UNIVERSITY OF COPENHAGEN
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Faculty of Health and Medical Sciences

Foetal programming and long-term implications for metabolic and endocrine function

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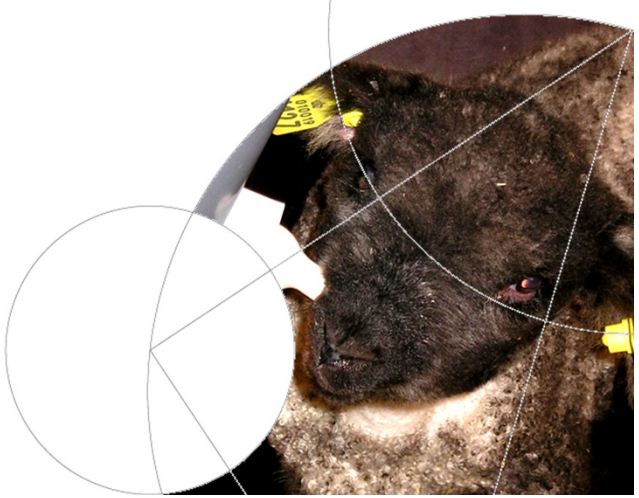
Centre for Fetal Programming

EAAP Tuesday 26 August 2014



Low *and high* birth weight increase disease risk in adult life

Barker, 1998

Low *and high* birth weight increase disease risk in adult life

In DK: appr. 25% of babies have birthweights deviating more than 10-15% from the average.
Are all at risk?
No!!! But some of them!!!

Is birth weight a reliable marker?
No!!! Compensatory growth later in gestation

After 25yrs of research can we point out the ones at risk?
No, not with certainty!!!

Do we have a cure or a treatment?
No, not yet !!!

Aim of studies

Improve understanding of:

- Mechanisms underlying malnutrition induced fetal programming
- How manifestation of fetal programming is impacted by the postnatal diet

- Biological markers -> ID of programmed individuals early in life
- Intervention strategies (dietary?) -> Reverse/alleviate adverse programming outcomes

Fetal programming: The sheep as experimental model

Advantages:

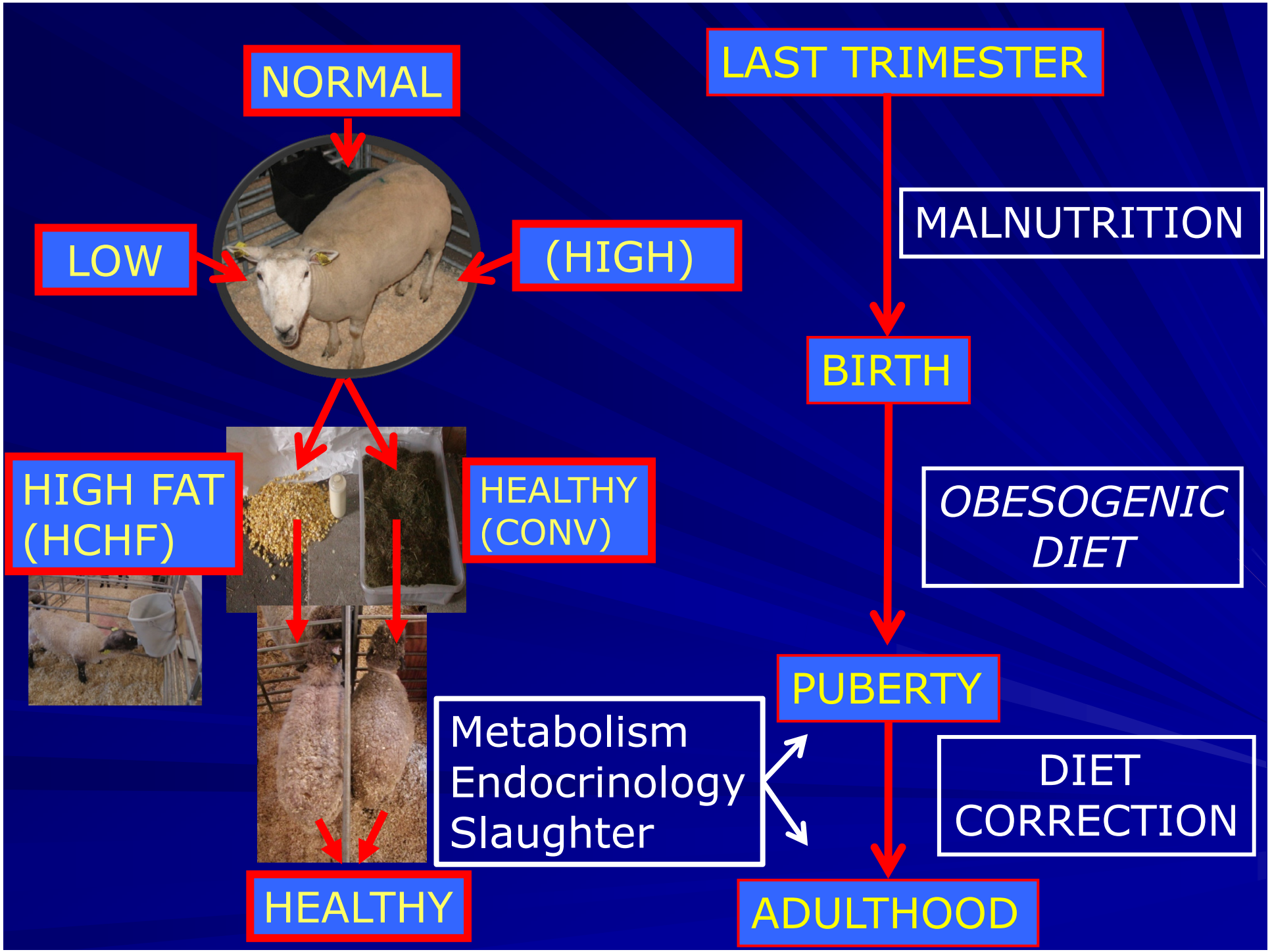
- Size (50-75 kg)
- **Litter size: Singletons and twins (triplets)**
- **Long gestation (time windows; ~147 d)**
- Interventions possible without abortion
  - Fetal intervention studies (catheterisations)
- **Off-spring at birth: comparable to the human**
  - ***Last trimester interventions***

Fetal programming: The sheep as experimental model

Disadvantage:

- **Ruminants** ie. distinctive digestive function
  - Little glucose absorption (SCFA)
  - Tolerate rather low levels of fat in the diet
- Makes **postnatal dietary interventions** difficult to study
  - But **special tricks can be applied**
  - Suckling
    - Esophageal groove reflex
    - **By-pass rumen (liquid feed)**

Nielsen et al. 2013. Brit J Nutr 109, 2098-2110


NORMAL
LOW
(HIGH)
HIGH FAT
(HCHF)
HEALTHY
(CONV)
HEALTHY
LAST TRIMESTER
MALNUTRITION
BIRTH
OBESOGENIC
DIET
PUBERTY
Metabolism
Endocrinology
Slaughter
DIET
CORRECTION
ADULTHOOD

Metabolic, endocrine and fasting tolerance tests – 6 mo + 2 years

1. Intravenous bolus injections of:
    1. glucose, insulin (nutrient surplus)
    2. propionate (hepatic gluconeogenesis; fed+fasted)
    3. fasting (nutrient deficiency)
    4. thyroxine (thyroid hormone axis)
2. Blood sampling at specific time points after injections OR onset of fasting

6 months old lambs

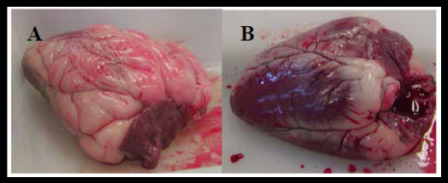
- By the end of the period of differential postnatal feeding

Growing lambs (6 months):

