EARLYNUTRITION

Long-term effects of early nutrition on later health

Regulatory Role of the Placenta in Materno-Fetal Nutrient Transfer

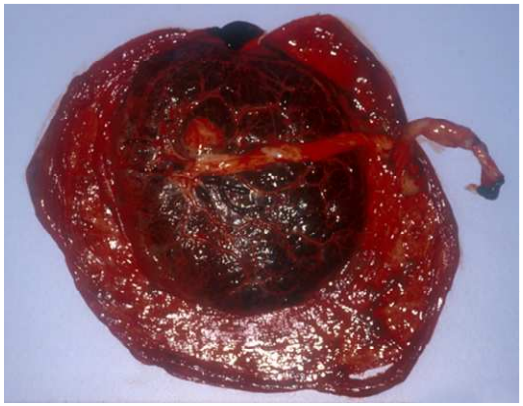
Kick-off Meeting, March 21-23, 2012

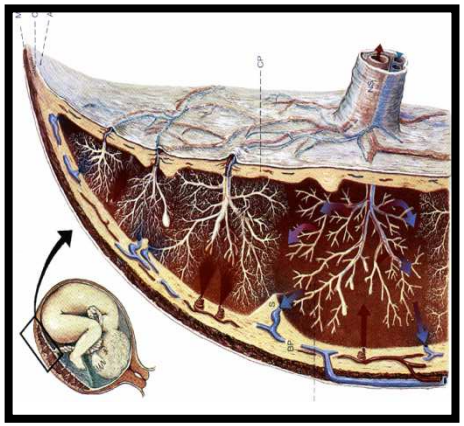
Gernot Desoye

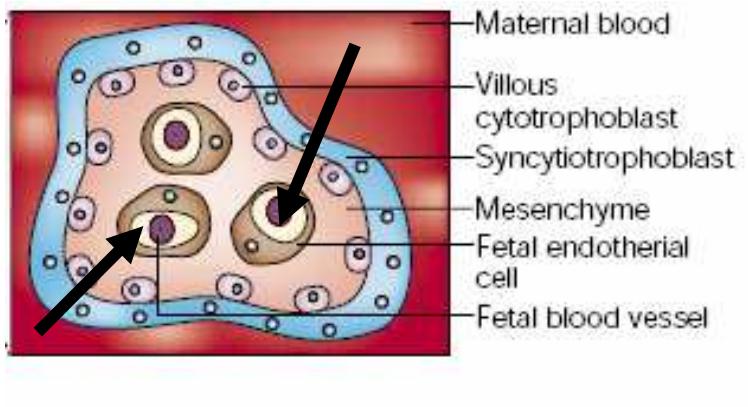
For non commercial-purposes only

This project receives funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 289346

The Human Placenta

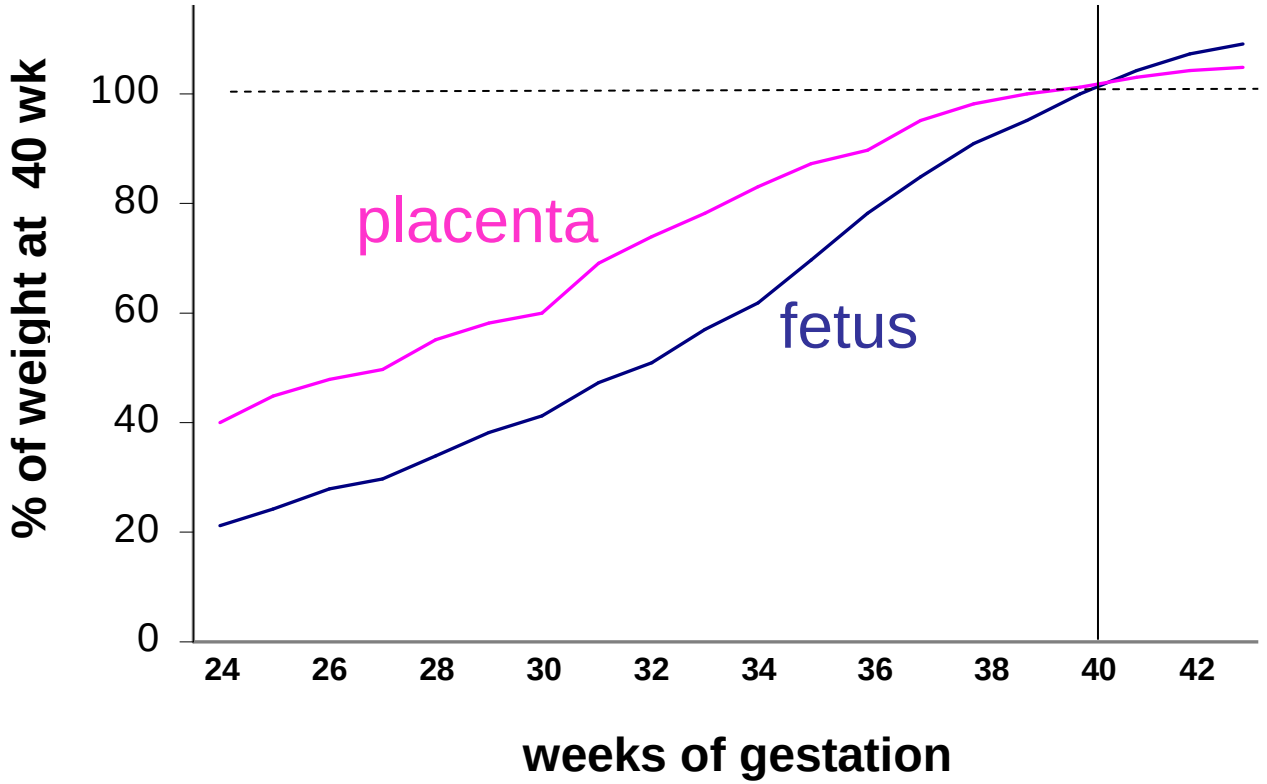






Moe et al, 1995; Rossant & Cross Nature Rev Gen 2001

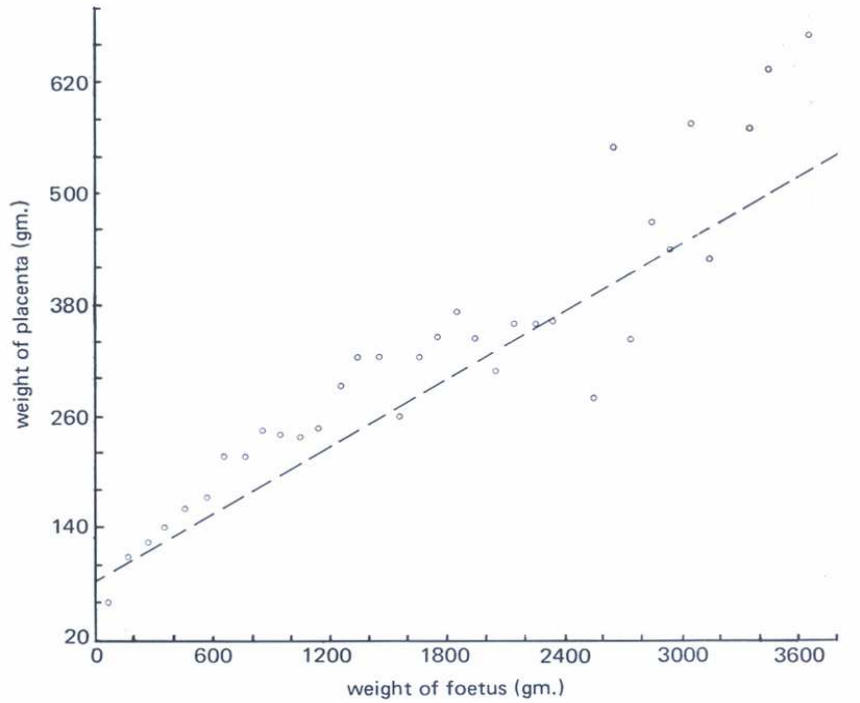
Placental growth precedes foetal growth



Hendricks Obstet Gynecol 24:357, 1964

Foetal and placental weight correlate

Weight/Diameter



1g placenta tissue sustains:

Human	6 g
Rat/Mouse	10 g
Sheep	10 g
Guinea Pig	20 g

Boyd & Hamilton, The Human Placenta 1970; Desoye & Shafrir, Mol Asp Med 1994

Foetal anthropometric parameters* directly associated with:

- Placental volume at week 14 of gestation
- Rate of placental growth between week 14 and 17 of gestation

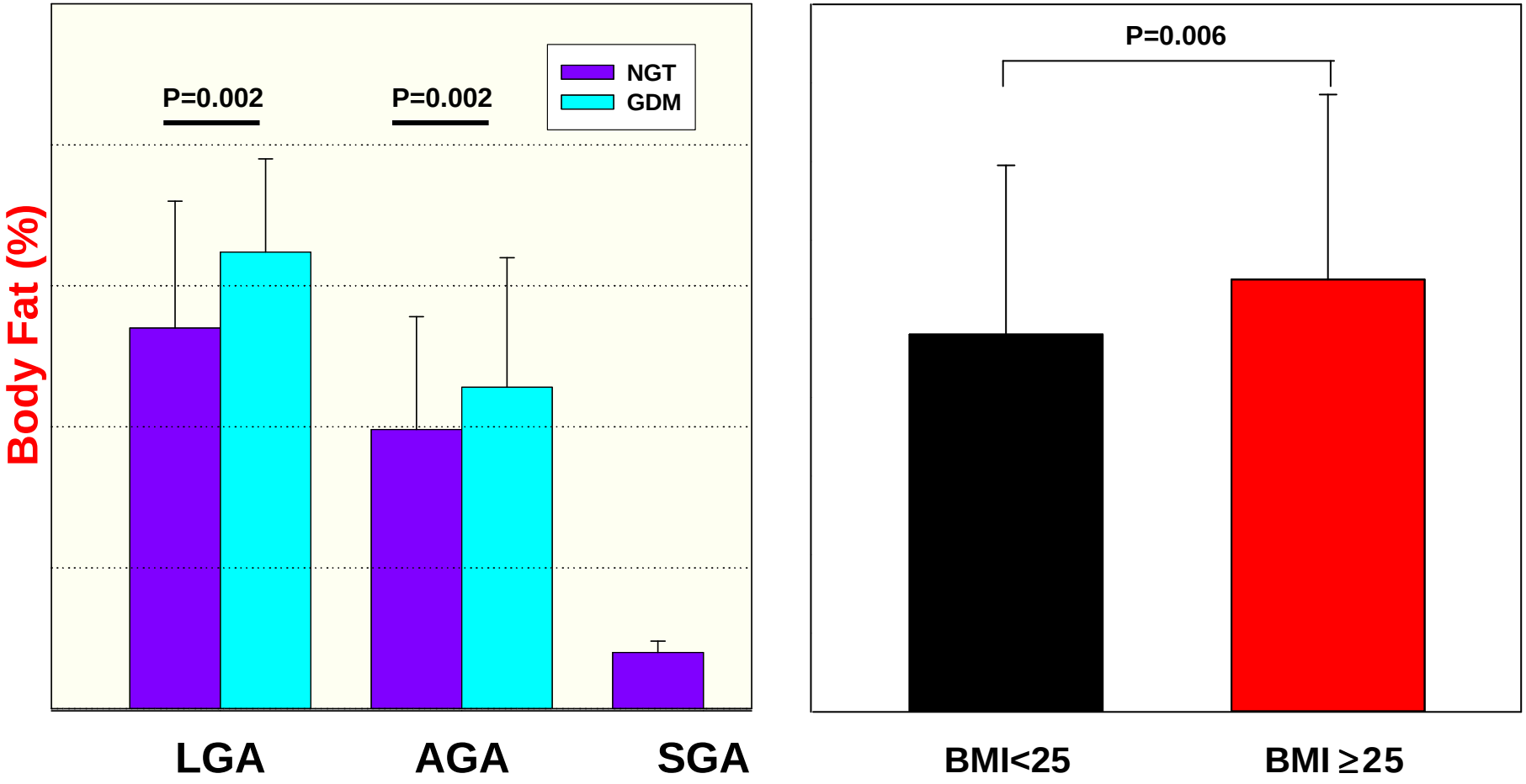
*abdominal circumference, femoral length, head circumference, biparietal diameter

Thame et al Eur J Clin Nutr 58: 894, 2004

Body Composition at Delivery

- Fat mass: 12 – 15 %
- Fat free mass: 85 – 88 %

Body Fat (%) in Offspring of Women with GDM and Obesity



Petersen 1988; Catalano AJOG 2003; Durnwald AJOG 2004; Sewell AJOG 2006

Foetus in Diabesity

characterised by:

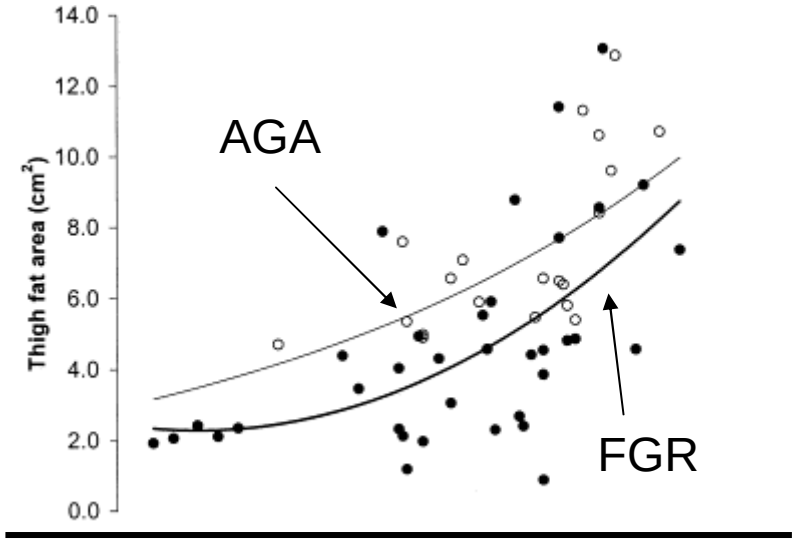
Fat Free Mass: Diabesity ~ control

Fat Mass: Diabesity > control

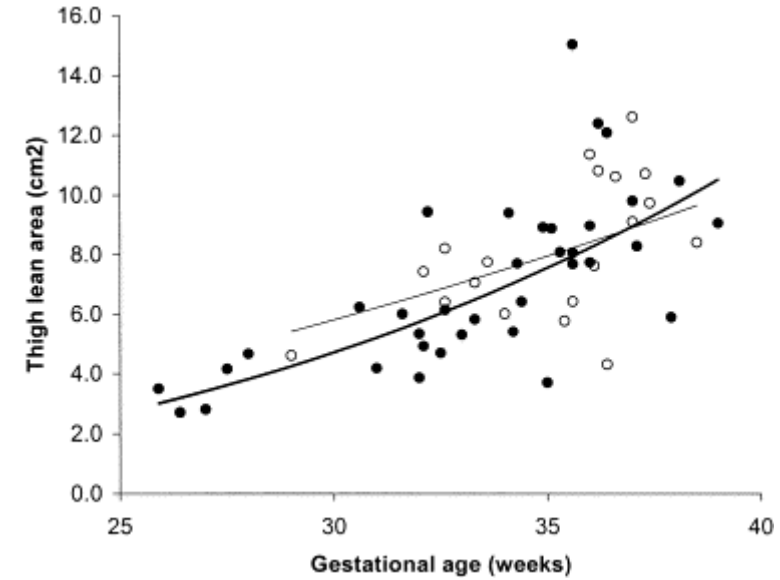
Kehl et al. 1996; Petersen 1988; Catalano AJOG 2003; Durnwald AJOG 2004, Sewell AJOG 2006

Foetal Body Fat is Reduced in FGR

Fat mass



Lean body mass



FGR:

Fetal AC < 2 SD

Abnormal Doppler:

