Impacts of prenatal malnutrition and an early obesogenic diet on adipose tissue morphology and gene expression in adult sheep

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Introduction: Adipose tissue and metabolic disorders

- Adipose tissue- appear from mid gestation onwards (Symonds et al., 2012)
- Sensitive to *in utero* nutritional insults (under- and overnutrition)~ predisposed for abdominal adiposity and metabolic disorders (Khanal et al., 2014)
- Adipose tissue expansion occurs by two different mechanisms

In obesity, adipose tissue expansion;
1. **Hypertrophic** (increased adipocyte size)
2. **Hyperplasic** (increased adipocyte number) (Cheo *et al.*, 2016)
Objectives

• In the present study, we aimed to investigate whether;

  1) phenotypic manifestations in adulthood of such a prenatal programming on adipose tissue structure and functional traits (gene expression) can be affected by the nutrition exposure in early postnatal life, and

  2) whether dietary correction later in life can reverse the long-term consequences of early life malnutrition

  3) whether mechanisms of expansion are affected?
Materials and methods

Sheep: Cross breed Texel ewes

Prenatal (late gestational) diet:
NORM: Normal; LOW: Undernutrition; HIGH: Overnutrition

Early postnatal:
CONV: Conventional/ moderate (hay and milk replacer (only until 8 weeks))
HCHF; High-starch-high-fat (cream milk replacer mix in a 1:1 ratio supplemented with rolled maize)

Adipose tissue histology (subcutaneous, mesenteric, perirenal and epicardial)

Gene expression:
- Lipolysis (ATGL, CGI-58, FABP4, HSL, leptin, PLIN-1)
- Lipogenesis (LPL, FAS)
- Glucose metabolism (FBPase, GLUT-1)
- Insulin signaling (AdipoQ, GLUT-4)
- Cell differentiation/proliferation (CD34, CD44, GcR, IGF1R, PPARγ, TGF-β1)
- Angiogenesis (VEGF, VEGF-A)
- Inflammation (IL6, MCP-1, TLR-4)
Effect of ewe diet*lamb diet*sex on adipocytes size

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Epicardial adipocytes size
Subcutaneous adipose tissue

Males

NORM CONV: M
NORM HCHF: M
LOW CONV: M
LOW HCHF: M
HIGH CONV: M
HIGH HCHF: M

Females

NORM CONV: F
NORM HCHF: F
LOW CONV: F
LOW HCHF: F
HIGH CONV: F
HIGH HCHF: F
Subcutaneous adipose tissue

- Reduced hyperplasic growth

Genes involved in adipogenesis and angiogenesis:

Prenatal x gender:

Prenatal x postnatal:

(Adapted from Lise K. Lyngman' master thesis (2017))
Mesenteric adipose tissue

Males

NORM CONV: M

NORM HCHF: M

LOW CONV: M

LOW HCHF: M

HIGH CONV: M

HIGH HCHF: M

Females

NORM CONV: F

NORM HCHF: F

LOW CONV: F

LOW HCHF: F

HIGH CONV: F

HIGH HCHF: F
Perirenal adipose tissue

Males

NORM CONV: M
NORM HCHF: M
LOW CONV: M
LOW HCHF: M
HIGH CONV: M
HIGH HCHF: M

Females

NORM CONV: F
NORM HCHF: F
LOW CONV: F
LOW HCHF: F
HIGH CONV: F
HIGH HCHF: F

Males

NORM CONV: M
NORM HCHF: M
LOW CONV: M
LOW HCHF: M
HIGH CONV: M
HIGH HCHF: M

Females

NORM CONV: F
NORM HCHF: F
LOW CONV: F
LOW HCHF: F
HIGH CONV: F
HIGH HCHF: F
Perirenal adipose tissue

- The HIGH-HCHF and LOW-HCHF groups showed distinct fat deposition patterns
- These groups do not stand out in terms of gene expression

(Adapted from Lise K. Lyngman's master thesis (2017))
Epicardial adipose tissue

Males

NORM CONV: M

NORM HCHF: M

NORM CONV: F

NORM HCHF: F

LOW CONV: M

LOW HCHF: M

LOW CONV: F

LOW HCHF: F

HIGH CONV: M

HIGH HCHF: M

HIGH CONV: F

HIGH HCHF: F

Females
Epicardial adipose tissue

- Targeted by postnatal diet
- Genes lipid metabolism (lipid synthesis and breakdown) and adipogenesis - up-regulated (HCHF groups)

(Adapted from Lise K. Lyngman’s master thesis (2017))
Conclusion

• Subcutaneous and perirenal, but not mesenteric and epicardial adipose tissues were targets of fetal programming with long-term implications for structure and gene expression, which were expressed in LOW irrespective of the postnatal diet, but surprisingly in HIGH mostly upon exposure to the mismatching CONV diet.

• Implications of early obesity development were not reversed by dietary correction later in life, and were expressed mostly in epicardial tissue.

• Pre- and/or early postnatal malnutrition predisposes for (presumably less healthy) hypertrophic rather than hyperplasic growth, and males appeared to attain a more female-like phenotype upon exposure to malnutrition in early life.

• Structural changes in particularly mesenteric and perirenal adipose tissue could not be explained by altered expression of the studied genes, and other mechanisms must be involved.

• Fetal programming is "heritable" – programmed animals should not enter reproduction

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References


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