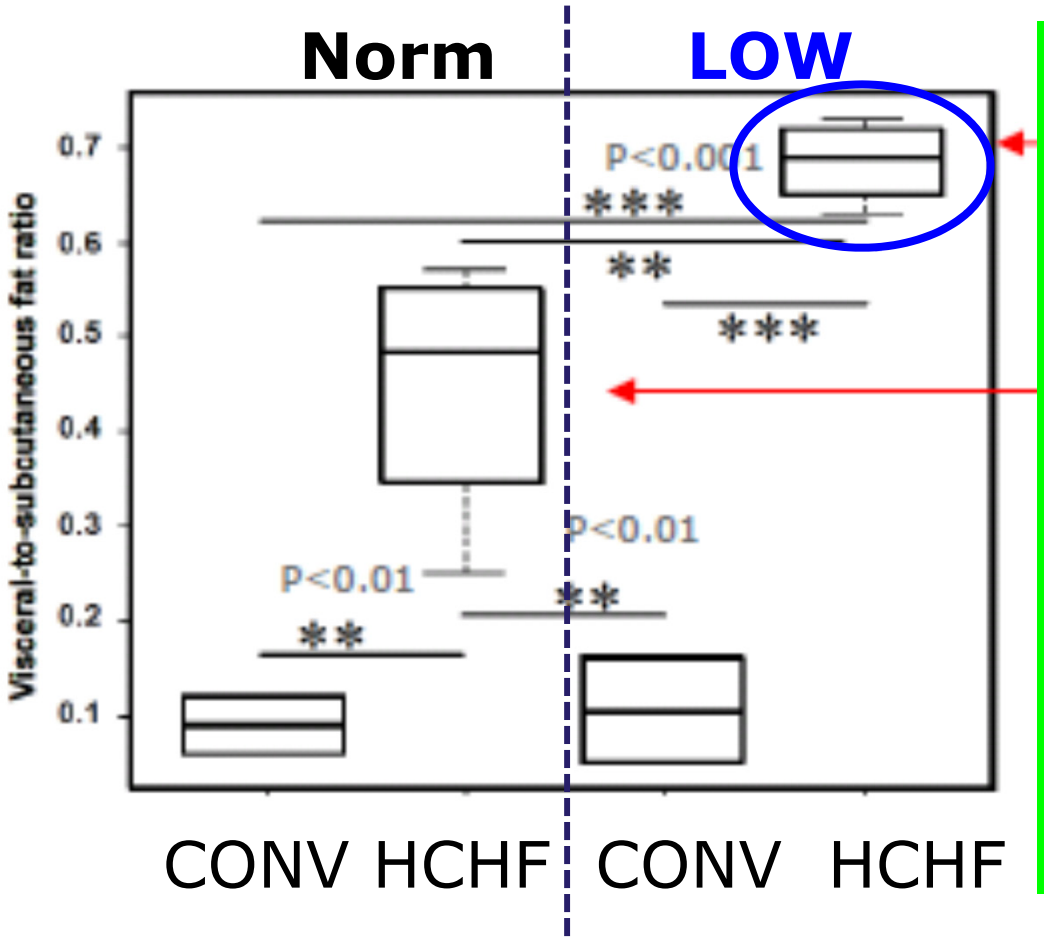
HCHF

Fat% in soft tissue in HCHF: ~ 30 (obese)

CONV



Visceral:subcutaneous fat ratio (6 mo) (CT scanning)



Prenatal LOW
+Postnatal HCHF:

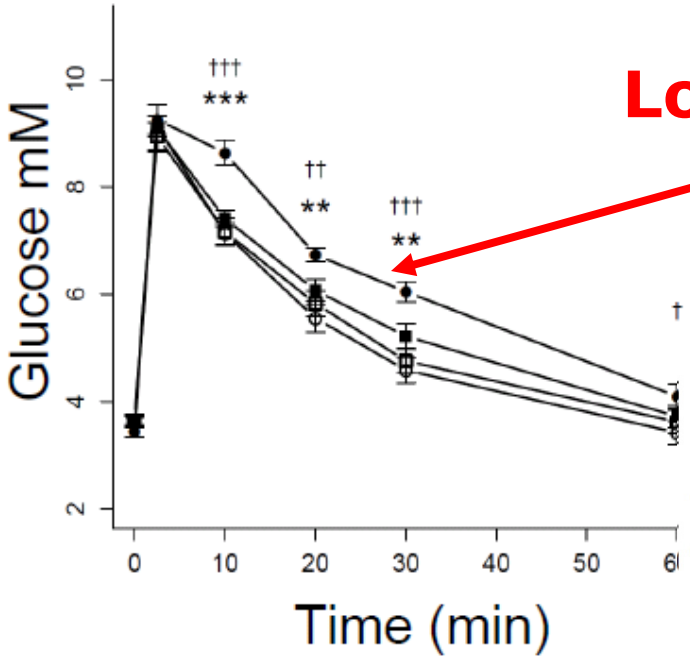
- Worst case scenario:
  ↑ Visceral adiposity
- ↓Subcutaneous expandability?

Humans:

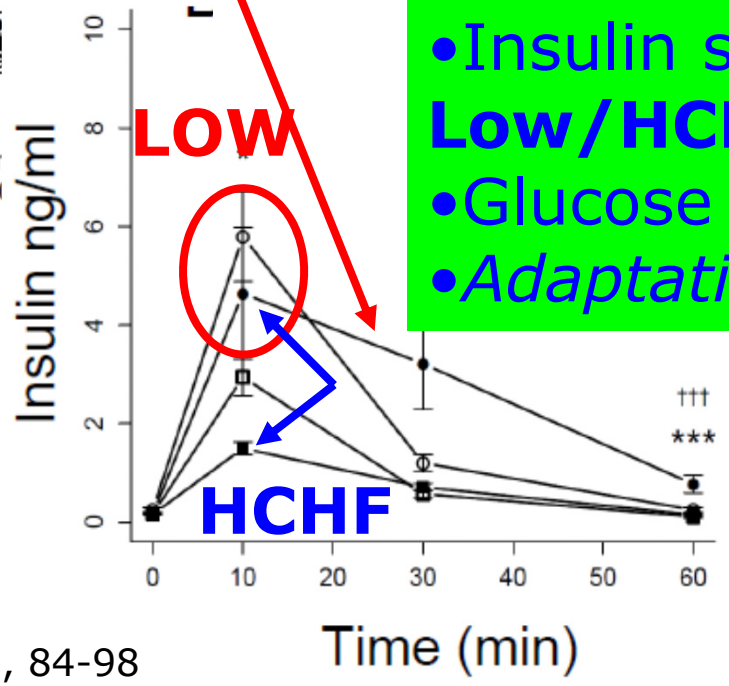
- Insulin insensitivity
- Metabolic syndrome

Nielsen et al. 2013. Brit J Nutr 109, 2098-2110

Glucose tolerance test - 6 mo: Worst case = glucose intolerant



Low/HCHF



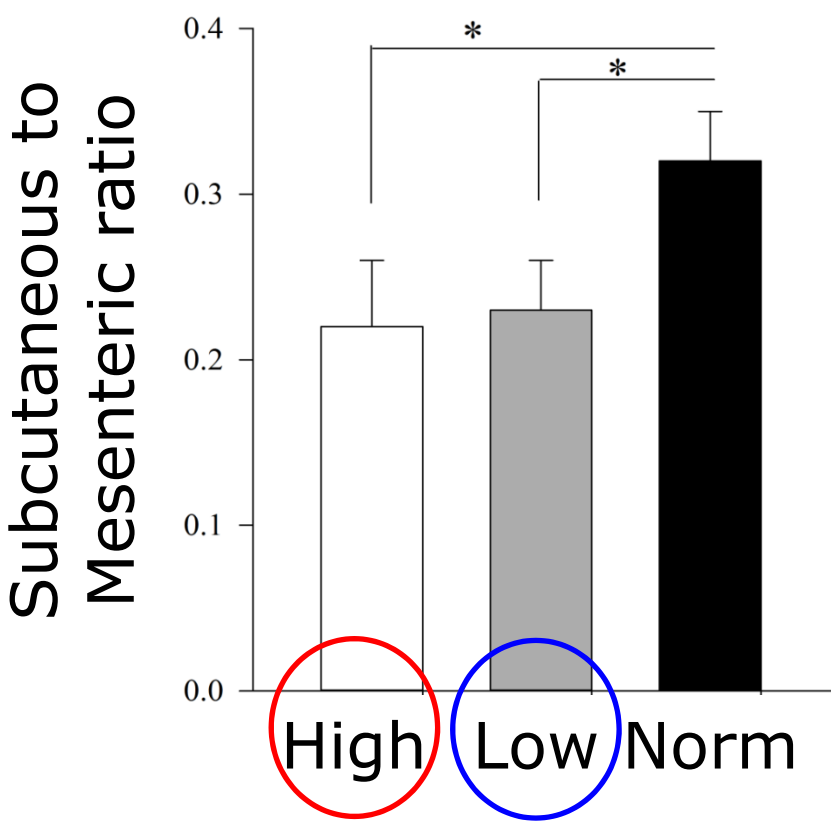
Low:
- Insulin insensitive
- Pancreatic stress↑?