- A. umbilicalis
- A. uterina

Padoan et al, AJOG 2004

Foetal Growth

- Fat Free Mass / Lean Body Mass

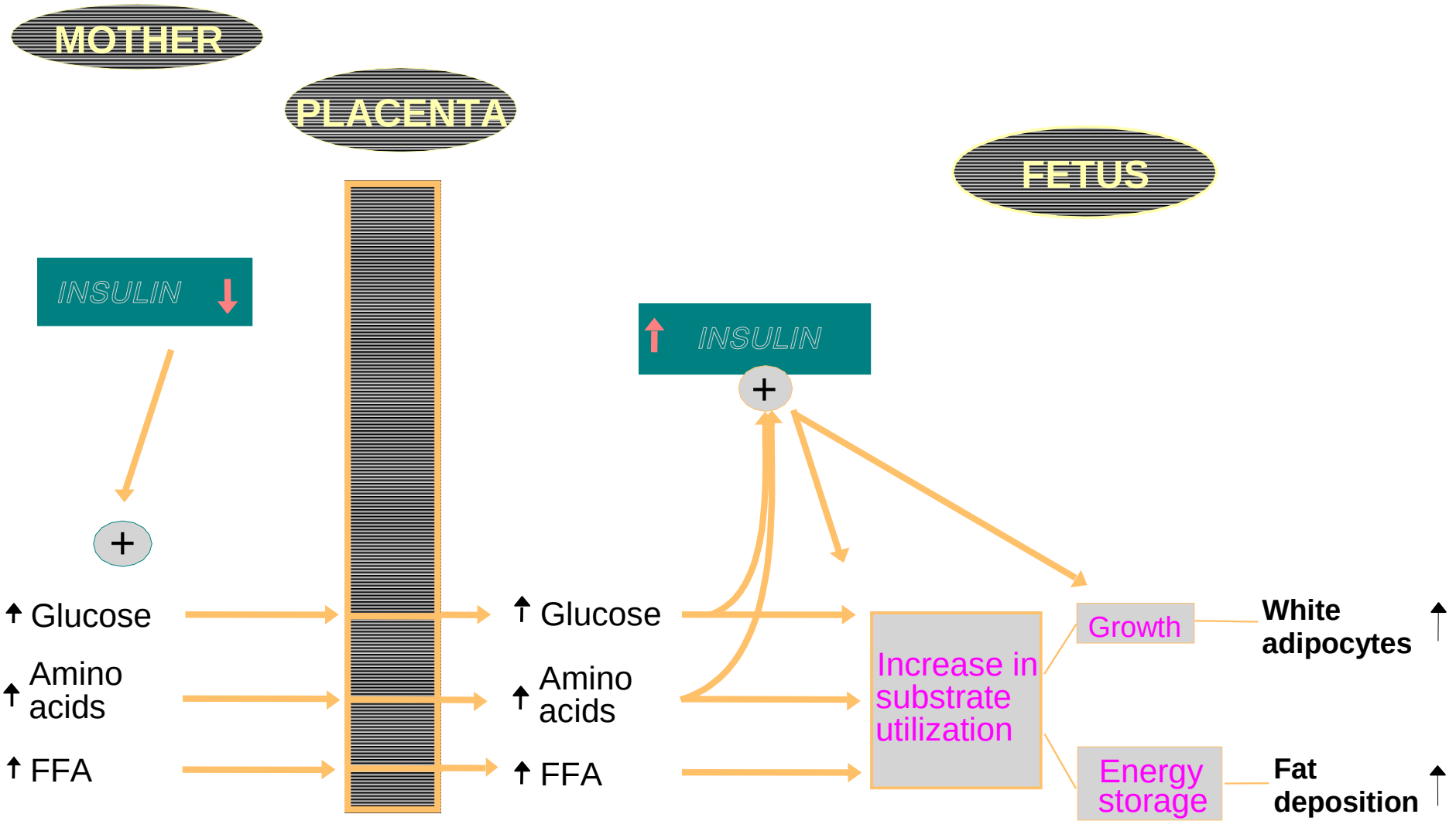
  Genes

- Fat Mass

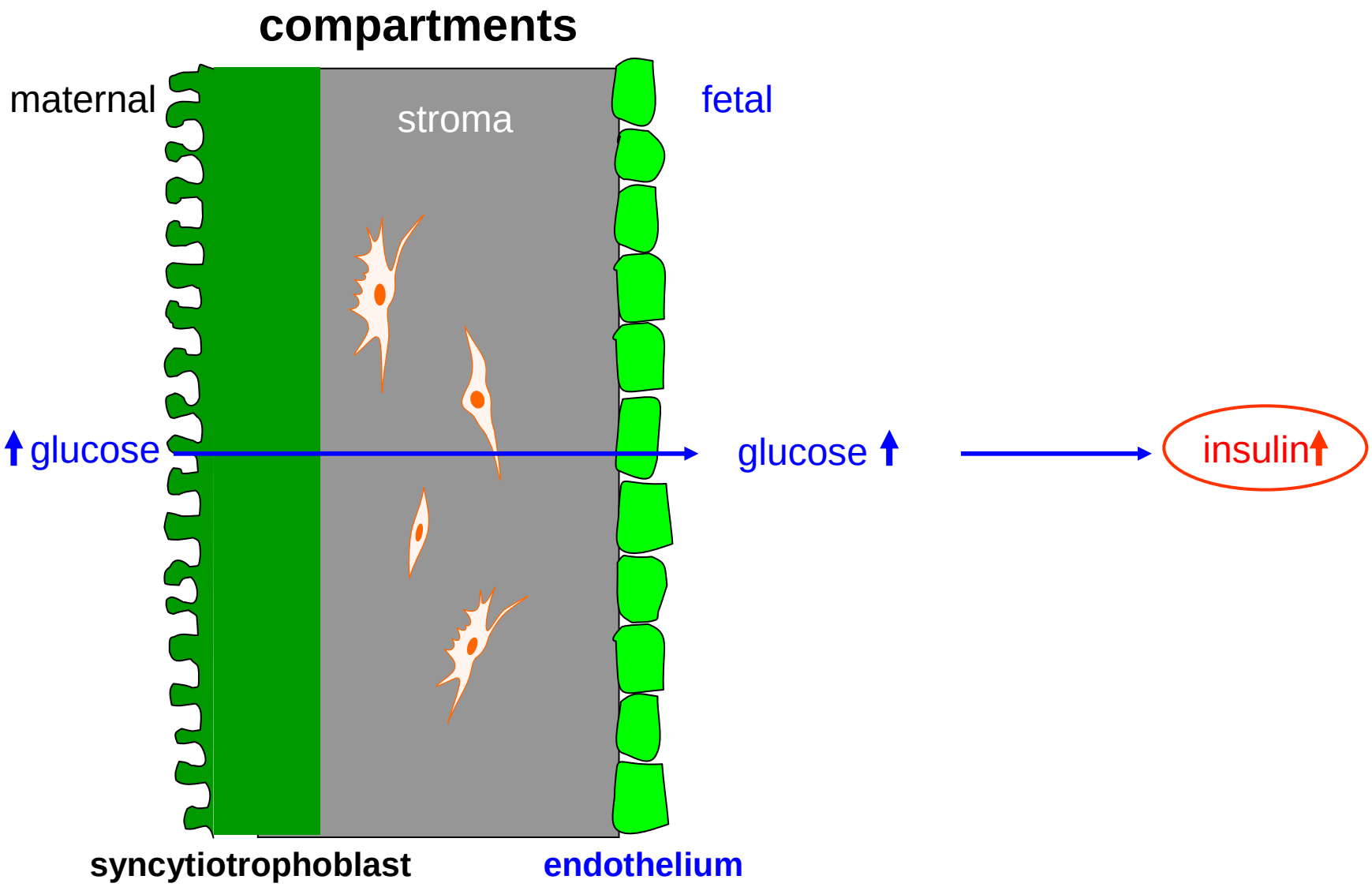
  Intrauterine Environment

Moulton; J Biol Chem, 1923
Sparks; Sem in Perinat, 1989

THE ‘FUEL-MEDIATED‘ TERATOGENESIS CONCEPT



Foetal hyperinsulinism



AF insulin at 14-20 wks gestation
(n=247)

Higher AF insulin (by 1 MOM)

associated with

3-fold risk for foetal birth weight > 90th centile:

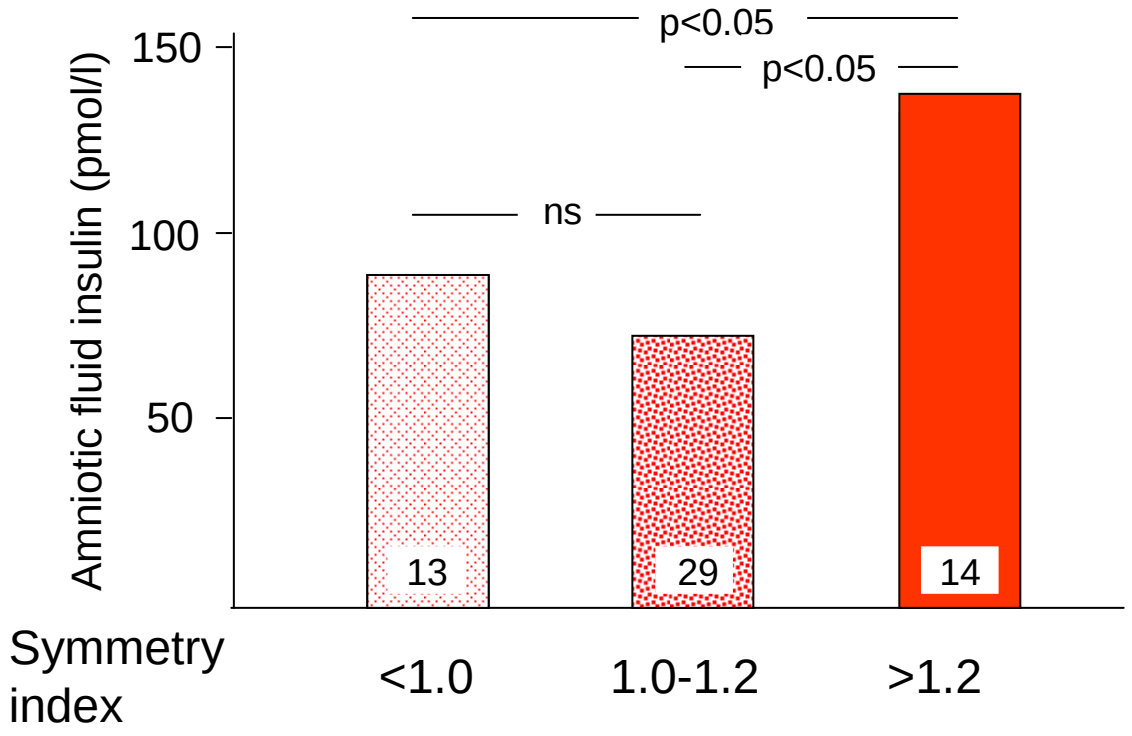
OR 3.1

[95% CI: 1.3-4.9; P=0.048]

Carpenter MW Diabetes Care 24: 1259, 2001

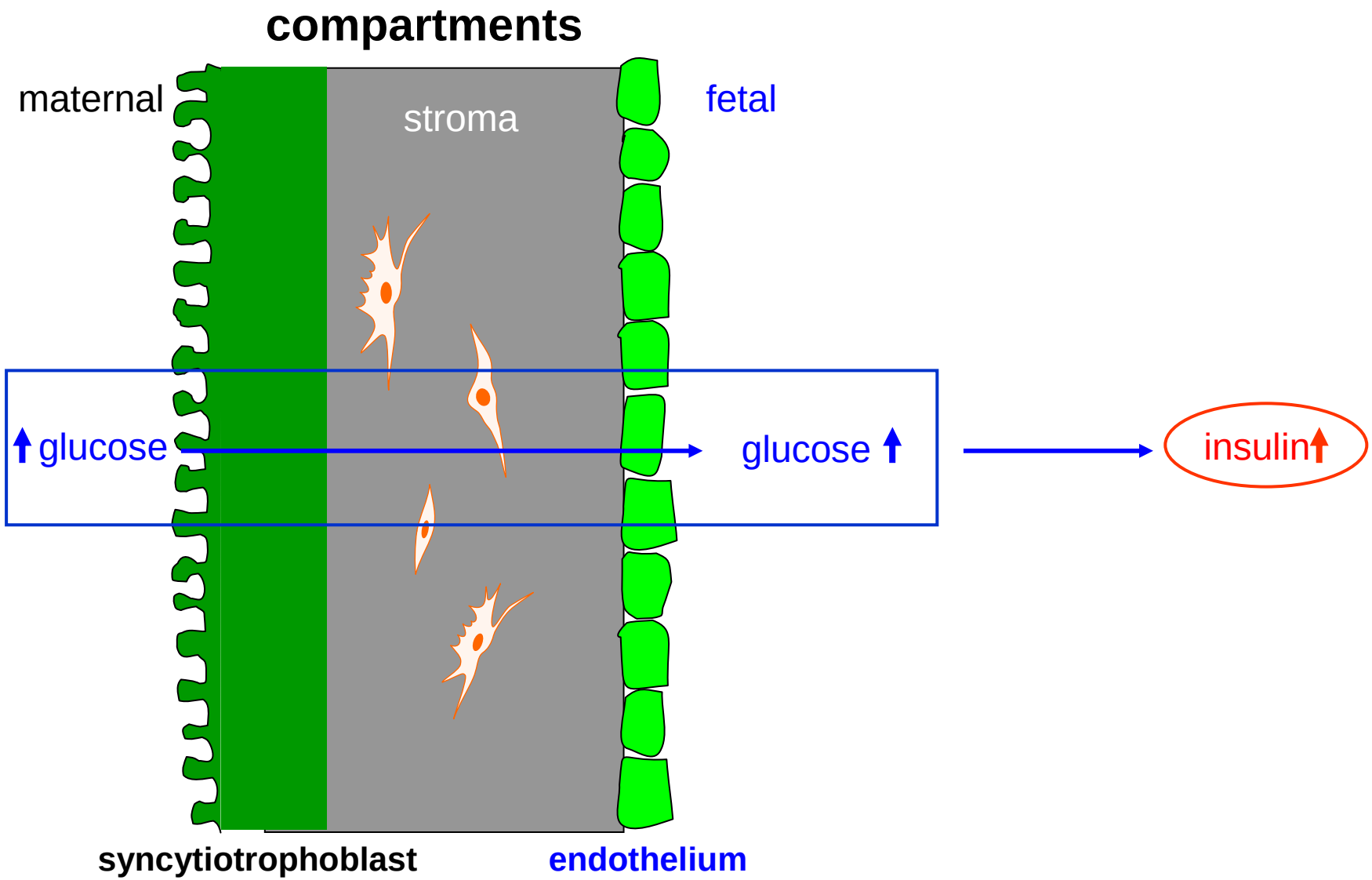
Third trimester amniotic fluid insulin & childhood growth at age 6

$$\text{Symmetry index} = \frac{\text{Observed weight/median for age}}{\text{Observed height/median for age}}$$



Metzger et al. Arch Dis Childh 65:1050, 1990

Foetal hyperinsulinism



Nutrient transfer across the placenta:

Glucose

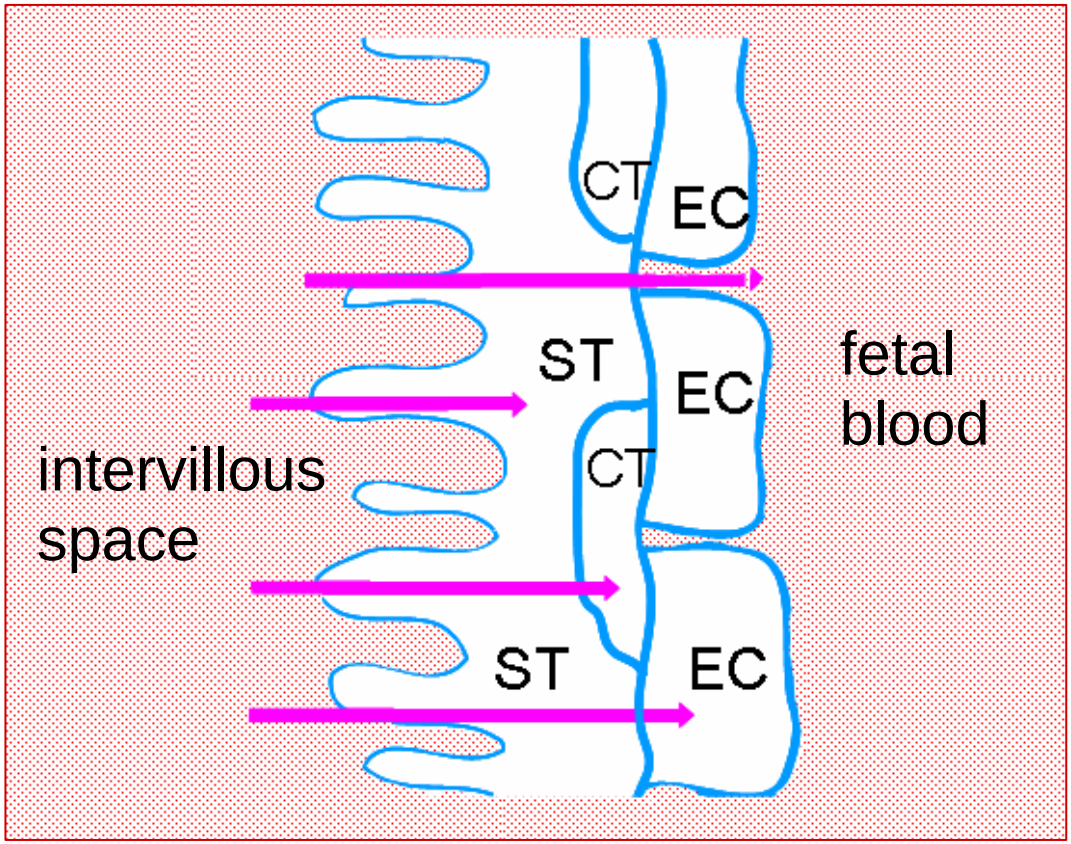
The foetus requires ~ 40 g glucose per day

The foetus does not produce glucose

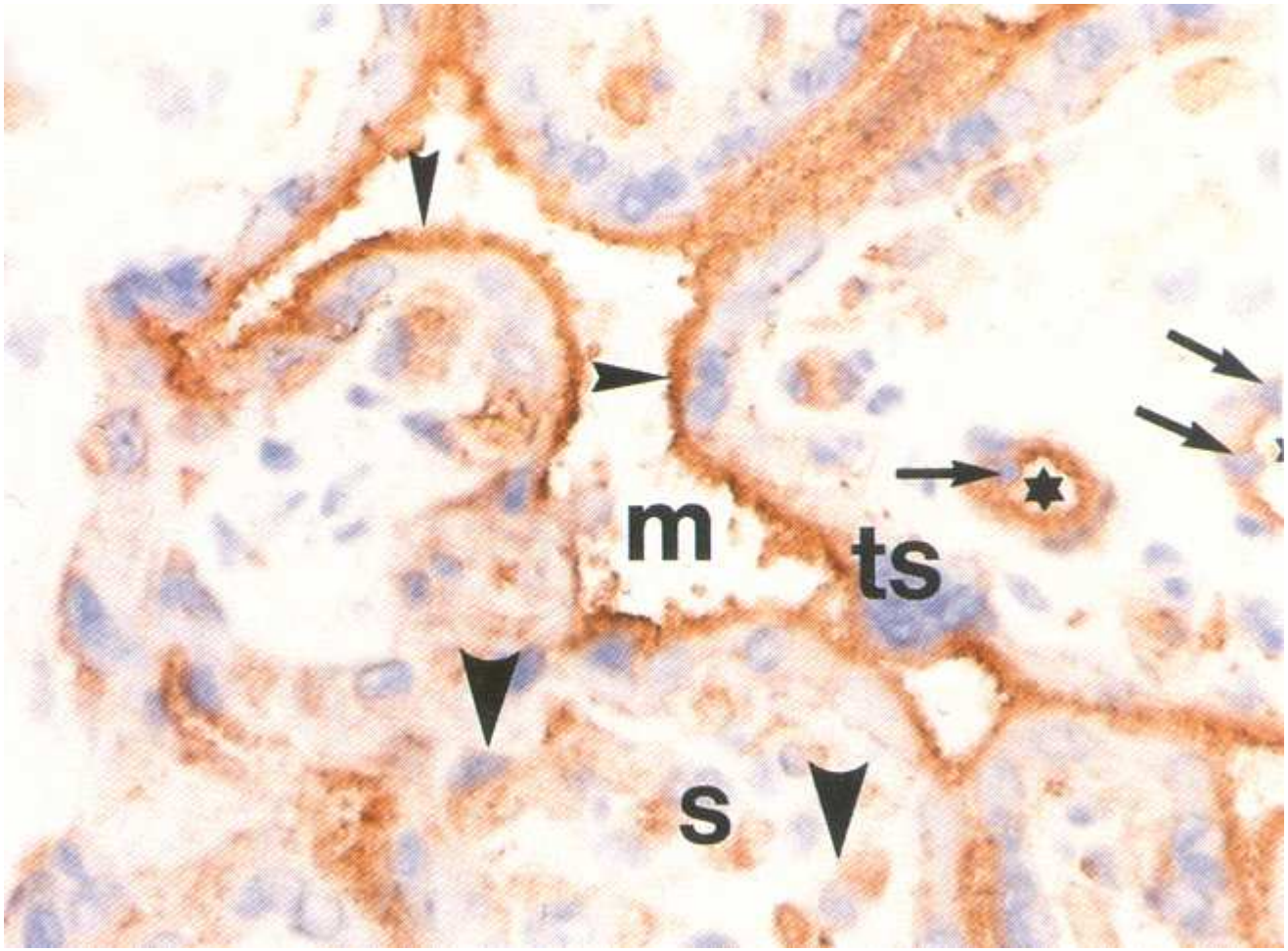
Pathways of Materno-Foetal Transport

Glucose:

* $[gluc]_m > [gluc]_f$
* *saturable*
* *stereospecific*
* *Na -indep.*
* *GLUT1*
* *mvm:bm ~ 3:1*



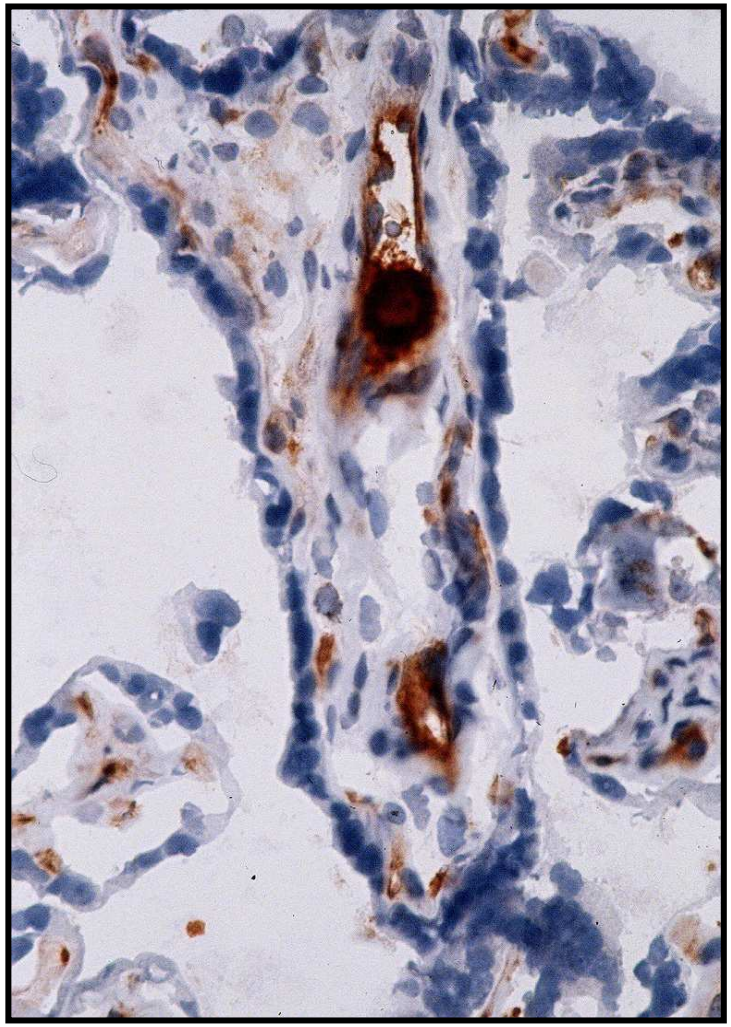
GLUT 1 in Term Placentas



Hahn et al, Cell Tiss Res 280, 1995

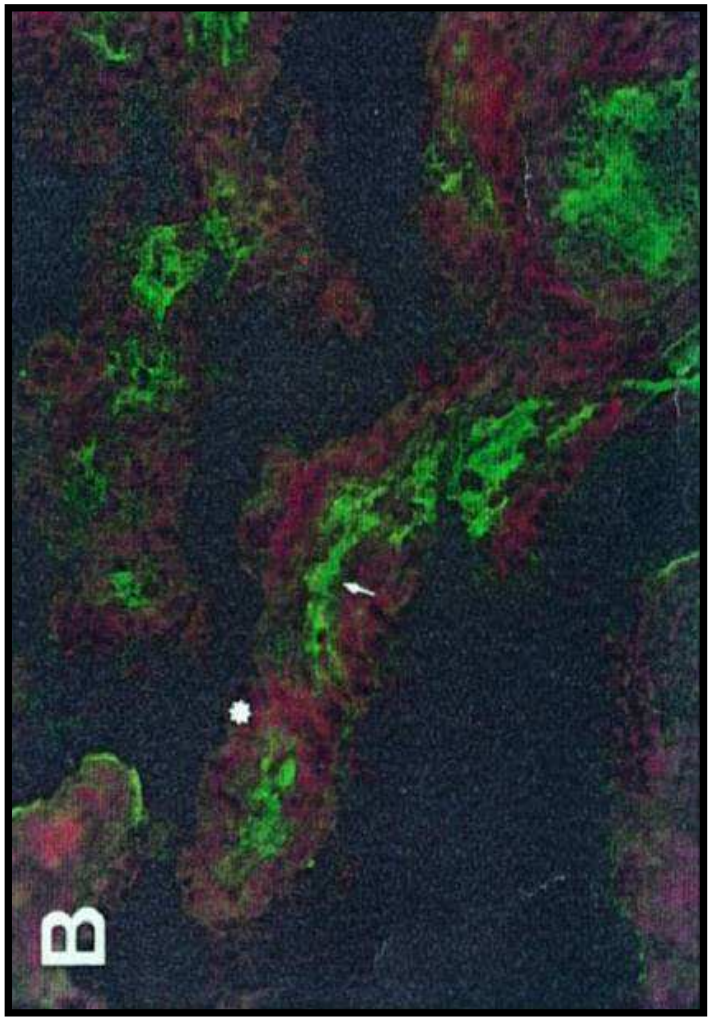
Term Placenta

GLUT3



Mol Hum Reprod 2001 7:1173

GLUT4



JCEM 1998 83:4097

Placental Glucose Transporters *in vitro* Regulation

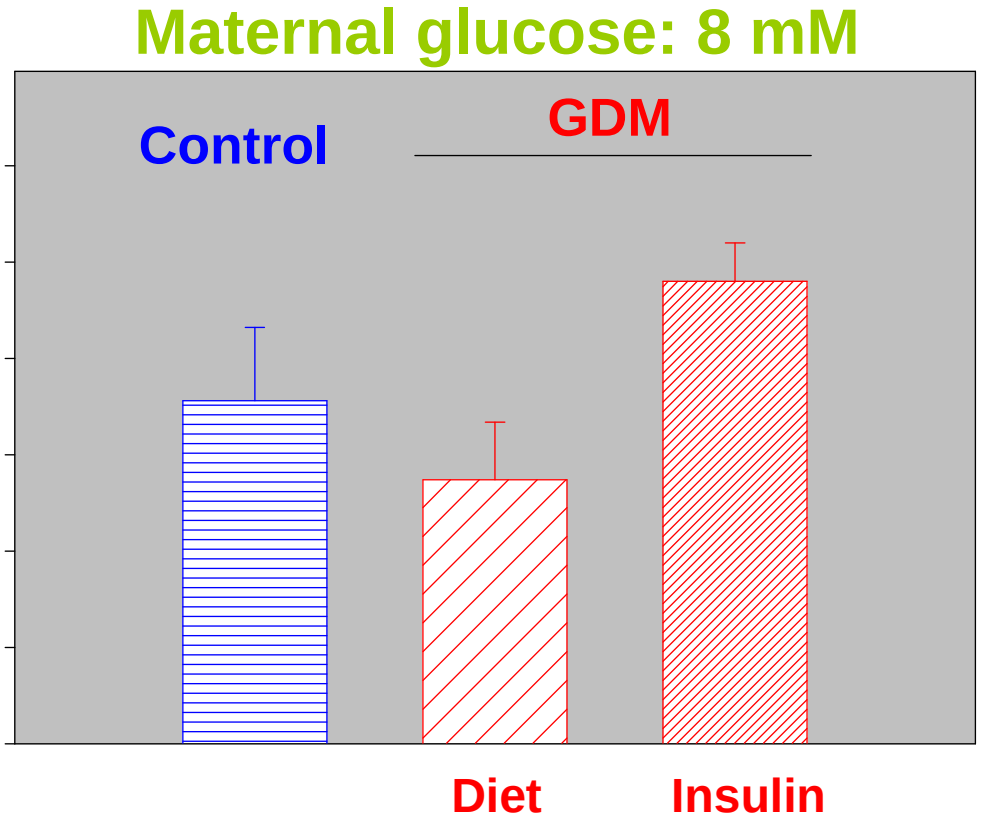
Hyperglycemia *in vitro* downregulates glucose uptake and GLUT1 in human term trophoblasts

Hahn et al., FASEB J 12: 1221, 1998

Hyperglycemia *in vitro* induces GLUT1 translocation in term human trophoblasts

Hahn et al., Diabetologia 43: 173, 2000

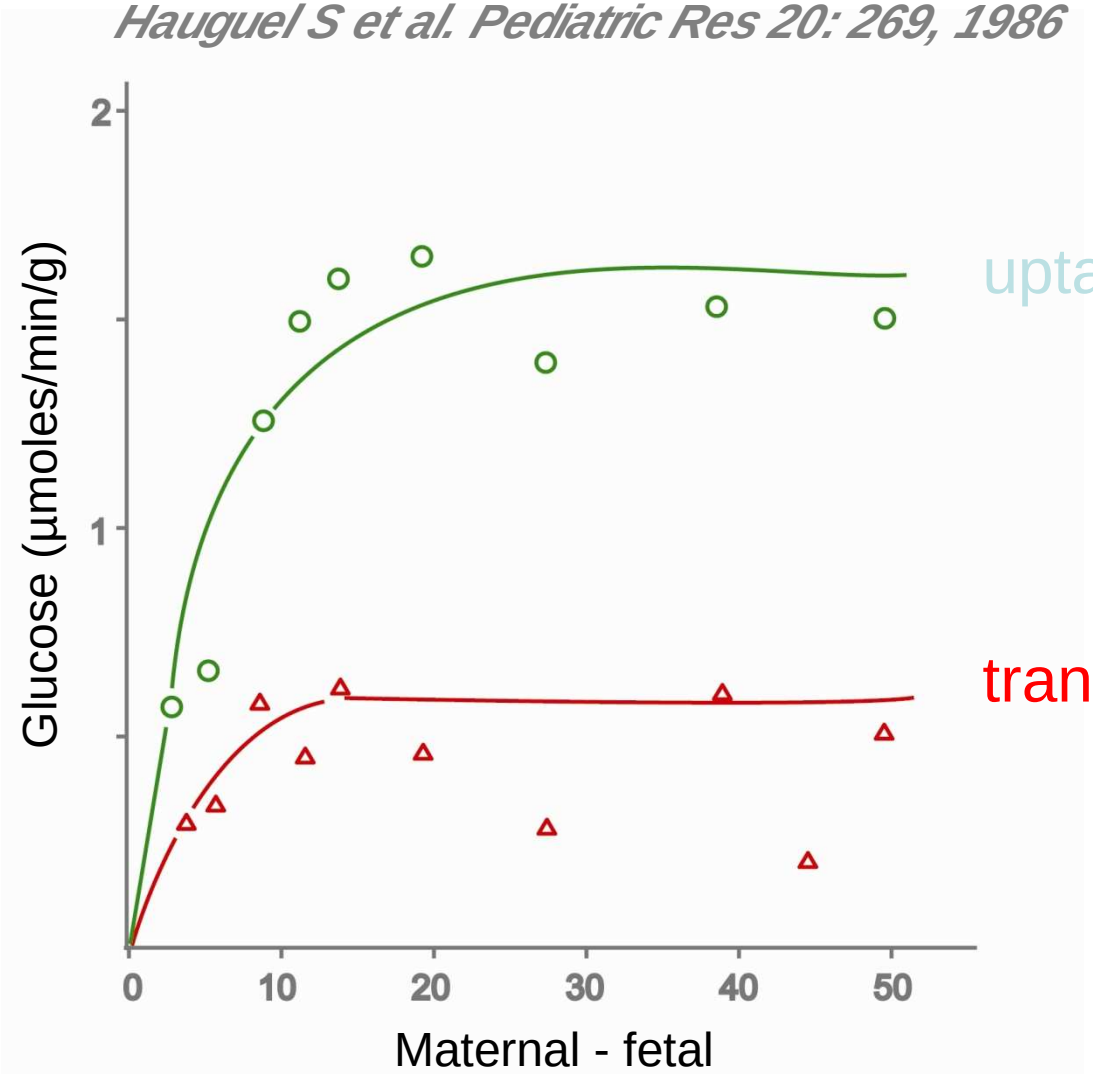
Total transplacental net transfer of glucose



