Metabolic programming during prenatal and early postnatal life: an intriguing phenomenon beyond the genes

Martin Kaske
Epidemiological studies confirm a strong correlation between low birth weight and the risk for chronic diseases.

<table>
<thead>
<tr>
<th>Birth weight [ kg ]</th>
<th>Impaired glucose tolerance [ % ]</th>
<th>Typ 2 Diabetes [ % ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5 (20)</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>2.51 – 2.95 (47)</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>2.96 – 3.40 (104)</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>3.41 – 3.87 (117)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>3.88 – 4.31 (54)</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>&gt; 4.31 (28)</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

(Hales et al. 1991)
Prenatal undernutrition leads to permanent changes of the metabolism

Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview

Tessa J. Roseboom *, Jan H.P. van der Meulen, Anita C.J. Ravelli, Clive Osmond, David J.P. Barker, Otto P. Bleker

Department of Clinical Epidemiology, Academic Medical Centre, Amsterdam, The Netherlands

Sept 1944: embargo on all food transports to the western Netherlands

Nov 1944 – April 1945: harsh winter extreme shortage of food
Prenatal undernutrition leads to permanent changes of the metabolism

<table>
<thead>
<tr>
<th>Exposure to famine in</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Born before</td>
<td>Late gestation</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Adult characteristics</td>
<td>702</td>
</tr>
<tr>
<td>Plasma glucose 120 min* (mmol/l)</td>
<td>5.7</td>
</tr>
<tr>
<td>Plasma insulin 120 min* (nmol/l)</td>
<td>160</td>
</tr>
<tr>
<td>CHD</td>
<td>3.8%</td>
</tr>
<tr>
<td>General health poor</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Exposition in early gestation: increased risk of coronary heart disease poorly health

Exposition in mid/late gestation: reduced glucose tolerance

( Ravelli et al. 1998, Roseboom et al. 2001 )
The metabolism of mammals can be programmed

Early adaptations to a short nutritional perinatal stimulus permanently change the physiology and metabolism of the organism and continue to be expressed even in the absence of the stimulus that initiated them.

"fetal programming"
"metabolic imprinting"
"fuel mediated teratogenesis"
"developmental programming"
"perinatal programming"
"fetal imprinting"
"nutritional programming"
Metabolic programming: an explanation for the increasing prevalence of the „metabolic syndrome“?
"Programming": a hot topic ...

PubMed references using the phrases
"metabolic programming“ OR "fetal imprinting“ OR
"developmental programming“ OR "fetal programming"
“Metabolic programming” - one aspect of epigenetics
The immune system of mammals can be programmed

-intestinal glucose absorption ↑
-milk yield ↑
-veterinary costs ↓
-lactocrine mediated effects ↑
-colostrum
-maturation of the GIT ↑
-lactose digestion ↑
-maturation of the somatotropic axis ↑
-passive immunity ↑
-postnatal growth ↑

How can we explain long-lasting effects of colostral supply?

maternal antibodies

anti-idiotypic antibodies

anti-anti-idiotypic antibodies

antigen-specific memory cells
Colostrum induces an immunological programming

- antibodies
- cells
- immunomodulators

transient passive immunity + stimulation of active immunity
Brain development of mammals can be programmed

Preliminary Evidence for Sensitive Periods in the Effect of Childhood Sexual Abuse on Regional Brain Development

Susan L. Andersen, Ph.D.
Akemi Tomada, M.D., Ph.D.
Evelyn S. Vincow
Elizabeth Valente, M.A.
Ann Polcari, R.N., C.S., Ph.D.
Martin H. Teicher, M.D., Ph.D.

TABLE 3. Adjusted Size of Brain Regions for Comparison Subjects and Abused Subjects at Stages of Greatest Vulnerability to Childhood Sexual Abuse

<table>
<thead>
<tr>
<th>Region</th>
<th>Stage (years)</th>
<th>Abused at Index Stage(s)</th>
<th>Abused but Not at Index Stage(s)</th>
<th>Comparison Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus (cm³)</td>
<td>3–5</td>
<td>3.030 ± 0.215 (12)</td>
<td>3.175 ± 0.213 (9)</td>
<td>3.371 ± 0.217 (15)</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>9–10</td>
<td>70.311 ± 19.792 (6)</td>
<td>93.334 ± 18.443 (18)</td>
<td>95.958 ± 18.896 (16)</td>
</tr>
<tr>
<td>Frontal Cortex</td>
<td>14–16</td>
<td>83.589 ± 4.322 (7)</td>
<td>90.499 ± 4.355 (15)</td>
<td>88.428 ± 4.359 (14)</td>
</tr>
</tbody>
</table>
Consequences of ‘shaping‘ of the brain

Adverse Childhood Experiences and Prescribed Psychotropic Medications in Adults

Robert F. Anda, MD, MS, David W. Brown, MSPH, MS, Vincent J. Felitti, MD, J. Douglas Bremner, MD, Shanta R. Dube, PhD, MPH, and Wayne H. Giles, MD, MS