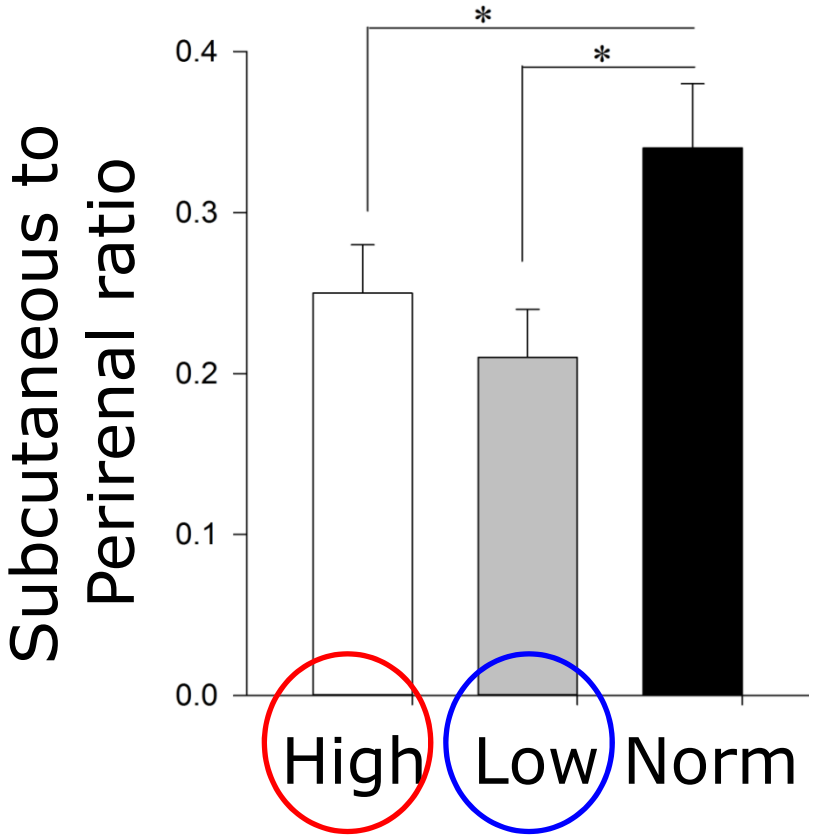
HCHF:
- Insulin secretion ↓
- Insulin sensitivity↑

Low/HCHF:
- Glucose intolerant
- *Adaptation conflict!*

Kongsted et al. 2014. Acta Physiol 210, 84-98

Fat distribution patterns



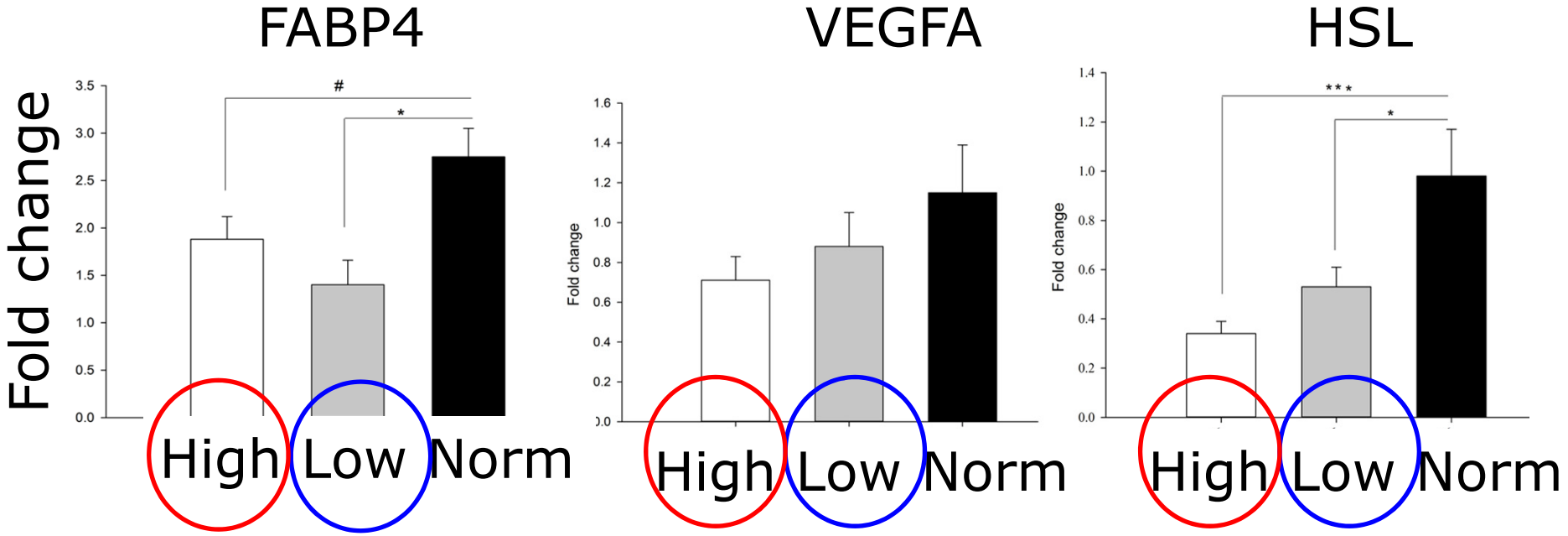


Prenatal **overnutrition** and **undernutrition:**

- *lower deposition* of subcutaneous adipose tissue
- associated with visceral adipocity

Khanal et al . (2014) Acta Physiologica 210, 110-126

Gene expression (subcutaneous fat)



Prenatal **overnutrition** and **undernutrition**:

- ↓ Fatty acid transport (Fatty acid binding protein 4)
- ↓ Vasculogenesis/angiogenesis (Vascular endothelial growth factor A)
- ↓ Fatty acid release (Hormone sensitive lipase)

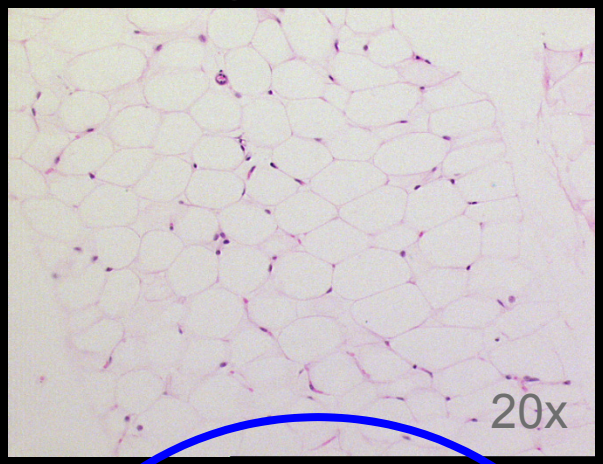
Khanal et al . (In preparation)

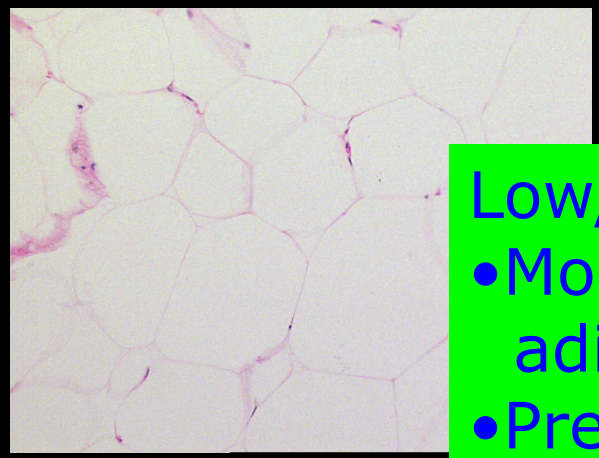
Subcutaneous adipose tissue - 6 mo. (H&E staining)

Postnatal CONV

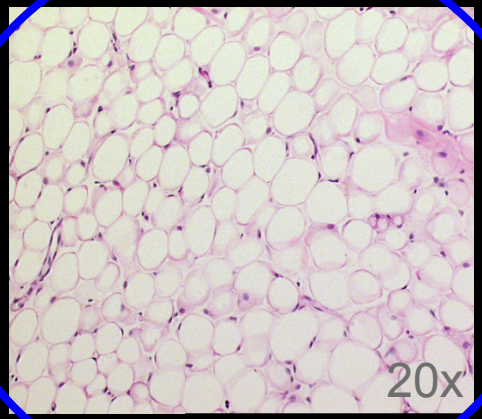
Postnatal HCHF

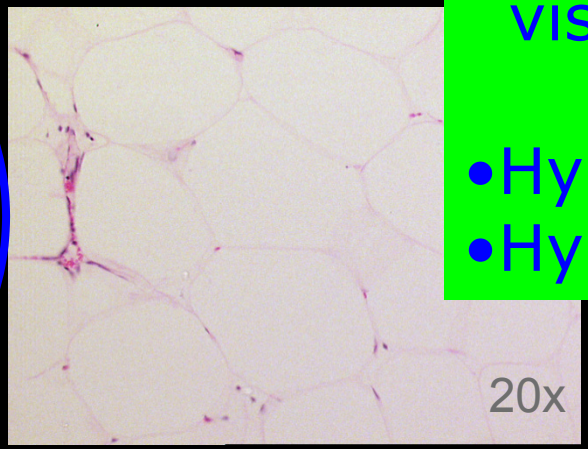
Prenatal Norm





Prenatal Low





Low/CONV:

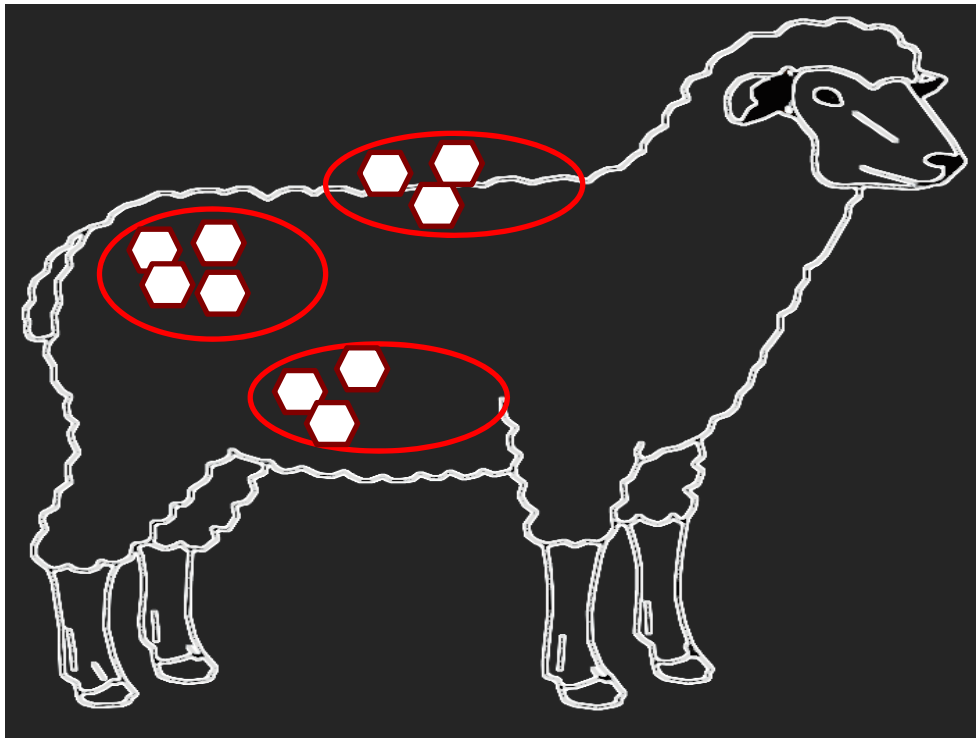
- More premature adipocytes?
- Predisposing for visceral adiposity?

⬇

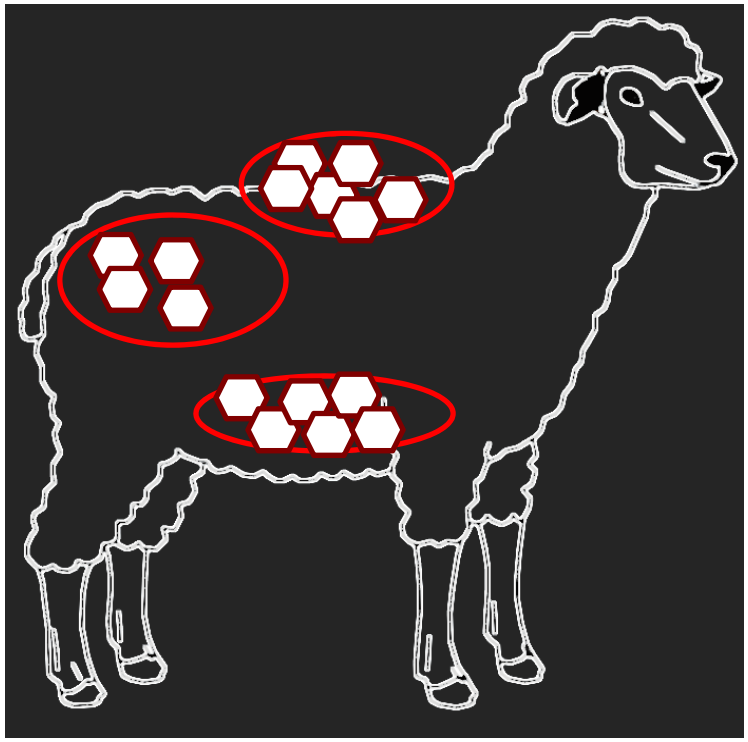
- Hyperplasia?
- Hypertrophy?

Cell no. index: Non-obese state

HIGH and **LOW**



NORM



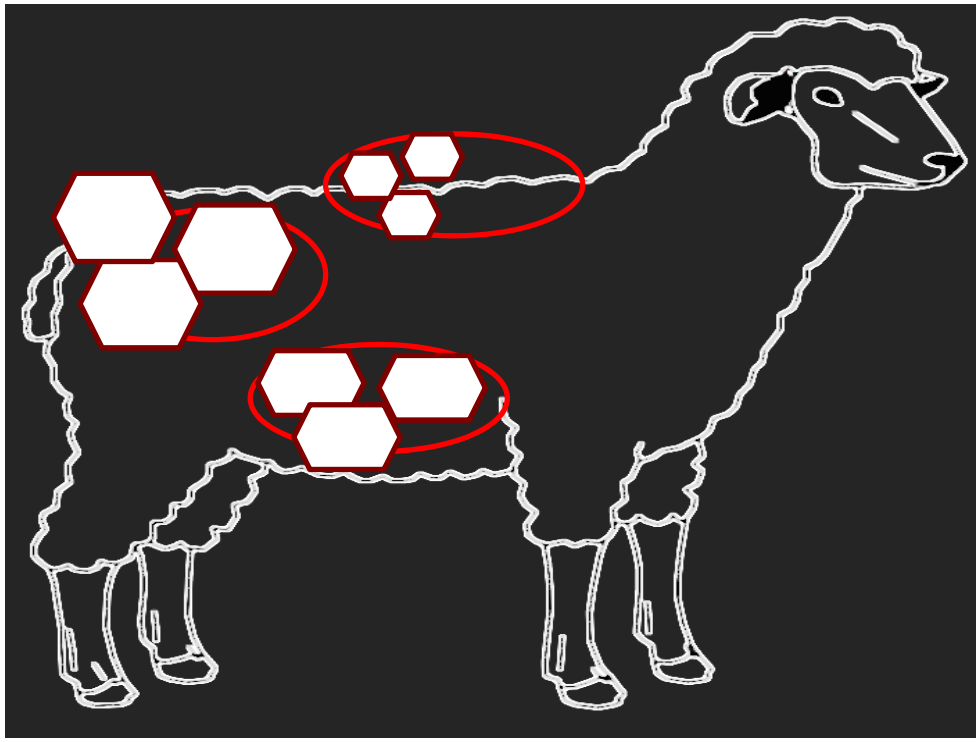
Prenatal **overnutrition** and **undernutrition**:

- Reduce ***non-obese cellularity*** in subcutaneous and mesenteric fat

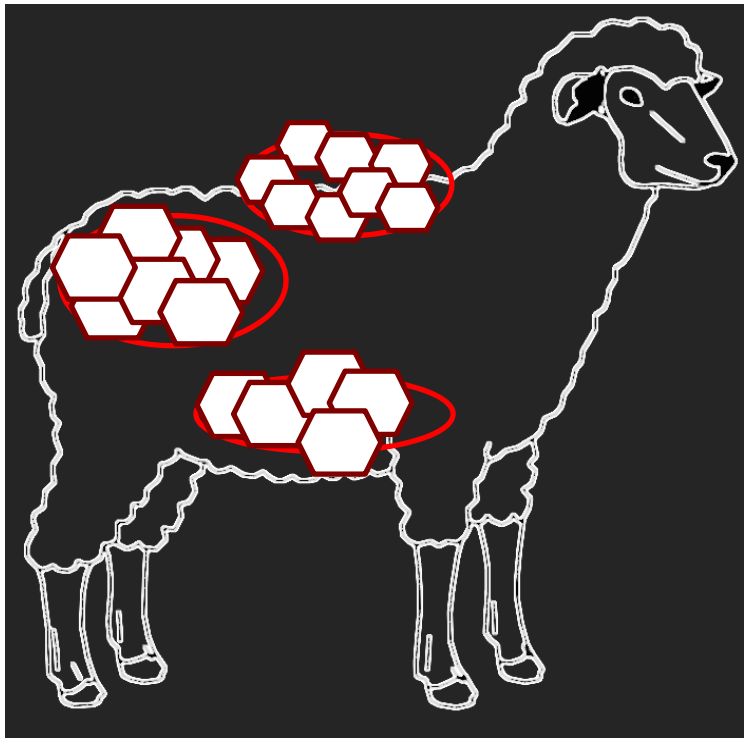
Khanal et al . (In preparation)