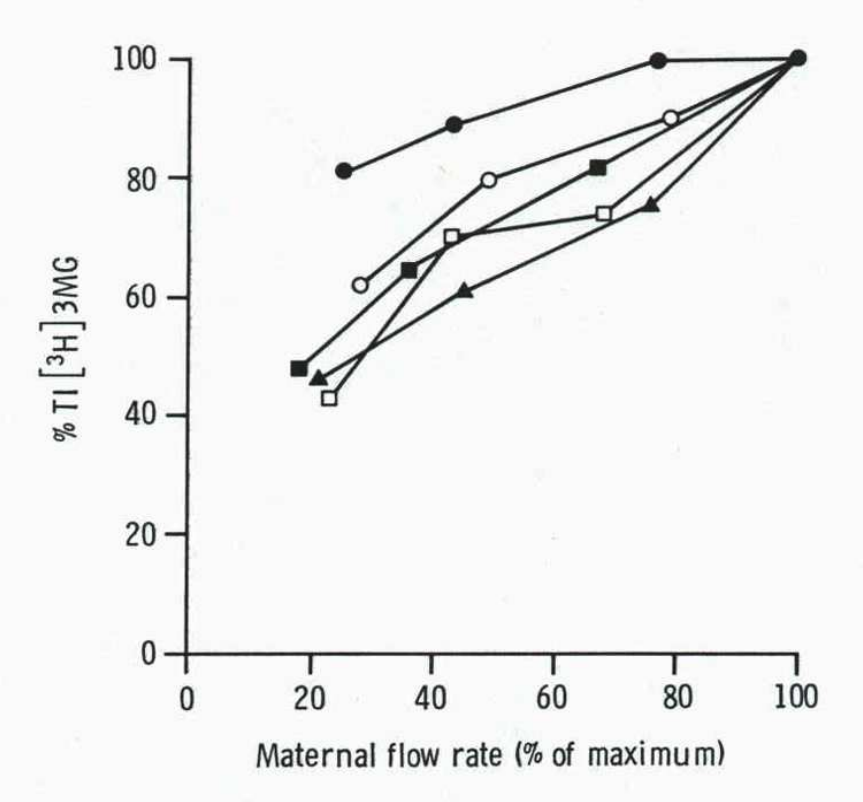
Osmond et al, Diabetologia 2001

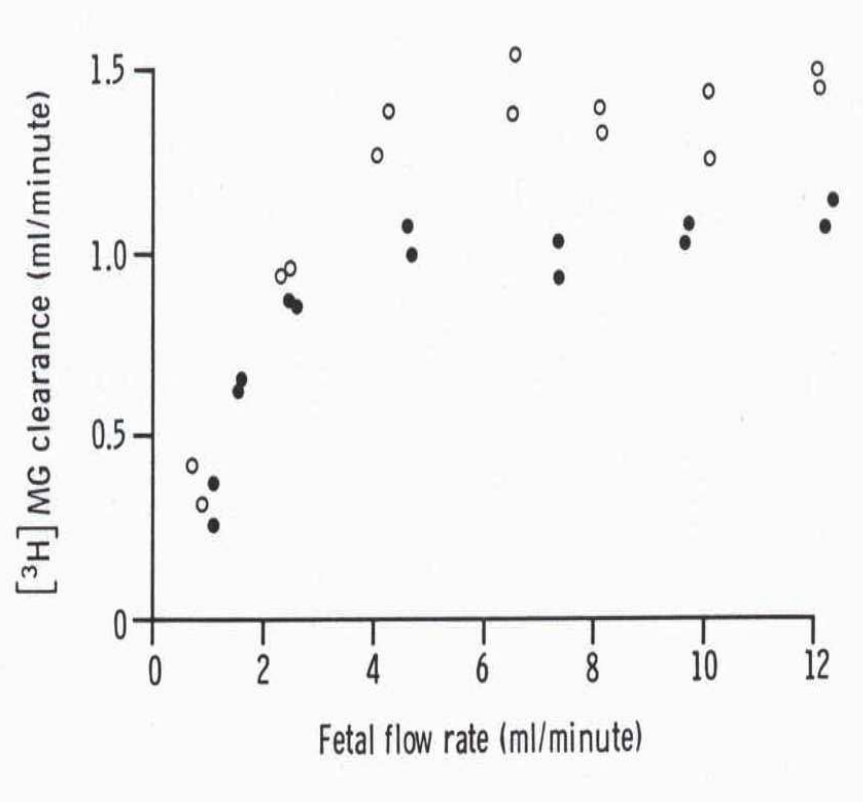
Glucose uptake and transfer depend on maternal-fetal concentration gradient

Hauguel S et al. Pediatric Res 20: 269, 1986



Transplacental glucose transport depends on **maternal and foetal blood flow**





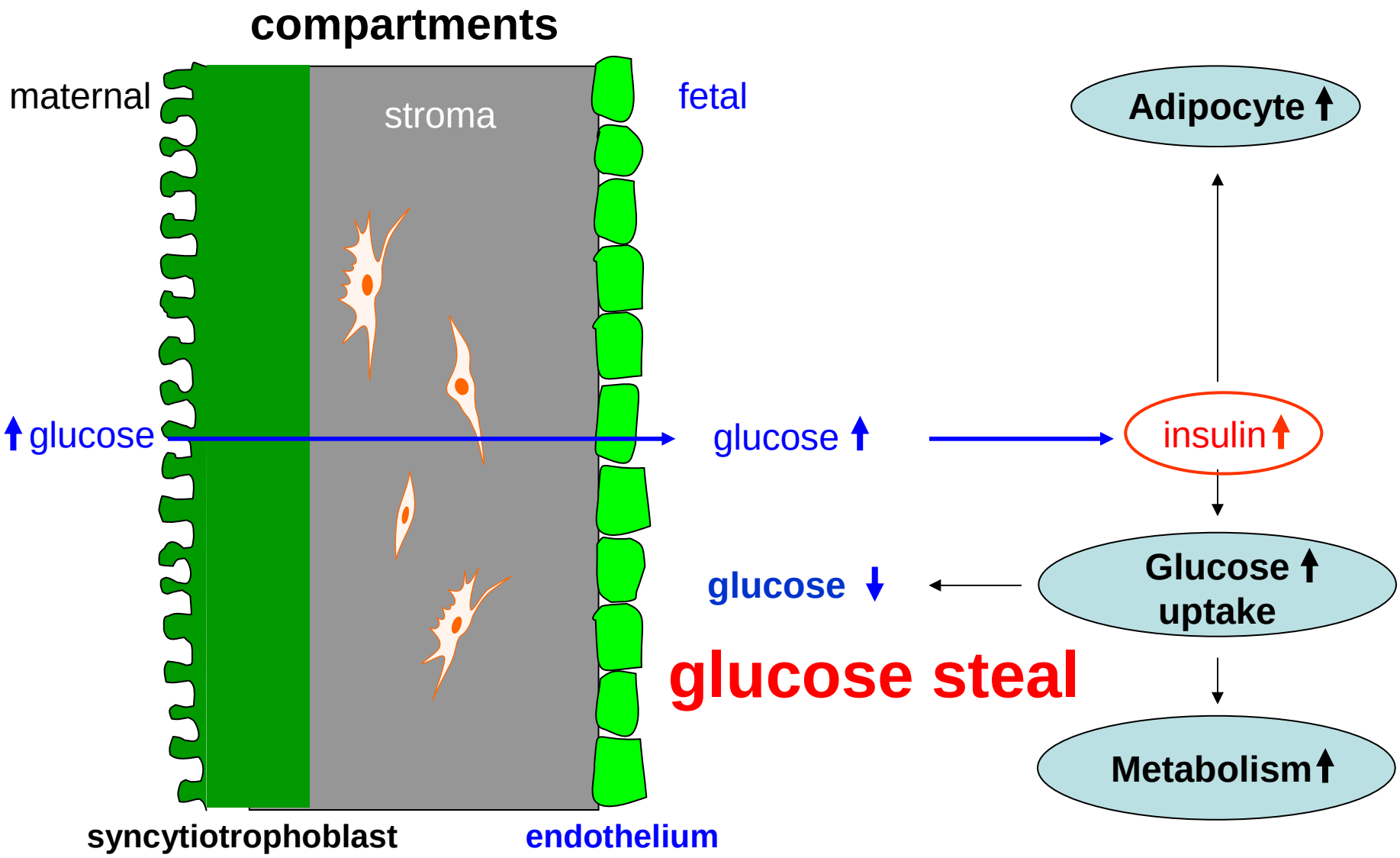
Illsley et al. Trophoblast Res. 2: 535, 1987

Transplacental Glucose Flux

Depends on the MATERNAL-FOETAL concentration gradient

Is flow limited

Fetal hyperinsulinism leads to multiple changes



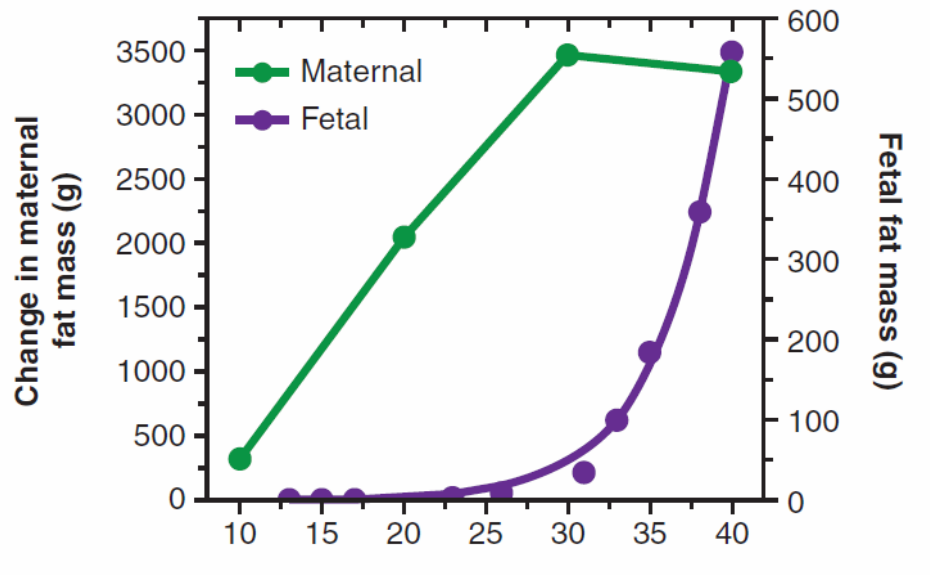
Foetal Hyperinsulinism – A Vicious Circle

Hyperinsulinism

Nutrient transfer across the placenta:

Lipids – Fatty Acids

Maternal and Foetal Fat During Gestation

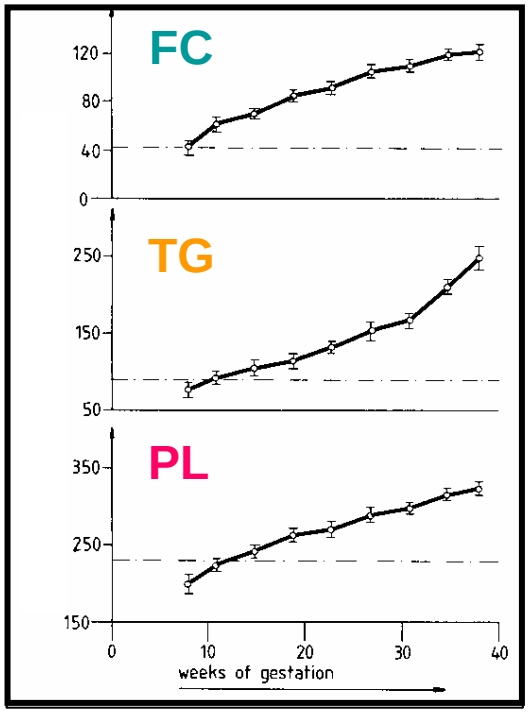


Foetal lipid accretion maximum at term of gestation:

7 g/day

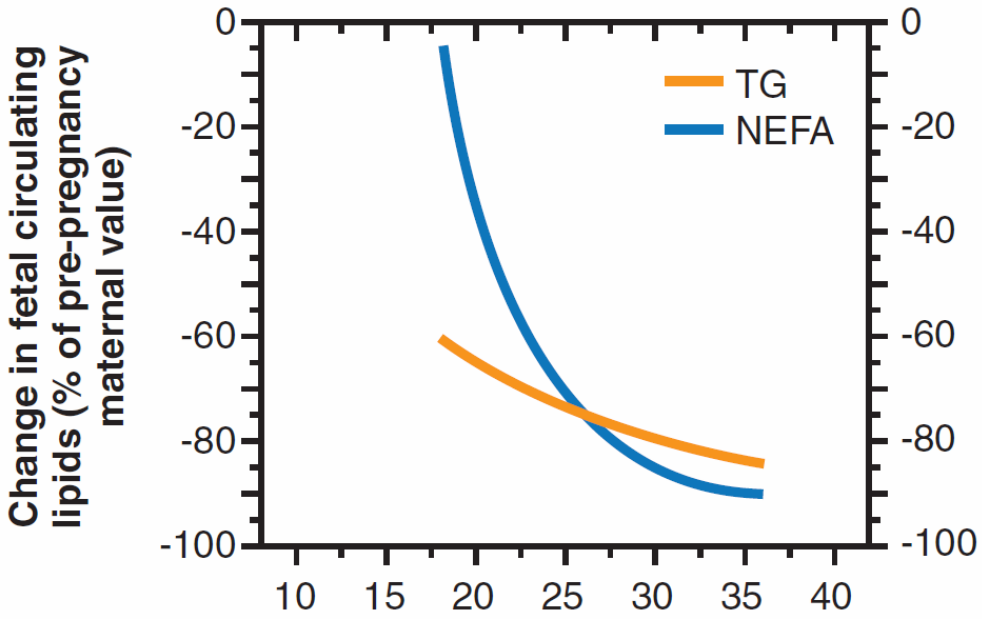
EM Widdowson, 1968; P Haggarty Ann Rev Nutr 30:237, 2010