<table>
<thead>
<tr>
<th>Antipsychotic drugs</th>
<th>Mood stabilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>1.0</td>
</tr>
<tr>
<td>Score 4</td>
<td>4.8</td>
</tr>
<tr>
<td>Score 5-8</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>17.3</td>
</tr>
</tbody>
</table>

Anda et al. 2007
Programming: how does it work?
Intrauterine programming

Experimental model

maternal low protein diet (MLP) during pregnancy

- decreased birth weight (-15 %)
- thereafter „catch-up growth“
- higher insulin concentrations in MLP-pups fed a highly palatable diet

Intrauterine programming

Effects of maternal low protein diet on fetal endocrine pancreas

Holness et al. 2000
Intrauterine programming

Effects of maternal low protein diet on metabolic key pathways

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Control [U/g protein]</th>
<th>MLP [U/g protein]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucokinase</td>
<td>1.05</td>
<td>0.45</td>
</tr>
<tr>
<td>PEP-CK</td>
<td>5.8</td>
<td>8.7</td>
</tr>
</tbody>
</table>

12 week old rats:

→ glucose catabolism
→ glucose synthesis

(Desai et al. 1997, Ozanne et al. 2005)
Pre- and neonatal undernutrition

‘Low-protein-Model’
day 17 of life

Intrauterine growth restriction

(Fotos: A. Plagemann)
Intrauterine growth retardation

How does this fit to intrauterine growth retardation?

- **Fetal malnutrition**
- **Postnatal overnutrition**
- **Postnatal hyperinsulinism**

Permanent malprogramming of hypothalamic regulatory centres (food intake, body weight, metabolism)

- **Hyperphagia / Obesity**
- **Hyperinsulinemia**
- **Metabolic Syndrome**

(modified from Plagemann 2004)
An unfavourable intrauterine supply influences the metabolic and endocrine constellation of the fetus leading to reduced birth weight which favours survival under detrimental nutritional conditions after birth.

( Hales & Barker 1993 )
The degree of mismatch between the pre- and postnatal environments determines the forthcoming disposition for subsequent diseases.

(Gluckman and Hanson 2004)
Also a high birth weight has negative metabolic consequences in later life ...
Consequences of gestational diabetes

Gestational diabetes → Fetal overnutrition → Fetal hyperinsulinism → Permanent malprogramming of hypothalamic regulatory centres (food intake, body weight, metabolism) → Hyperphagia / Obesity, Hyperinsulinemia, Metabolic Syndrome

(modified from Plagemann 2004)
Metabolic programming: how does it work?

Fetal/perinatal hyperinsulinism

Hypothalamus

Hyperphagia Overweight

PVN

Neuropeptides in ARC

Leptin

Adipose tissue

Insulin

Insulin

Pancreas

(Plagemann et al. 2004)
Experimental model

- high carbohydrate milk formula via intragastric cannula for 21 d vs. control group
- hyperinsulinemia after 24 h
- lifelong increased number of Langerhans-islets
- increased risk for obesity and diabetes

(Srinivasan et al. 2003)
Experimental model:
postnatal nutrition of rat pups with milk of diabetic rats

- increased expression of neurotransmitters inducing increased feed intake
  (NPY 150 %, AGPR 280 %)
- decreased expression of neurotransmitters related to a low feed intake
  (MSH -60 %)
- lifelong hyperphagia
- development of obesity

( Fahrenkrog et al. 2003, Plagemann 2003, Armitage et al. 2005 )
The phenomenon of transgenerational effects

A high-carbohydrate milk formula (HC) induces lifelong hyperinsulinemia and insulin resistance

(Patel & Srinivasan 2002)
The spread of America's obesity epidemic

1994

% of obesity by state

10-14%

15-19%

Center of Disease Control 2010
Can we transfer results from humans and rodents on farm animals?

- nidifugous
- nidicolous

- Functional
- monogastric
- Ruminant

- Chronic diseases

- Weight gain
  Fertility
  Metabolic resilience
Established protocols for rearing of calves

- rapid separation of the calf from the dam; immediate supply with colostrum

- restrictive input of milk / milk replacer (MR) („expensive – perishable – labour-intensive“)
  
  ➢ amount
    - milk: ca. 10 % of BW / day
    - MR: 20-35 kg / calf
      454 g / calf / day

  ➢ interval of milk feeding
    - 70 days
    - 56 days
    - 35 days

- Objective: to enhance intake of starter as early as possible

Intensive postnatal feeding – a hot topic
Effects of feeding intensity in first weeks of life

Higher feeding intensity in first weeks of life

• short-term effects
  ➢ growth
  ➢ health

• long-term effects
  ➢ mammary development
  ➢ first breeding age
  ➢ first lactational yield

Growth potential of neonates is enormously high…
Postnatal feeding intensity affects the insulin response in later life

<table>
<thead>
<tr>
<th></th>
<th>Ad libitum</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calves</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Number of islets</td>
<td>9.1 ± 0.3</td>
<td>7.8 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Area of insulin stained cells (µm²)</td>
<td>107,180 ± 4,987</td>
<td>84,249 ± 4963</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