Cell no. index: Obesity-induced

HIGH and **LOW**



NORM



Prenatal **overnutrition** and **undernutrition**:

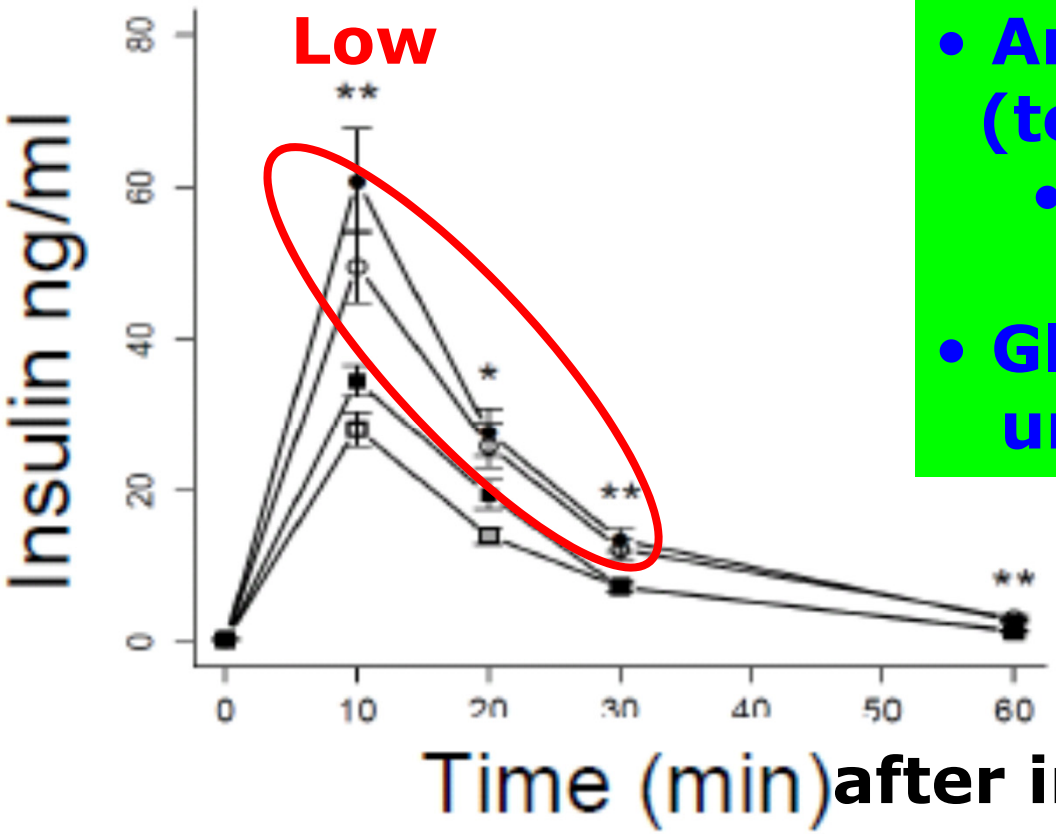
- ↓ Obesity-induced hyperplasia in subcutaneous, mesenteric and particularly perirenal fat
- ↑↑Obesity-induced hypertrophy in perirenal fat
  - In LOW also in mesenteric fat

2-2½ years adult sheep

- After 1½ - 2 years on a moderate diet
  - HCHF: body fat correction

Insulin tolerance test - adults: Insulin response

Prenatal: Low

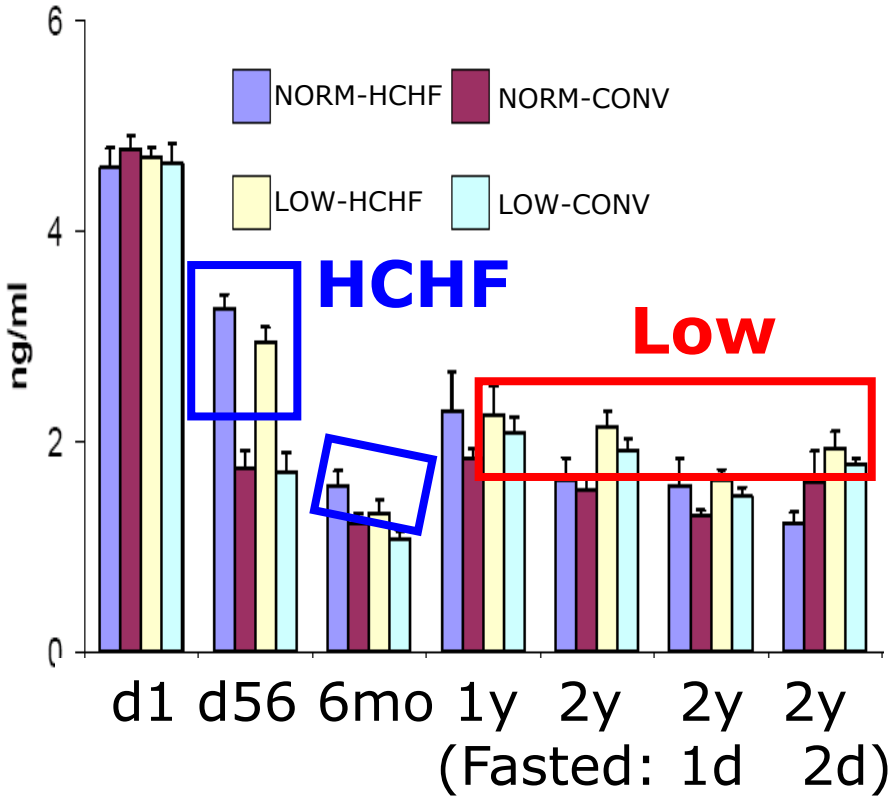


Low:
- ***Insulin insensitive*** **!**
- **Amplified in HCHF (tendency)**
  - **Higher AUC insulin**
- **Glucose tolerance unaffected**

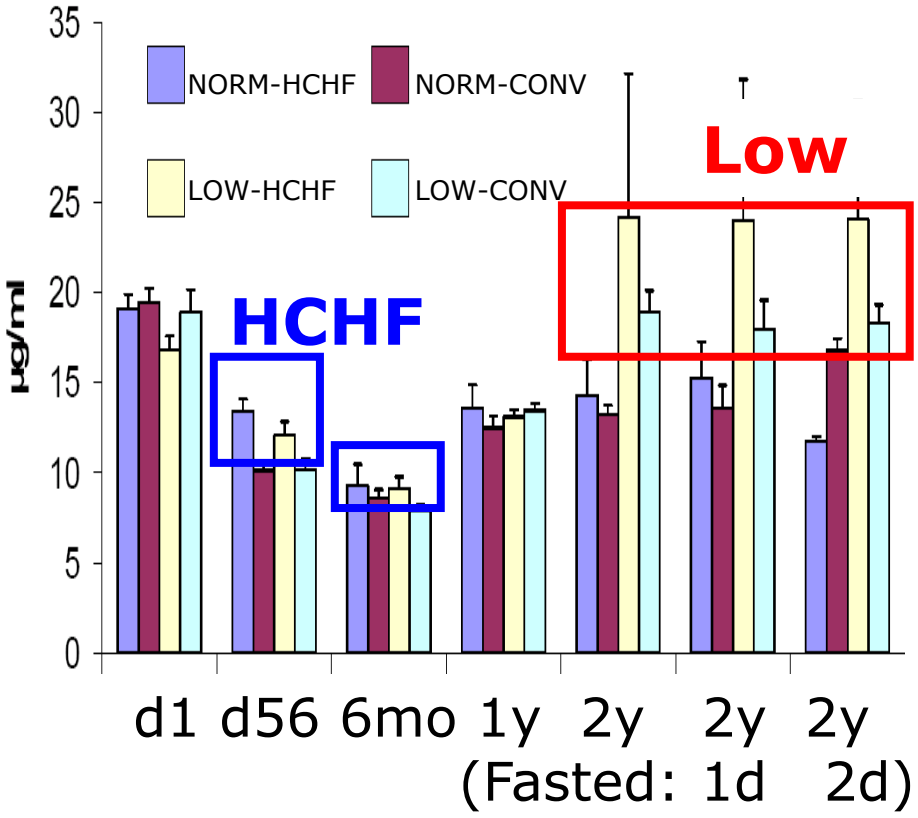
Kongsted et al. 2013. Acta Physiol 210, 84-98