Gestational Changes in Maternal and Foetal Lipids

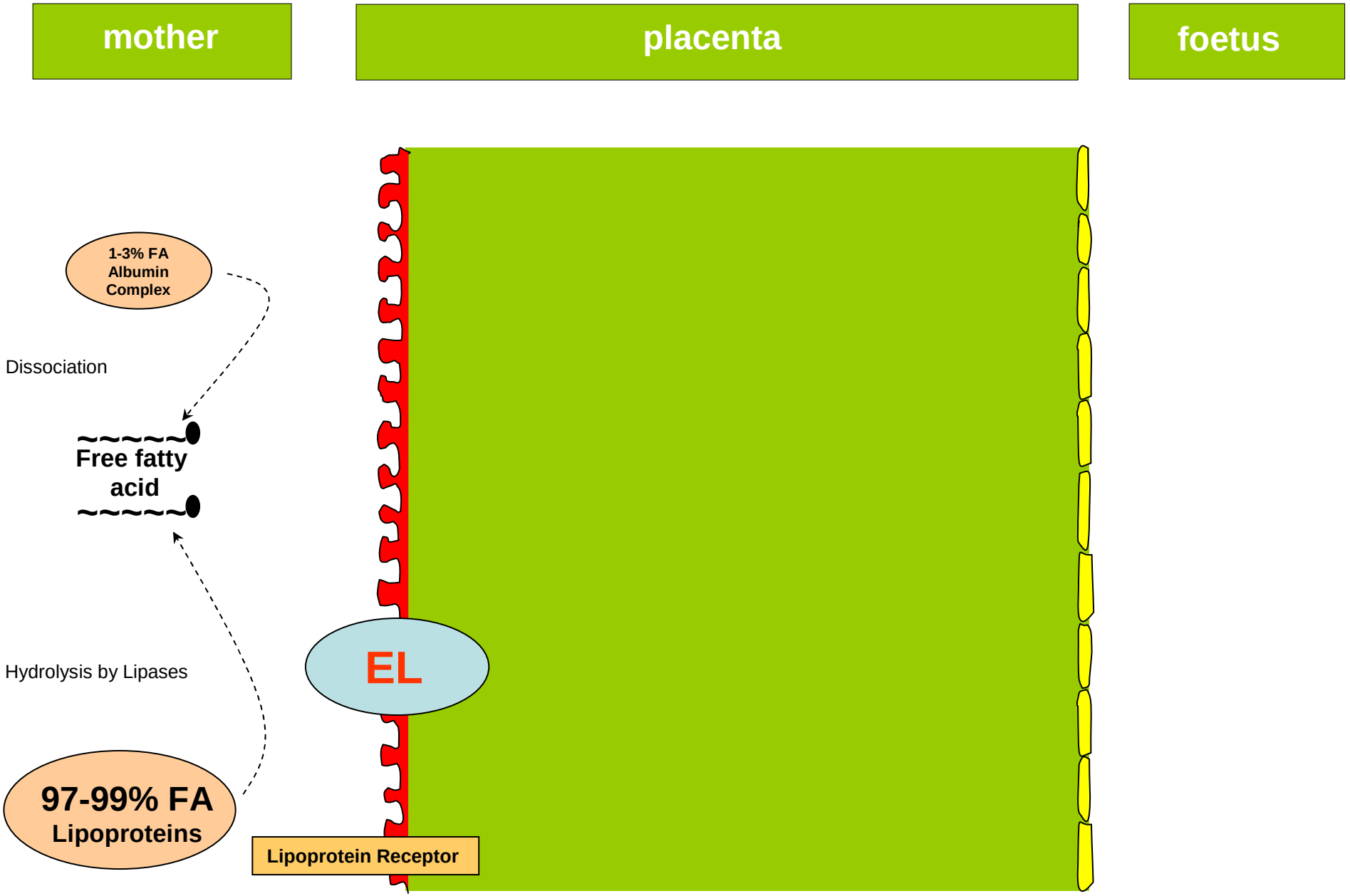


Desoye G et al. JCEM 1987

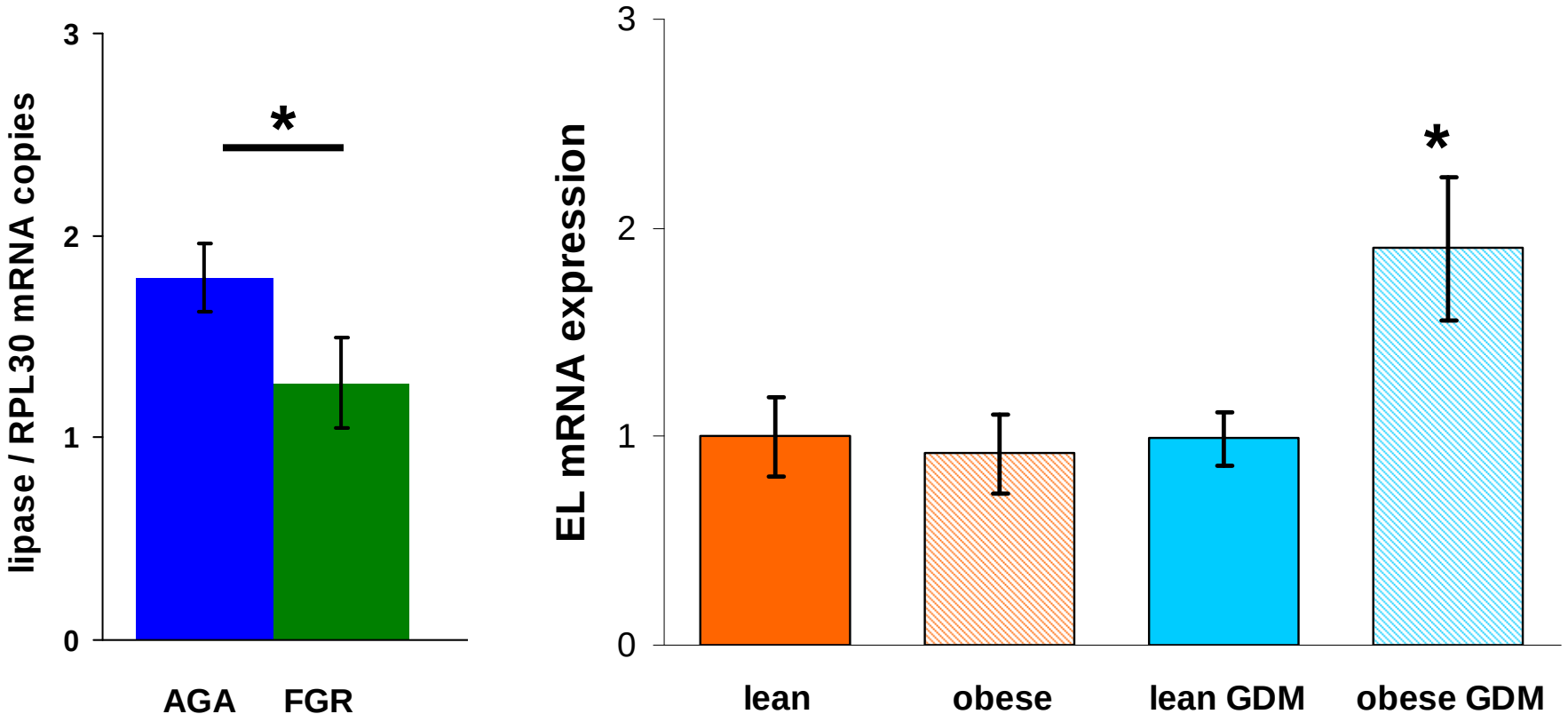
TG - NEFA



P. Haggarty Ann Rev Nutr 30:237, 2010

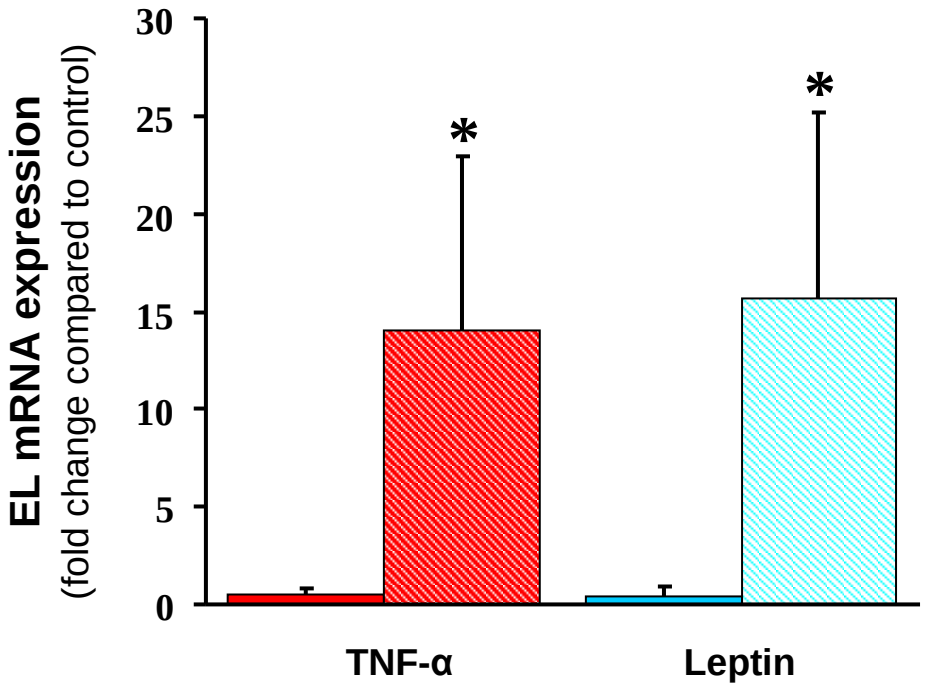

mother
placenta
foetus
1-3% FA
Albumin
Complex
Dissociation
Free fatty
acid
Hydrolysis by Lipases
EL
97-99% FA
Lipoproteins
Lipoprotein Receptor

Placental EL is downregulated in FGR and upregulated in obese GDM

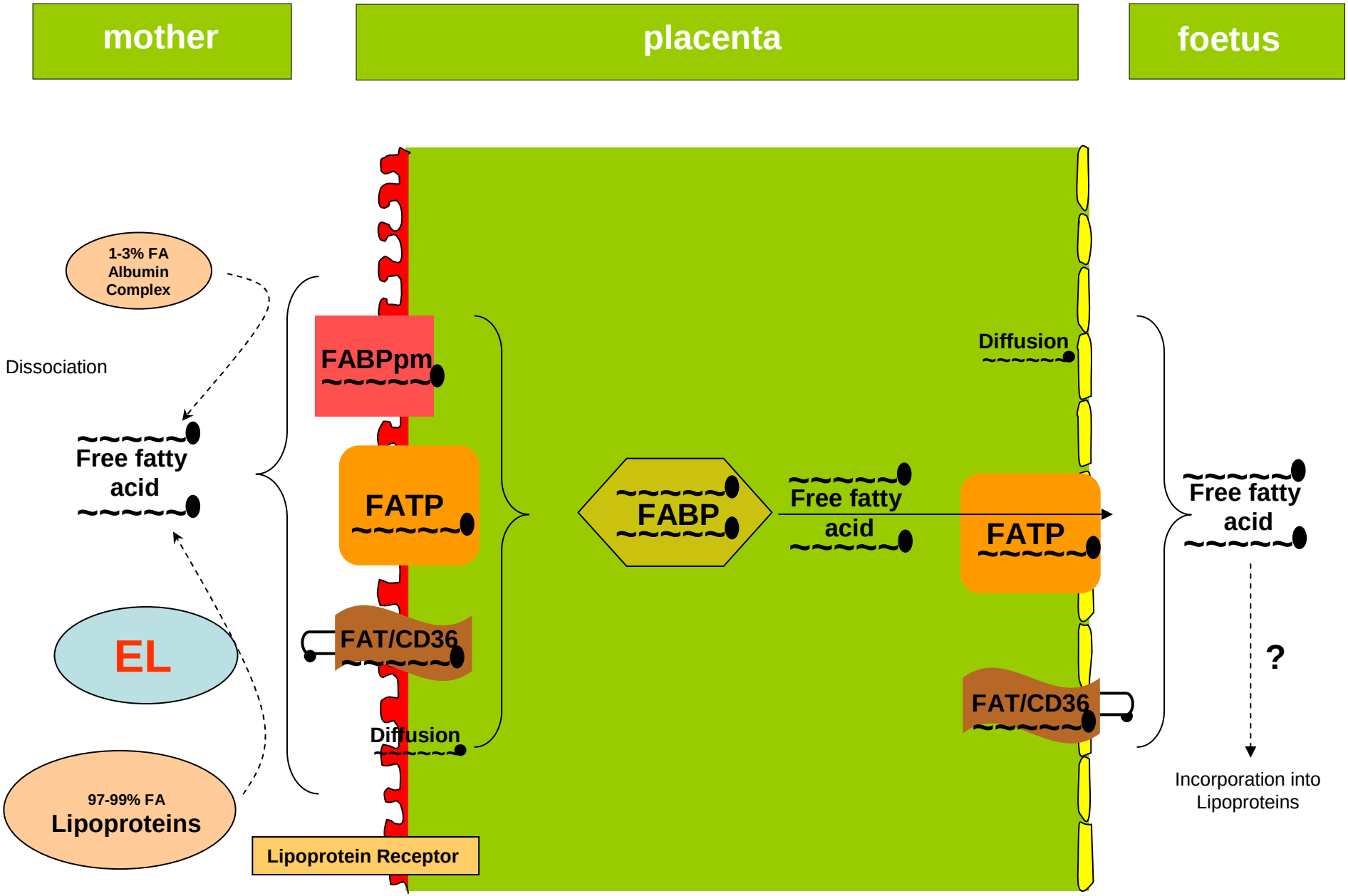


Gauster et al, modified from JCEM 92: 2256-63, 2007, Diabetes 60: 2457, 2011

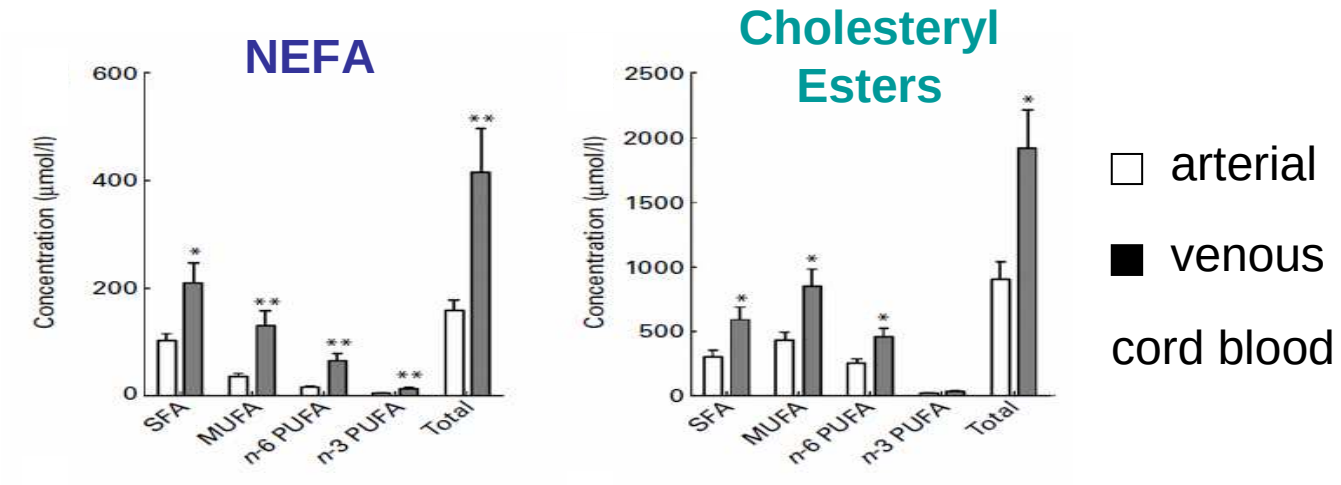
Inflammatory cytokines upregulate placental EL