(Prokop et al., 2015)
The basis of growth: the somatotrophic axis

Hypothalamus

Pituitary

Liver

IGF-I
Postnatal feeding intensity affects the somatotropic axis

Maccari et al. 2014
Malnutrition induces an uncoupling of the somatotrophic axis
Malnutrition induces an uncoupling of the somatotropic axis

Relationships between leptin, insulin, IGF-1 and IGFBP-3 in children with energy malnutrition

Kenan Haspolat a, Aydin Ece a,*, Fuat Gurkan a, Yildiz Atamer b, Murat Tutanç a, Ilyas Yolbas a

Maccari et al. 2014
Postnatal feeding intensity affects the development of the mammary gland

(brown et al. 2005)

<table>
<thead>
<tr>
<th>Energy/protein intake 2nd to 8th week of life</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchyma (g/100 kg body weight)</td>
<td>1.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy/protein intake 8th to 14th week of life</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchyma (g/100 kg body weight)</td>
<td>16</td>
<td>15</td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>
Meta-analysis: effect of intensive postnatal feeding on subsequent milk yield

<table>
<thead>
<tr>
<th>Reference</th>
<th>Groups</th>
<th>Diff. Milk [kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foldager / Krohn, 1994</td>
<td>suckling / restrictive</td>
<td>+ 1.402</td>
</tr>
<tr>
<td>Foldager et al., 1997</td>
<td>milk ad lib. / restrictive</td>
<td>+ 572</td>
</tr>
<tr>
<td>Bar-Peled et al., 1998</td>
<td>suckling / MR</td>
<td>+ 453</td>
</tr>
<tr>
<td>Ballard et al., 2005</td>
<td>milk ad lib / conv. MR</td>
<td>+ 1.250</td>
</tr>
<tr>
<td>Rincker et al., 2006</td>
<td>intens. MR / conv. MR</td>
<td>n.s. (60 DIM)</td>
</tr>
<tr>
<td>Moallem et al., 2006</td>
<td>intens. MR / conv. MR</td>
<td>1.134</td>
</tr>
<tr>
<td>Drackley et al., 2007</td>
<td>intens. MR / conv. MR</td>
<td>+ 921</td>
</tr>
<tr>
<td>Rincker et al., 2011</td>
<td>intens. MR / conv. MR</td>
<td>+ 291</td>
</tr>
</tbody>
</table>

MR=milk replacer

Soberon and Van Amburgh, 2013
Difference in milk yield

22% of the total variance of the milk yield in the first lactation are caused by the feeding intensity in the preweaning period.

Soberon and Van Amburgh, 2013
... and what about swine?
Birth weight affects subsequent growth.

![Graph showing birth weight and live weight for different birth weight groups. The graph illustrates the impact of birth weight on subsequent growth.](image-url)
Birth weight affects body composition

<table>
<thead>
<tr>
<th></th>
<th>HW</th>
<th>LW</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>$1.89 \pm 0.02$</td>
<td>$1.05 \pm 0.04$</td>
<td>0.001</td>
</tr>
<tr>
<td>Slaughter weight, kg</td>
<td>$111.6 \pm 0.9$</td>
<td>$111.9 \pm 0.8$</td>
<td>NS</td>
</tr>
<tr>
<td>Age at slaughter, d</td>
<td>$159.5 \pm 2.4$</td>
<td>$171.1 \pm 2.5$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Total average daily gain, g/d</td>
<td>$690 \pm 12$</td>
<td>$650 \pm 9$</td>
<td>0.008</td>
</tr>
<tr>
<td>Feed consumption, g/d</td>
<td>$2.25 \pm 0.06$</td>
<td>$2.28 \pm 0.05$</td>
<td>NS</td>
</tr>
<tr>
<td>Feed conversion ratio, g/g</td>
<td>$2.49 \pm 0.04$</td>
<td>$2.70 \pm 0.06$</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Carcass</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot carcass weight, kg</td>
<td>$89.5 \pm 0.6$</td>
<td>$90.2 \pm 0.7$</td>
<td>NS</td>
</tr>
<tr>
<td>Perirenal fat weight, g</td>
<td>$945 \pm 49$</td>
<td>$1226 \pm 69$</td>
<td>0.002</td>
</tr>
<tr>
<td>Backfat depth, mm</td>
<td>$15.0 \pm 0.4$</td>
<td>$18.2 \pm 0.7$</td>
<td>0.002</td>
</tr>
<tr>
<td>Estimated lean meat content</td>
<td>$63.0 \pm 0.2$</td>
<td>$61.1 \pm 0.4$</td>
<td>0.002</td>
</tr>
</tbody>
</table>

(Gondret et al. 2005)
Postnatal feeding intensity affects subsequent fertility

(Flowers 2008)
Conclusions

Environ-
ment

Developmental
plasticity

Genotype

Adult
phenotype
Thanks for your attention!