Plasma T3 and T4 (age)

Total T3

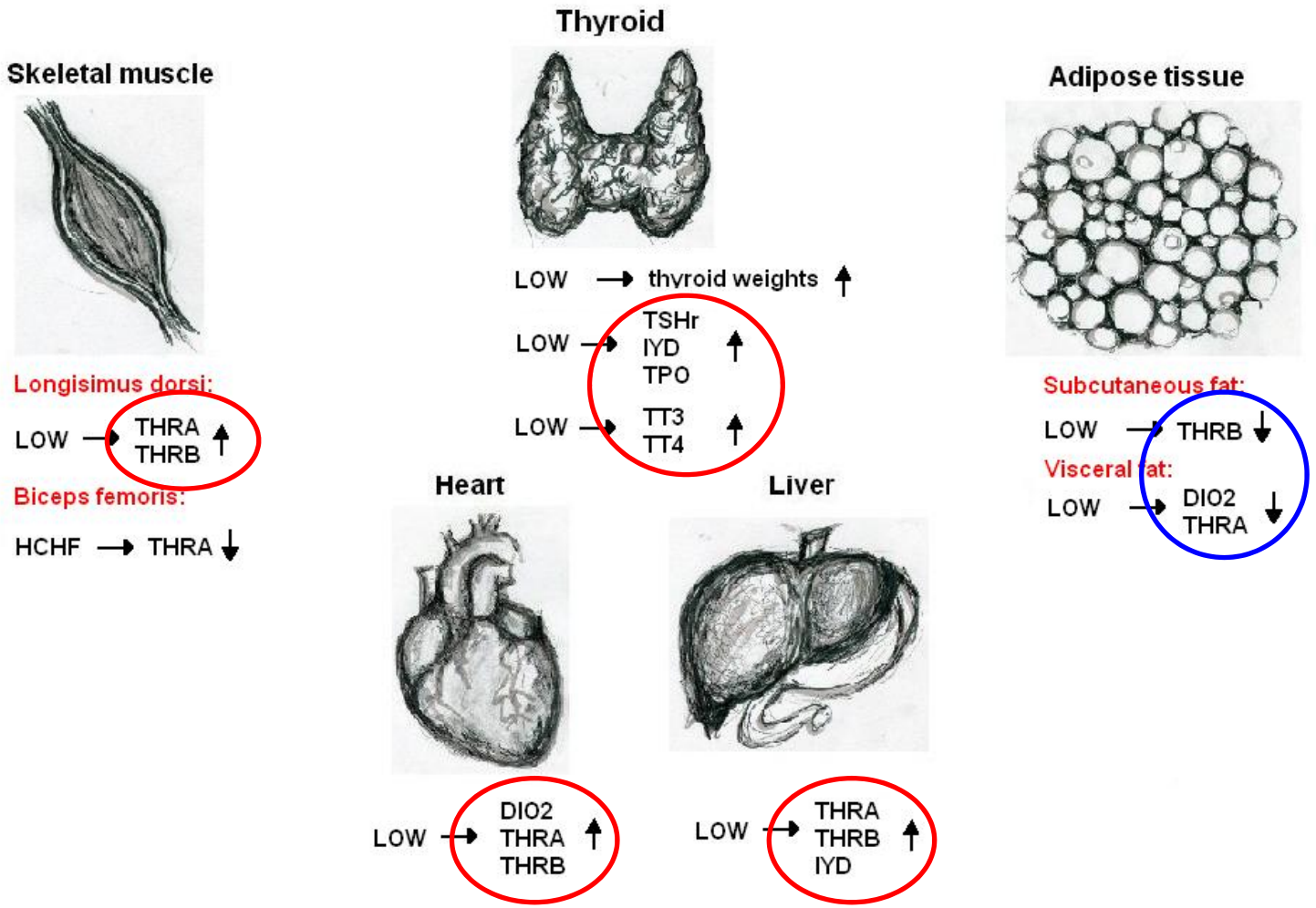


Total T4



Johnsen et al 2013. J Endocrinology 216, 389-402

Thyroid hormone axis function: Young adult sheep



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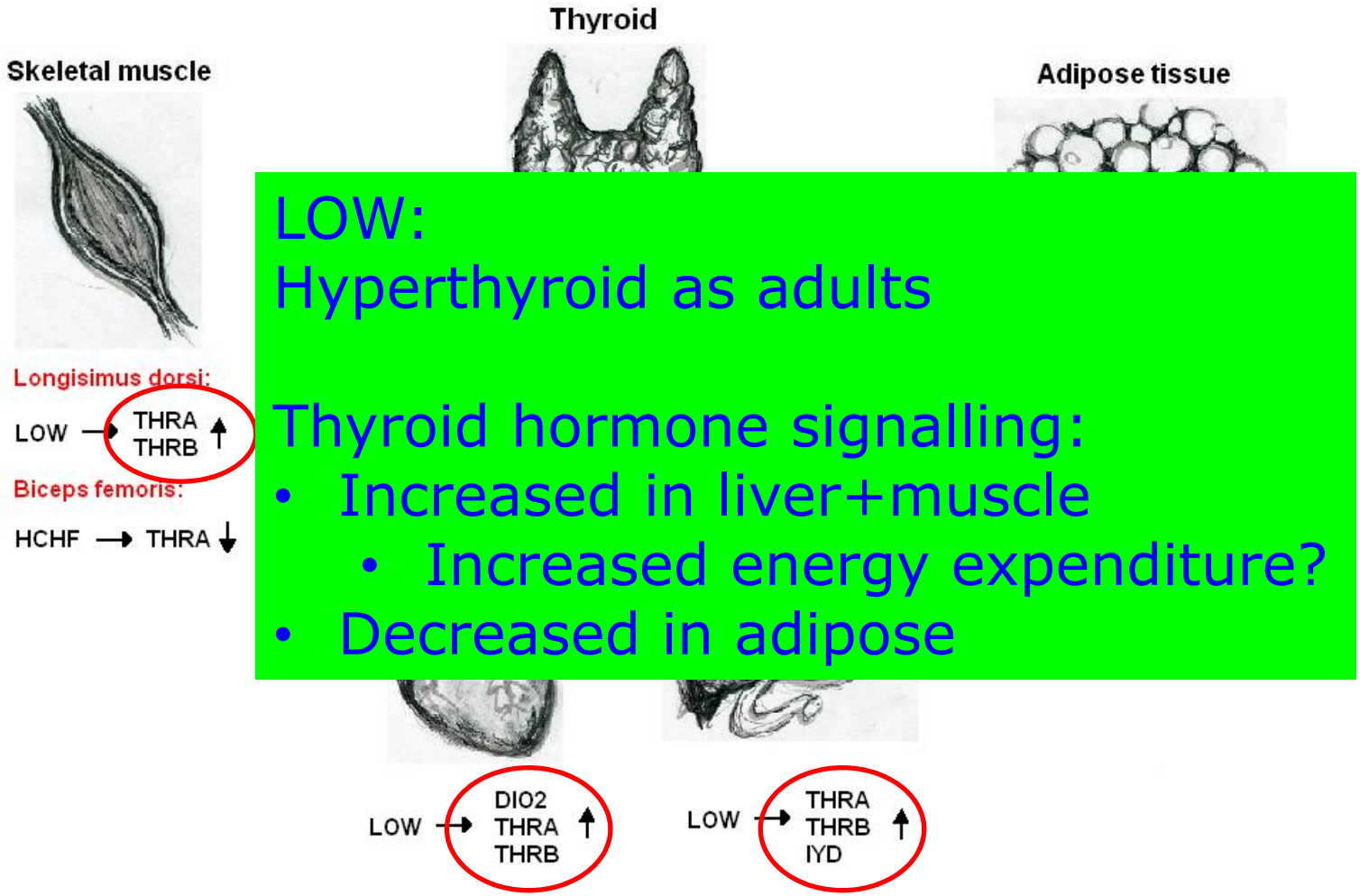
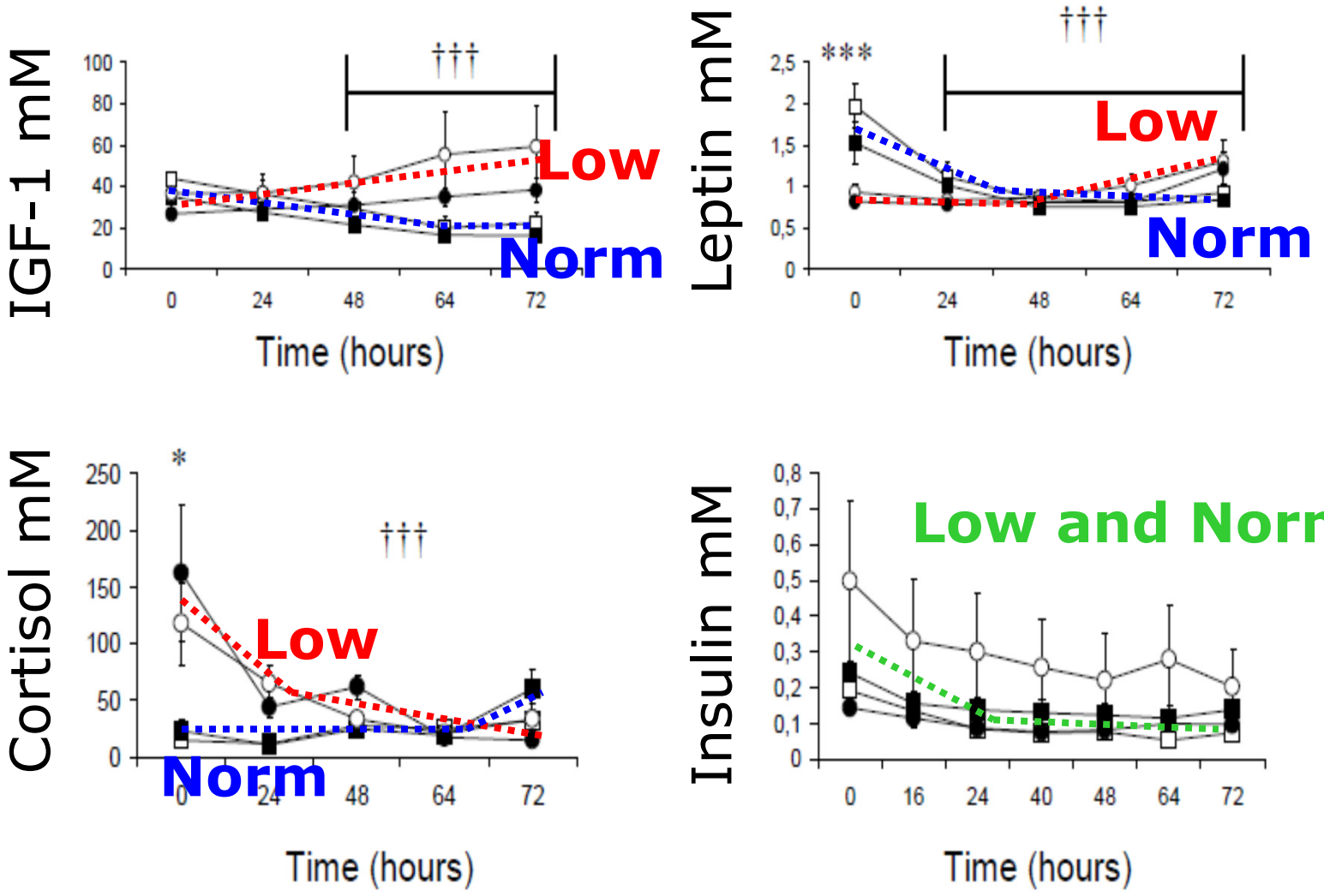