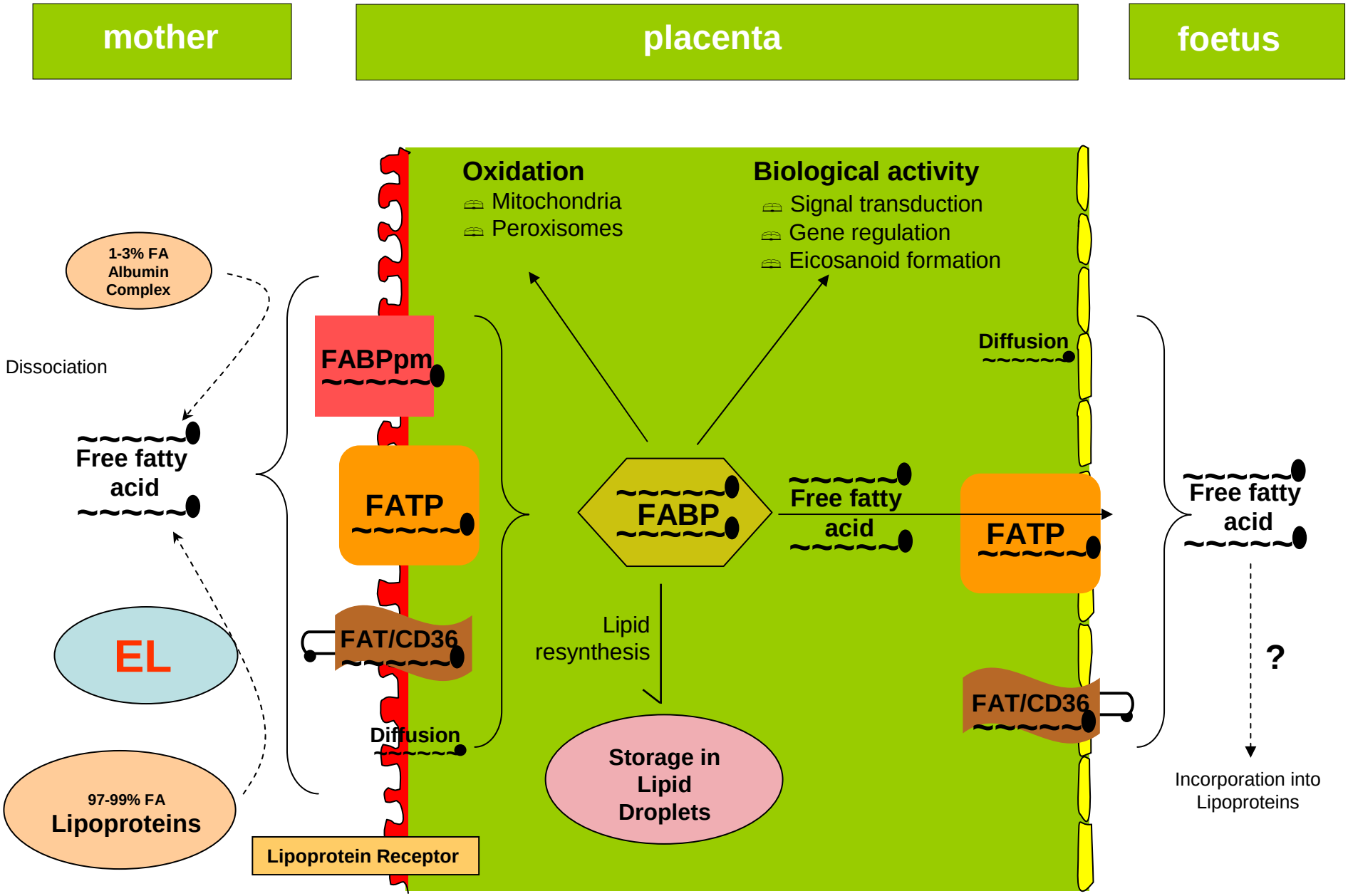
Gauster et al. Diabetes 60: 2457, 2011


mother
placenta
foetus
1-3% FA
Albumin
Complex
Dissociation
Free fatty
acid
EL
97-99% FA
Lipoproteins
FABPpm
FATP
FAT/CD36
Diffusion
Lipoprotein Receptor
FABP
Free fatty
acid
Diffusion
FATP
FAT/CD36
Free fatty
acid
?
Incorporation into
Lipoproteins

Selective FA contribution to foetal NEFA and cholesteryl ester pools



Lewis RM et al. Br J Nutr 106:463, 2011


mother
placenta
foetus
Oxidation
Mitochondria
Peroxisomes
Biological activity
Signal transduction
Gene regulation
Eicosanoid formation
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Albumin
Complex
Dissociation
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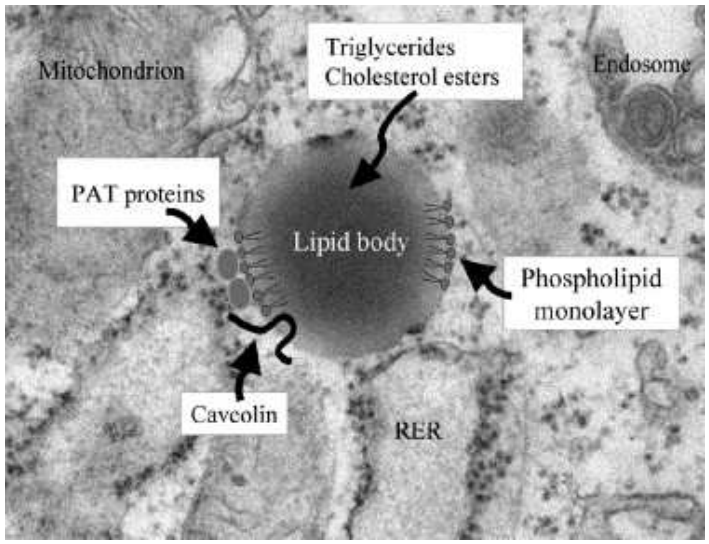
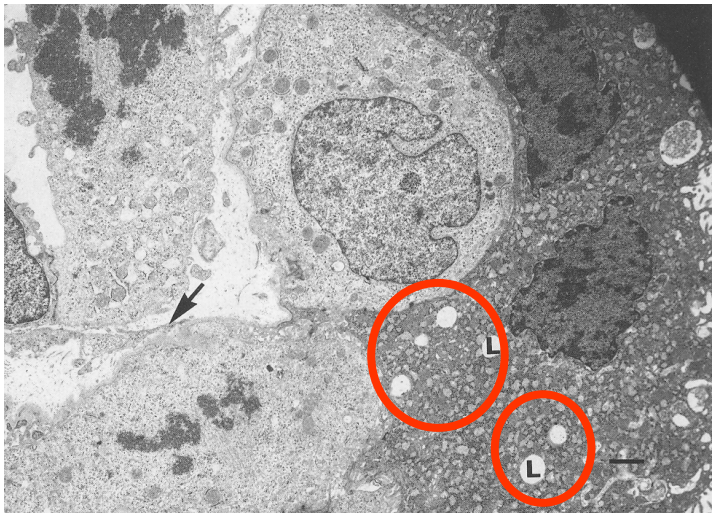
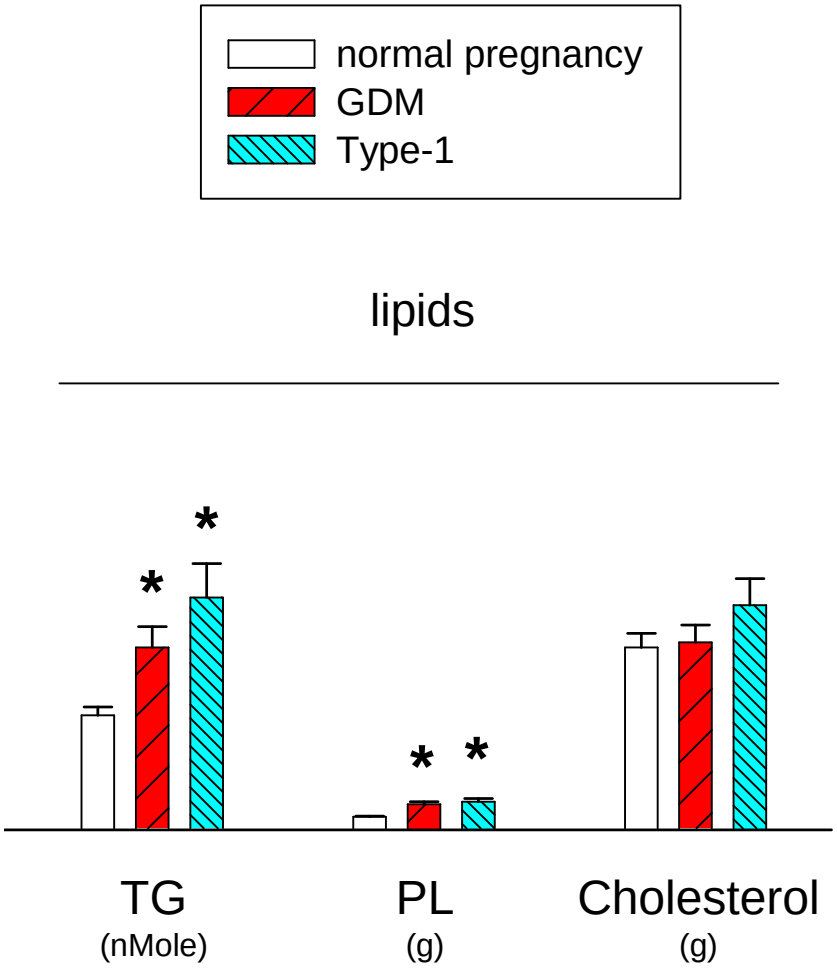
acid
EL
97-99% FA
Lipoproteins
FABPpm
FATP
FAT/CD36
Diffusion
Lipoprotein Receptor
FABP
Free fatty
acid
Lipid
resynthesis
Storage in
Lipid
Droplets
Diffusion
FATP
FAT/CD36
Free fatty
acid
?
Incorporation into
Lipoproteins

Human placenta contains lipid bodies in the syncytiotrophoblast

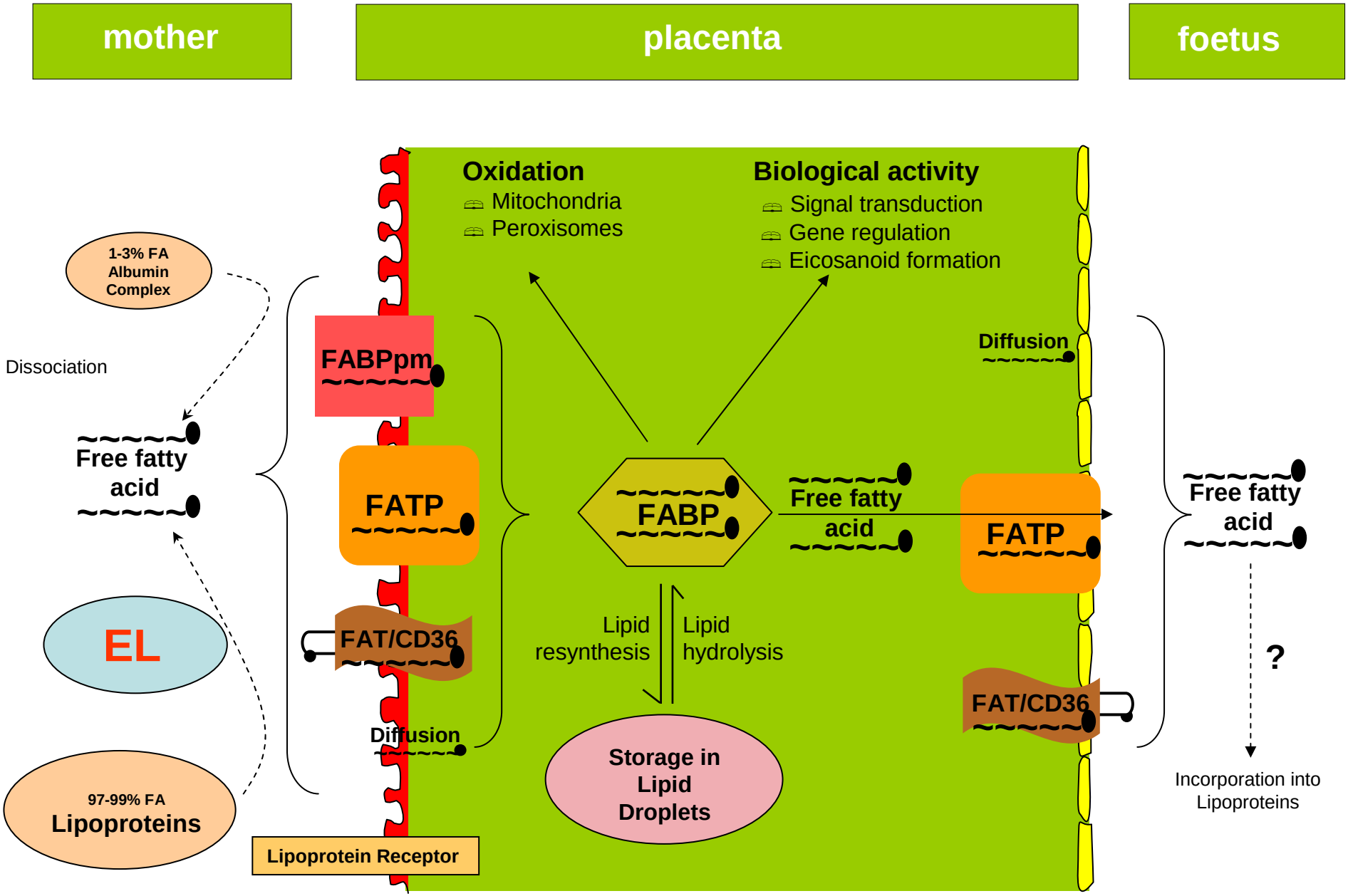






Jones & Fox, Electron Microsc Res 4: 129, 1991

Shafrir et al, AJOG 144: 5, 1982


mother
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resynthesis
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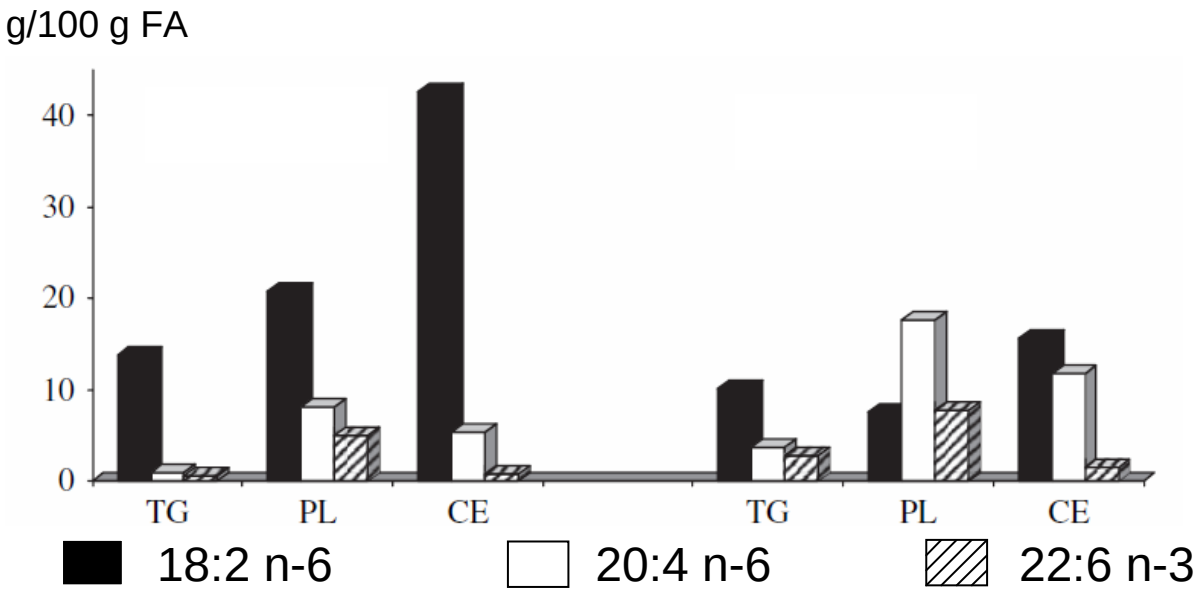
hydrolysis
Storage in
Lipid
Droplets
Diffusion
FATP
FAT/CD36
Free fatty
acid
?
Incorporation into
Lipoproteins

