Metabolic Programming

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metabolic programming

nutritional stress/stimuli

organogenesis of target tissues

early period critical window

consequence of stress/stimuli are observed much later in life

metabolic programming

permanently changes the physiology and metabolism of an organism
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 → 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


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

integrated responses to feeding and increased energy expenditure

GIT=gastrointestinal tract

PVN, LHA, DMN higher cortical centers

hindbrain/NTS

feeding, GIT afferents

Arcuate N.

NPY/AgRP

CART/POMC

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 ≥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.

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.

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.
Early environmental influences

1st week weight gain

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

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.

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

wiring the hypothalamus

morphological changes

neuropeptide levels

neuronal activity

hormonal responsiveness

litter size manipulation experiments

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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Nutrition of fetus is determined by supply via placenta - mostly glucose - late phase of gestation is glycogen synthesis – preparing for birth.

Rapid metabolic change – gluconeogenic enzymes – PEP carboxylase in response to high fat in milk (low carb).

Enzymes in lipogenesis and glucose utilization used for high carb rat chow.

Switched to high carb formula.
Correlation:

Obese mothers are more likely to have children with metabolic disorders.

High-fat diets (HFD) alter the circuitry in the hypothalamus. HFD consumed during the 3rd trimester results in the greatest risk.
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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The hypothesis that adverse early life exposures might increase susceptibility to diseases of affluence in later life was initially proposed by Barker and Osmond (1). Subsequent work confirmed and extended this hypothesis by demonstrating striking inverse correlations between birth weight and adult diabetes and cardiovascular disease risk (2-4). Analysis of adults who had been exposed to undernutrition in utero during the Dutch Hunger Winter showed that increased disease risk can occur even in individuals who do not exhibit profound prenatal growth failure (5, 6), suggesting that size at birth may be only a surrogate of more complex effects on fetal development.

The link between early nutritional exposures and later disease risk could be mediated by environmentally induced alterations to the epigenome (which include DNA methylation and histone modifications). Although usually stably maintained during mitosis, epigenetic marks are more labile than nucleotide sequence and thus are potentially susceptible to modulation in response to environmental influences. One class of genes regulated by epigenetic mechanisms is imprinted genes, whose expression is dependent on their parent of origin. Imprinted genes are important regulators of fetal outcomes, as they control fetal and placental growth and are involved in the adaptive response to the

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DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial

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