LOW:
Hyperthyroid as adults

Thyroid hormone signalling:
- Increased in liver+muscle
  - Increased energy expenditure?
- Decreased in adipose

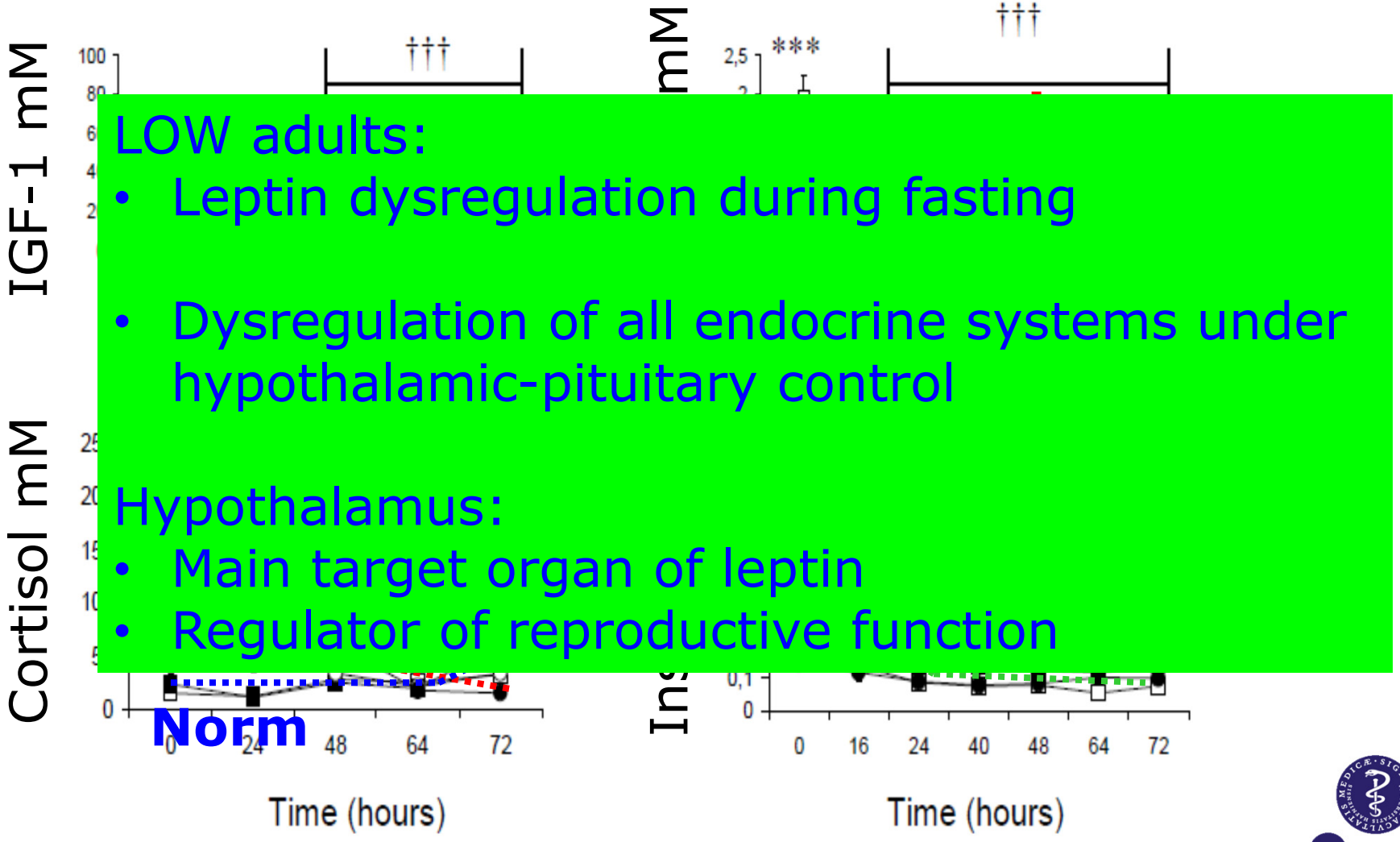
Johnsen et al 2013. J Endocrinology 216, 389-402

Endocrine adaptive responses to fasting – adult sheep



Kongsted et al. 2013. J Endocr 219, 159-171

Endocrine adaptive responses to fasting -adult sheep



LOW adults:

- Leptin dysregulation during fasting
- Dysregulation of all endocrine systems under hypothalamic-pituitary control

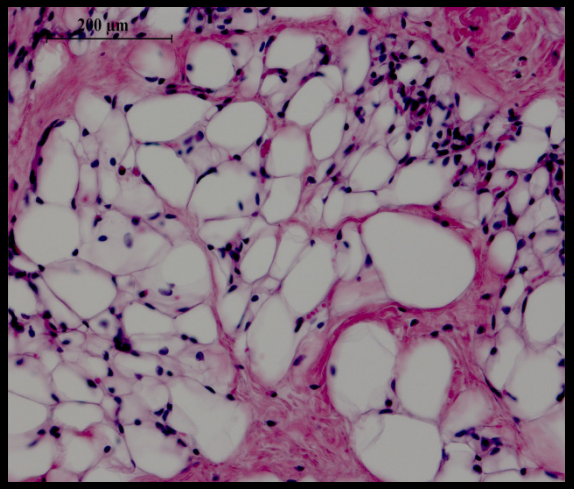
Hypothalamus:

- Main target organ of leptin
- Regulator of reproductive function

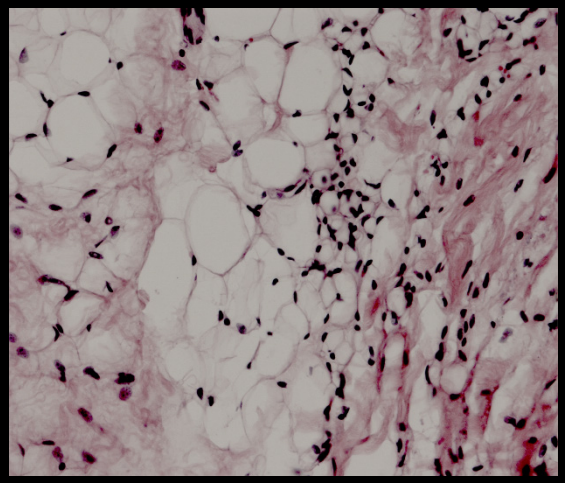
Kongsted et al. 2013. J Endocr 219, 159-171

Subcutaneous adipose tissue (H&E staining) – 24 mo. – prenatal LOW

Low-CONV

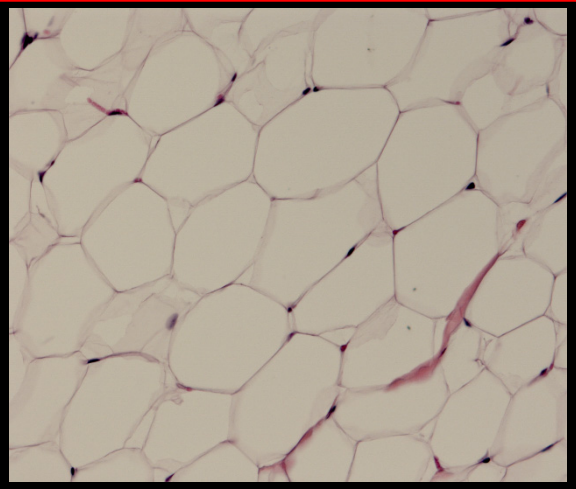


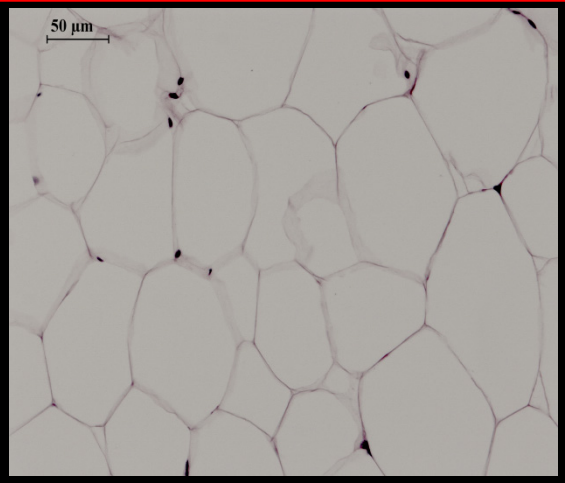
LOW



Low-HCHF

Norm-CONV

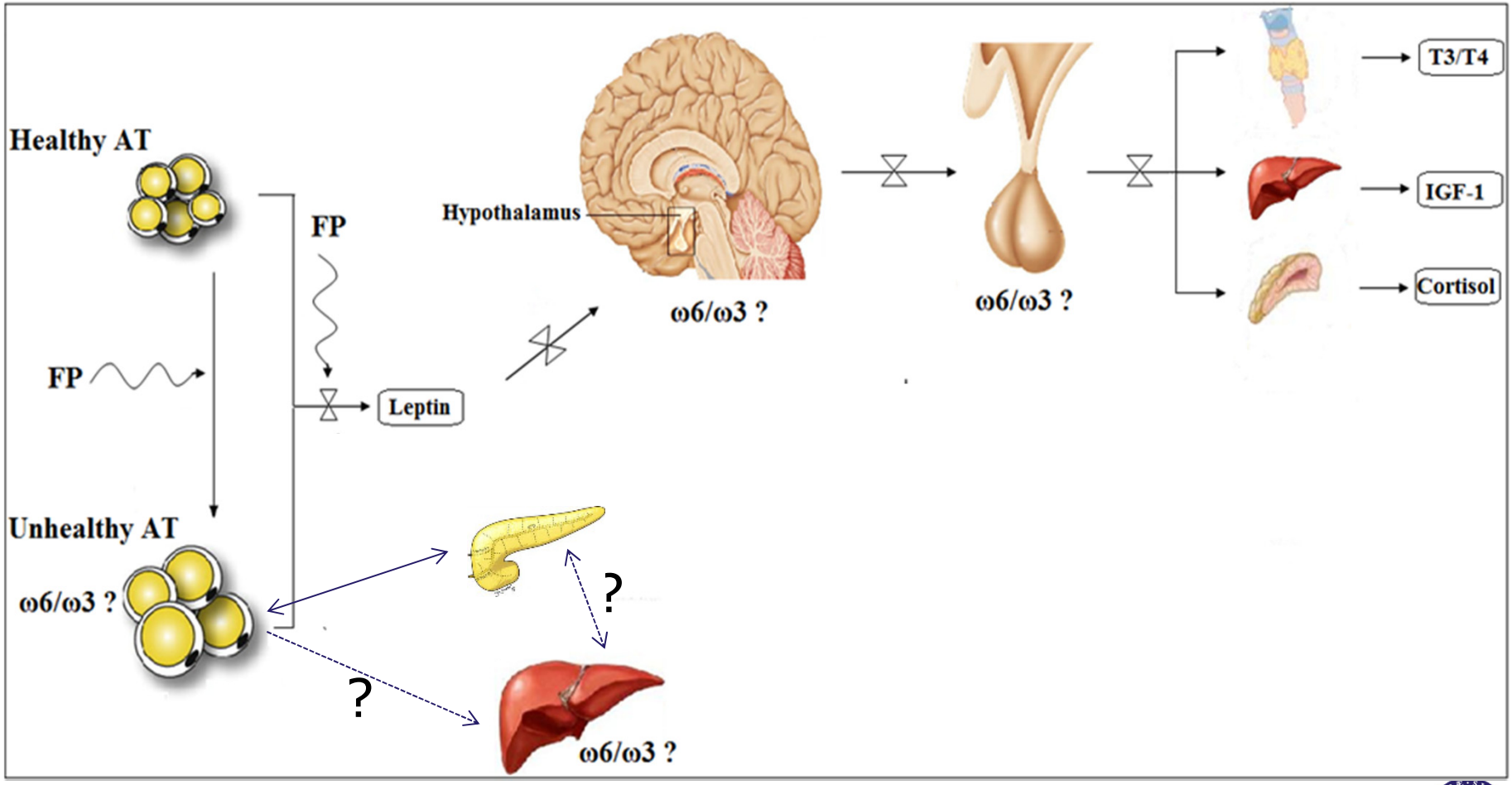




Norm-HCHF

Hou et al. In preparation

Fetal programming complex ?



What have we learnt from sheep ?

1. Malnutrition in late fetal life:
    1. Reduces birth weight (”marker” – but bad one)
    2. Growth stops earlier (smaller adult body size)
    3. Development of important organs is affected
        1. (Subcut.) adipose, liver, thyroid, (adrenals)
        2. Not muscle ! (Hou et al. 2014. PLoS ONE 8, 6, e65452)
    4. Metabolic and endocrine function changed
        1. Glucose-insulin axis
        2. Hypothalamus-pituitary controlled systems: Thyroid hormones, GH-IGF-1, corticosteroids
        3. Adipose-leptin dysregulation ↔ hypothalamus?
        4. Increasingly manifested with age

What have we learnt from sheep?

2. Impacts of an unhealthy diet after birth:
   1. Can to a remarkable extent be corrected by diet and body fat correction later in life

3. Is birth a critical set-point for many permanent programming effects (precocial animals)?

Management strategies ?

- ✓ **Prevention:** special attention to peri-conceptional and pre-partum nutrition = periods with greater risk of programming
- ✓ **Avoid negative production implications**: slaughter animals before adulthood
- ✓ **Avoid transgenerational transfer:** programmed animals should not be used in reproduction

Reproduction ???

- All other hypothalamic-pituitary axes affected

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Questions ?