LCPUFA are enriched in foetal plasma

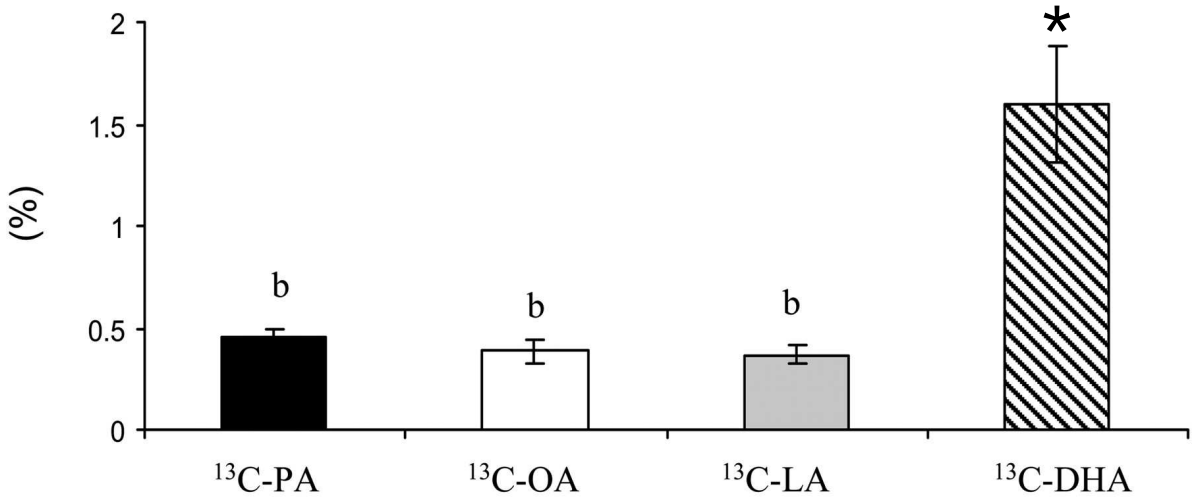
Maternal plasma Foetal plasma



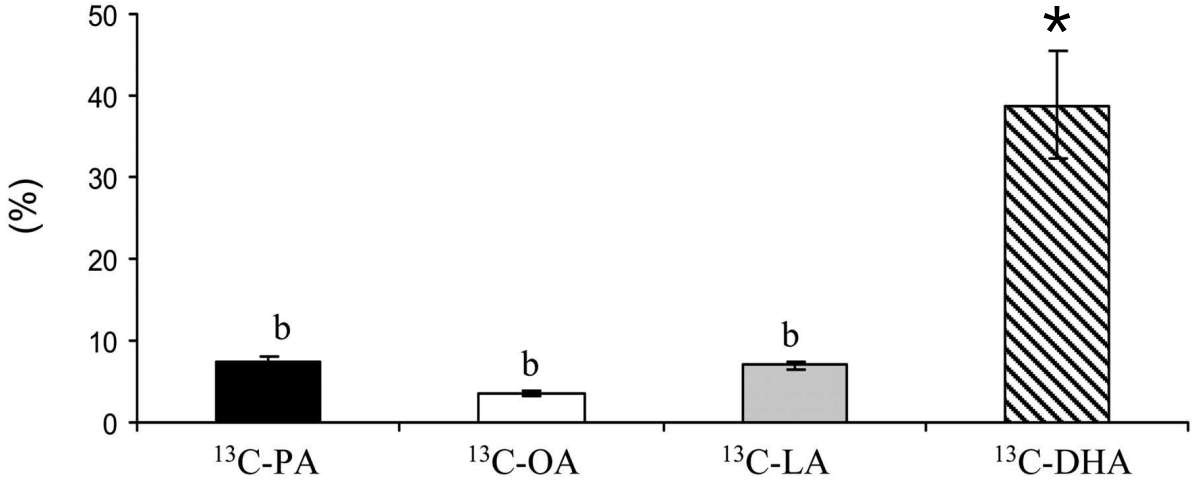
Innis S, Placenta 26 Suppl A:S70, 2005

DHA is enriched in placenta and cord blood 12 hr after maternal ^{13}C-FA administration

Cord blood/ Maternal

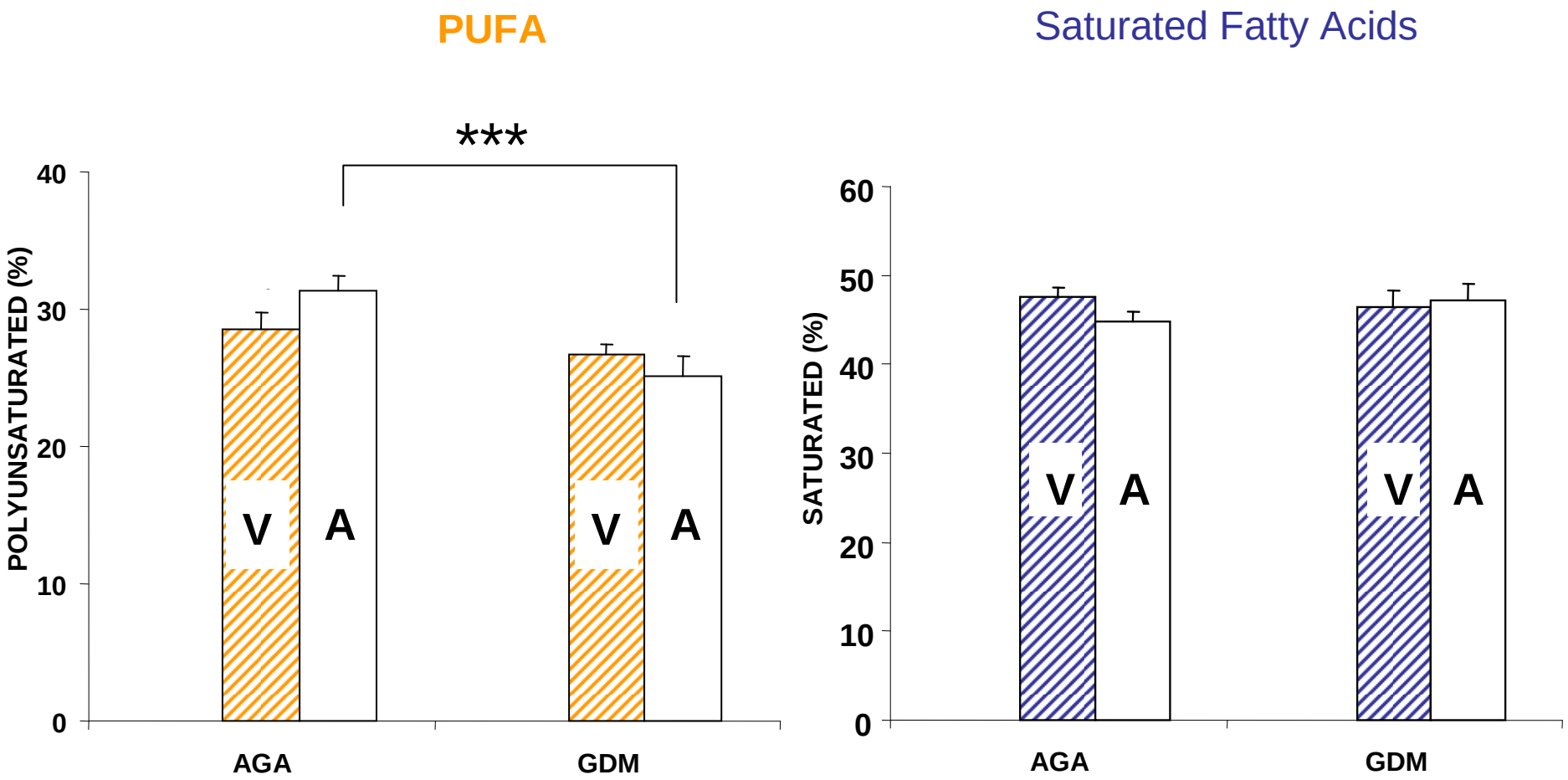


Placenta/ Maternal



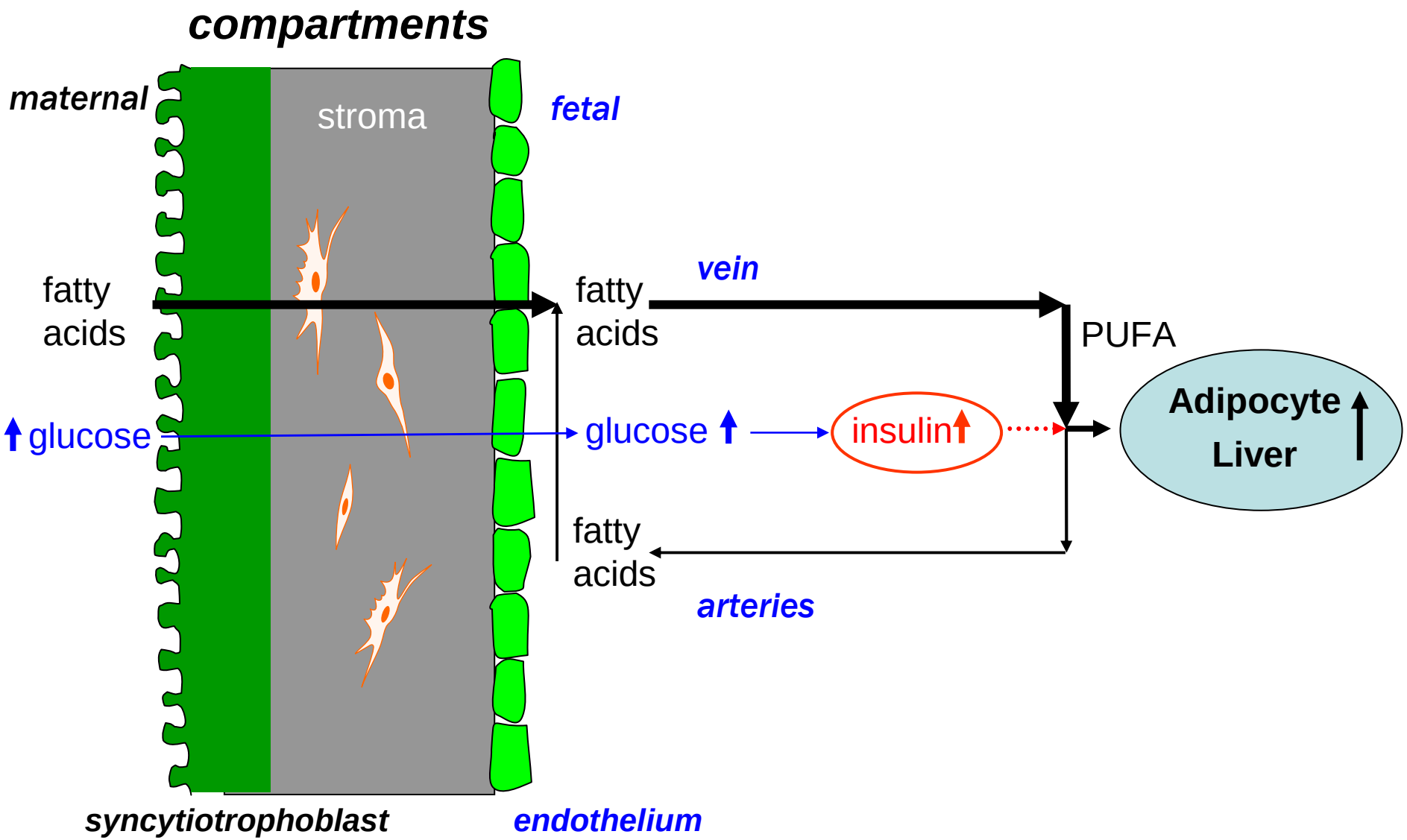
Gil-Sánchez A et al., Am J Clin Nutr 92:115, 2010

Fatty acids in umbilical cord plasma



Ortega-Senovilla H et al. Diabetes Care 32: 120, 2009

Foetal hyperinsulinism may stimulate extraction of polyunsaturated fatty acids



Nutrient transfer across the placenta:

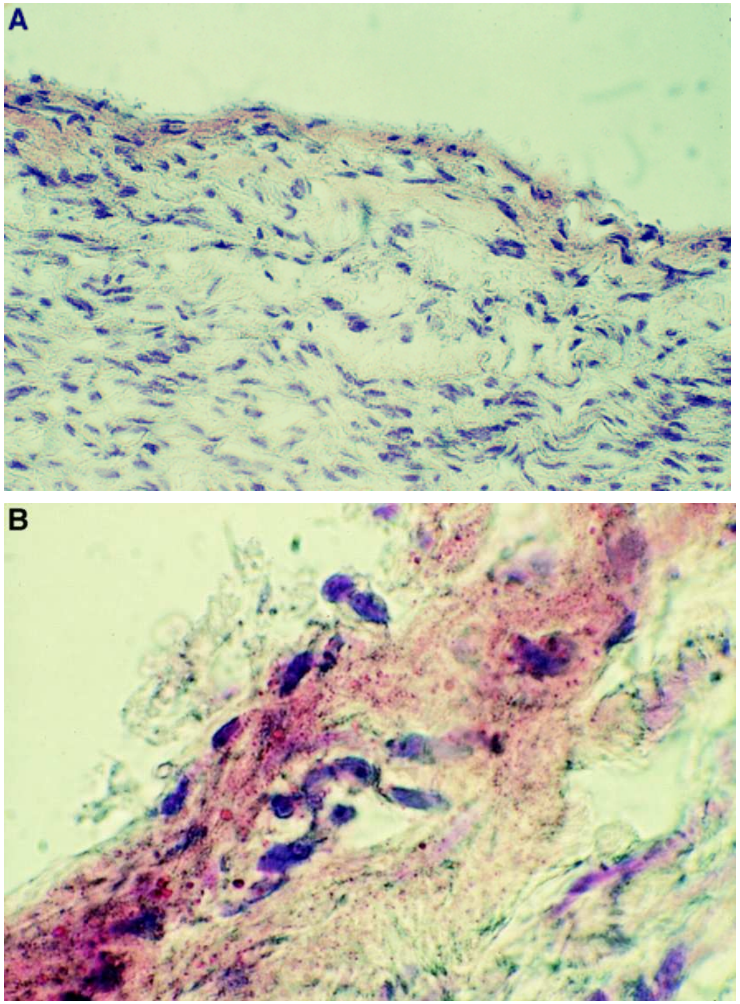
Lipids – Cholesterol

Cholesterol

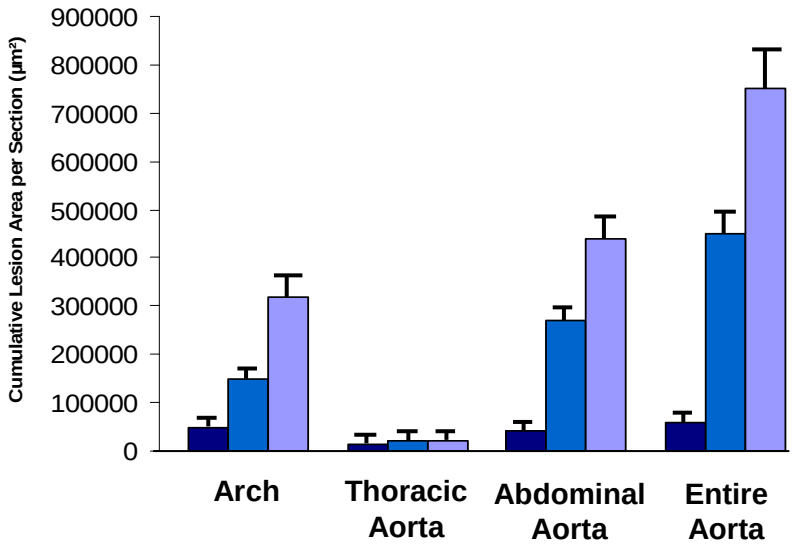
- Cell membrane constituent
- Stored in lipid droplets/bodies
- Synthesis of steroid and oxysterols
- Regulation of development (shh modification)

