afferents

integrated responses to feeding and increased energy expenditure

GIT=gastro intestinal tract

Leptin, Insulin
GIT hormones
Methods and Results— A cohort of European American formula-fed subjects, measured on 7 occasions during infancy as part of several infant formula studies, were contacted at age 20 to 32 years, when they reported usual adult weight and height. A life-course plot was used to identify critical periods of weight gain associated with adulthood overweight (body mass index $\geq 25$ kg/m²). These associations were tested with logistic regressions. Data were available for 653 subjects (72% of eligible subjects). Approximately 32% of them were overweight adults. The period between birth and age 8 days was identified as potentially critical. After adjustment for important confounding factors, weight gain during the first week of life was associated with adulthood overweight status (OR for each 100-g increase 1.28, 95% CI 1.08 to 1.52), as was weight gain during the first 112 days of life (OR 1.04, 95% CI 1.01 to 1.08). Similar results were obtained after standardization with $z$ scores from a reference population.

Conclusions— In formula-fed infants, weight gain during the first week of life may be a critical determinant for the development of obesity several decades later. These results contribute to the understanding of chronic disease programming and suggest new approaches to obesity prevention.

Background— Successful prevention of obesity and related cardiovascular risk factors requires a clear understanding of its determinants over the life course. Rapid infancy weight gain is associated with childhood obesity, whereas low infancy weight is associated with coronary heart disease. Our aim was to identify during which periods in infancy weight gain is associated with adult obesity.
Early environmental influences

1st week weight gain

- Obesity later in life
- Breast fed benefits
- PUFA enriched formulas don't show neg. effects
- Leptin levels in cord match fat mass

This may be due to increased satiety and have factors not in formula – i.e. leptin

At birth, cord blood levels of leptin are reflective of neonatal fat mass; infants with low cord leptin show increased rate of early weight gain

wiring the hypothalamus

morphological changes

perinatal hyperinsulinaemia acts as a programming cue which causes the malformation of hypothalamic structures

Hypothalamic ventromedial and arcuate neurons of normal and postnatally overnourished rats differ in their responses to melanin-concentrating hormone

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The nutrition of the fetus is determined by supply via the placenta - mostly glucose - during the late phase of gestation, preparing for birth.

Rapid metabolic changes occur during the fetal, suckling, weaning, and postnatal phases. Glucose metabolism is utilized for high carbohydrate utilization in the fetus. Enzymes involved in lipogenesis and gluconeogenic pathways are activated in response to high fat in milk (low carb).

Enzymes such as glycogen synthase, PEP carboxylase, and glucokinase malic enzyme are involved in metabolic changes during these phases.

Figure adapted from: Patel, M. and Srinivasan, M. (2010) Journal of Nutrition 140(3) 658-661
Correlation:

**obese mothers:**
more likely to have children with metabolic disorders

High-fat diets (HFD) alter the circuitry in the hypothalamus.

HFD consumed during 3rd trimester ➔ greatest risk
http://www.project-earlynutrition.eu/index.html
Metabolic programming in the immediate postnatal period

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Metabolic programming as a consequence of the nutritional environment during fetal and the immediate postnatal periods

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