Maternal Hypercholesterolemia Enhances Fatty Streak Formation in Foetal Aortas

Intimal Lipid Accumulations in Foetal Aortas



Cumulative area with lesions

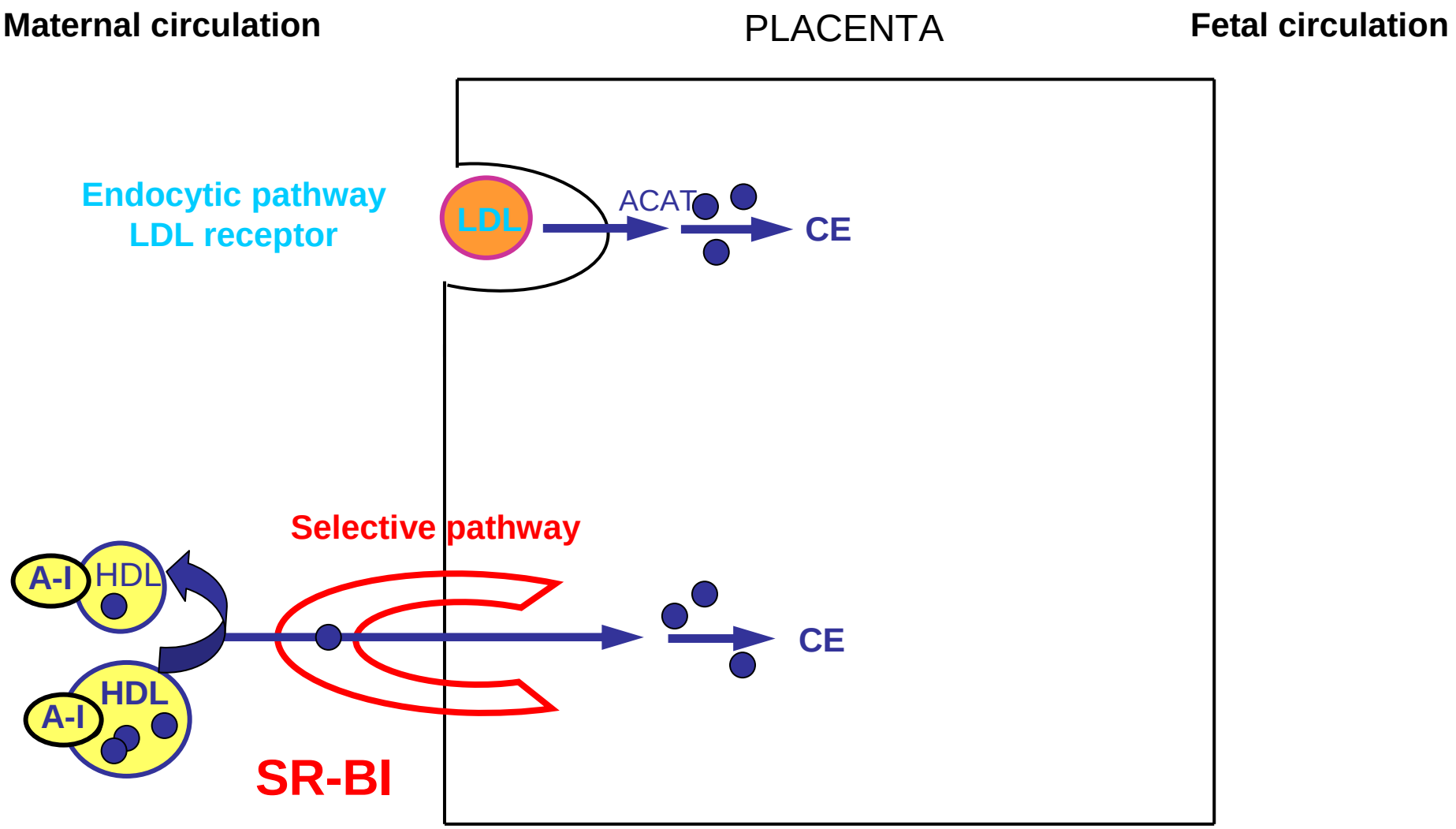


Foetal age: 6.2 ± 1.3 mo

- Normocholesterolemia
- Transient Hypercholesterolemia
- Hypercholesterolemia

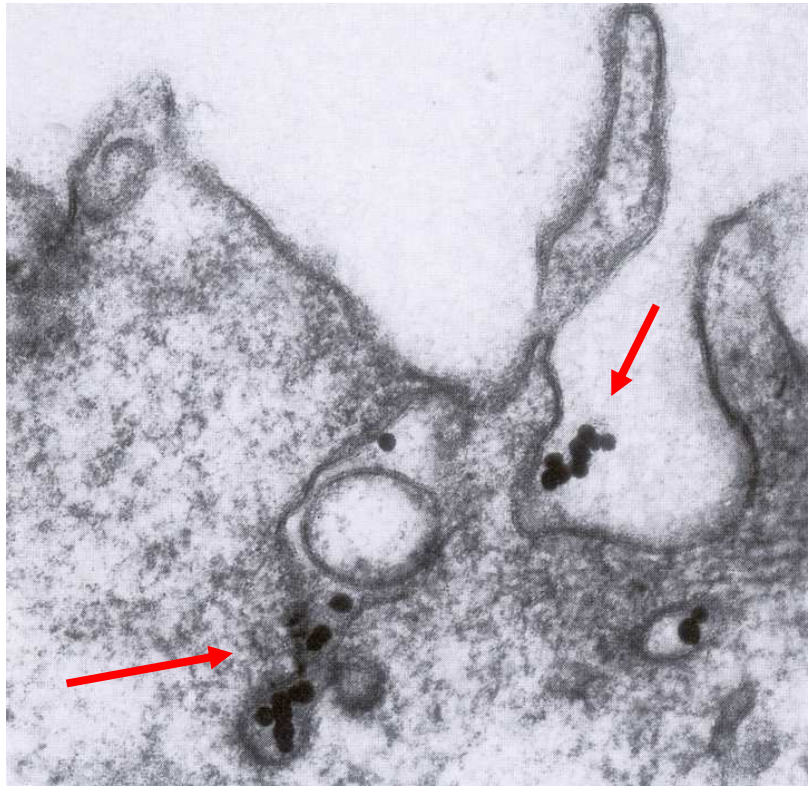
Napoli et al. JCI 100, 2680, 1997

Pathways of Placental Lipid Metabolism



LDL and HDL receptor are expressed on the syncytiotrophoblast

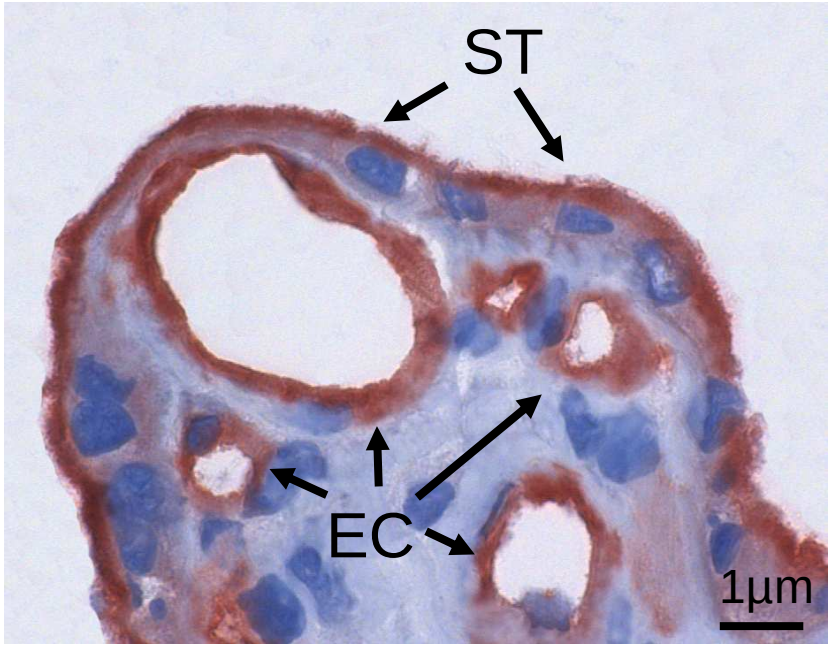
LDL-R



Malassine et al. Histochem 1987

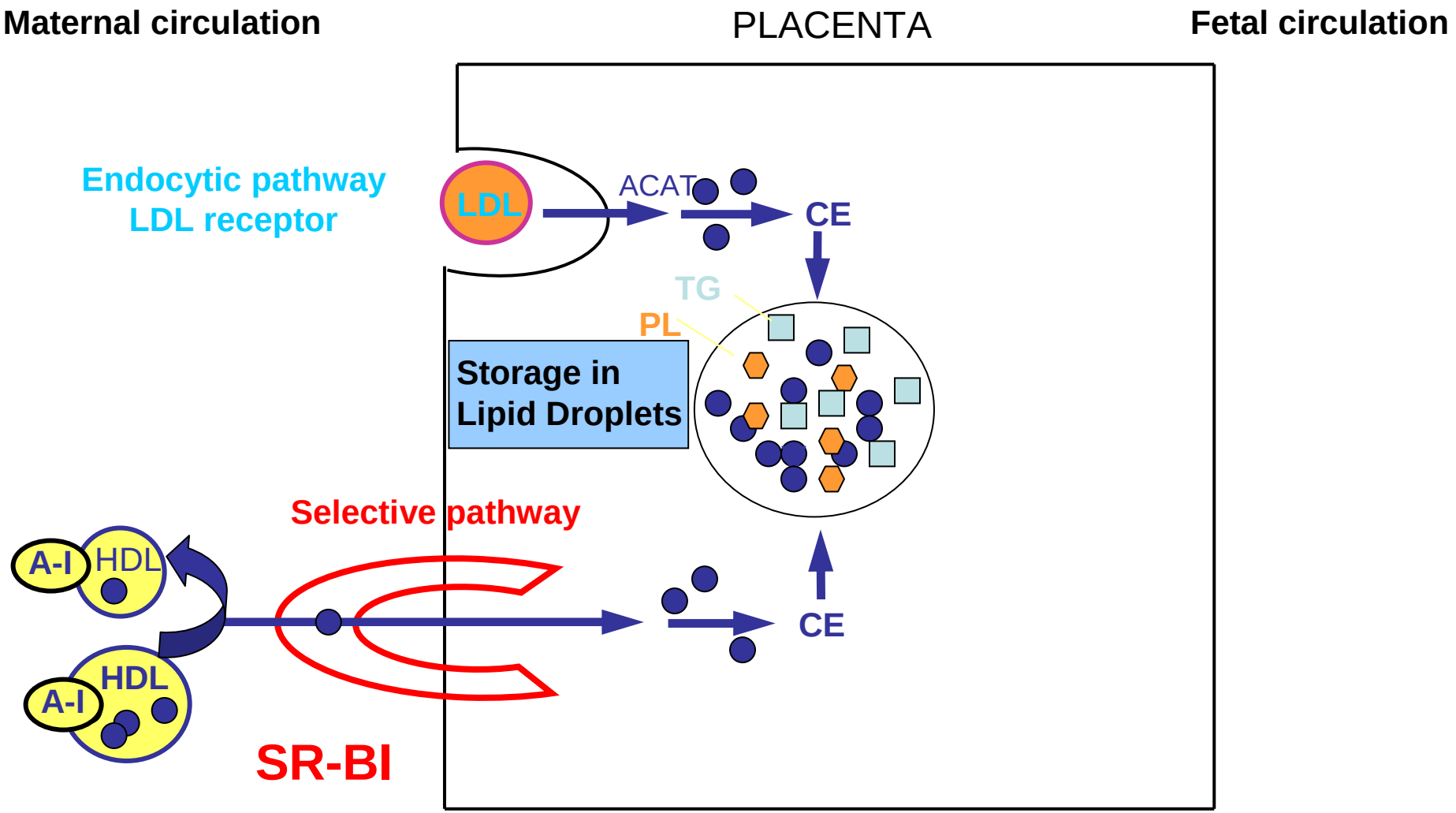
HDL-R

SR-B1

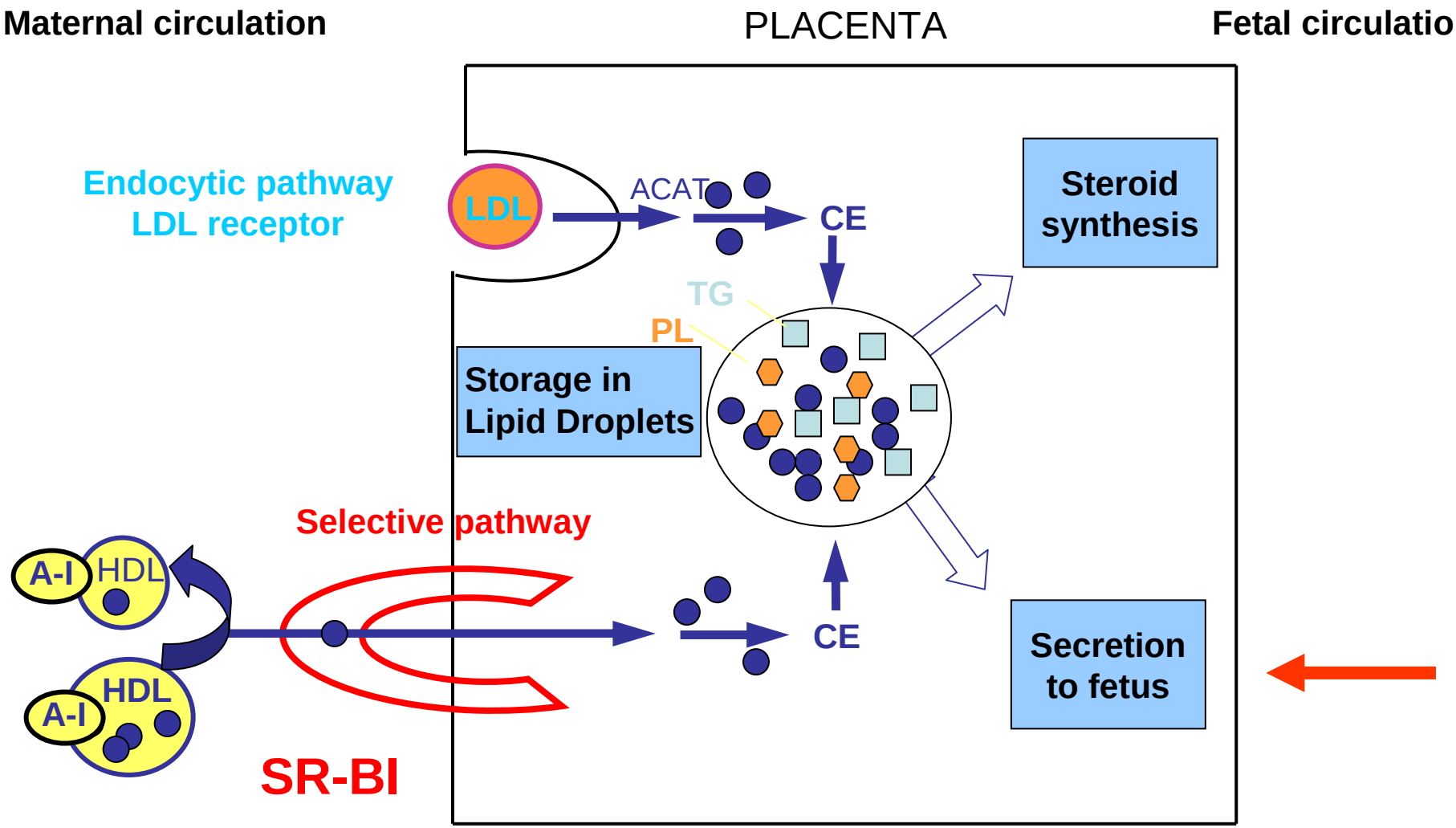


Wadsack & Desoye, unpublished

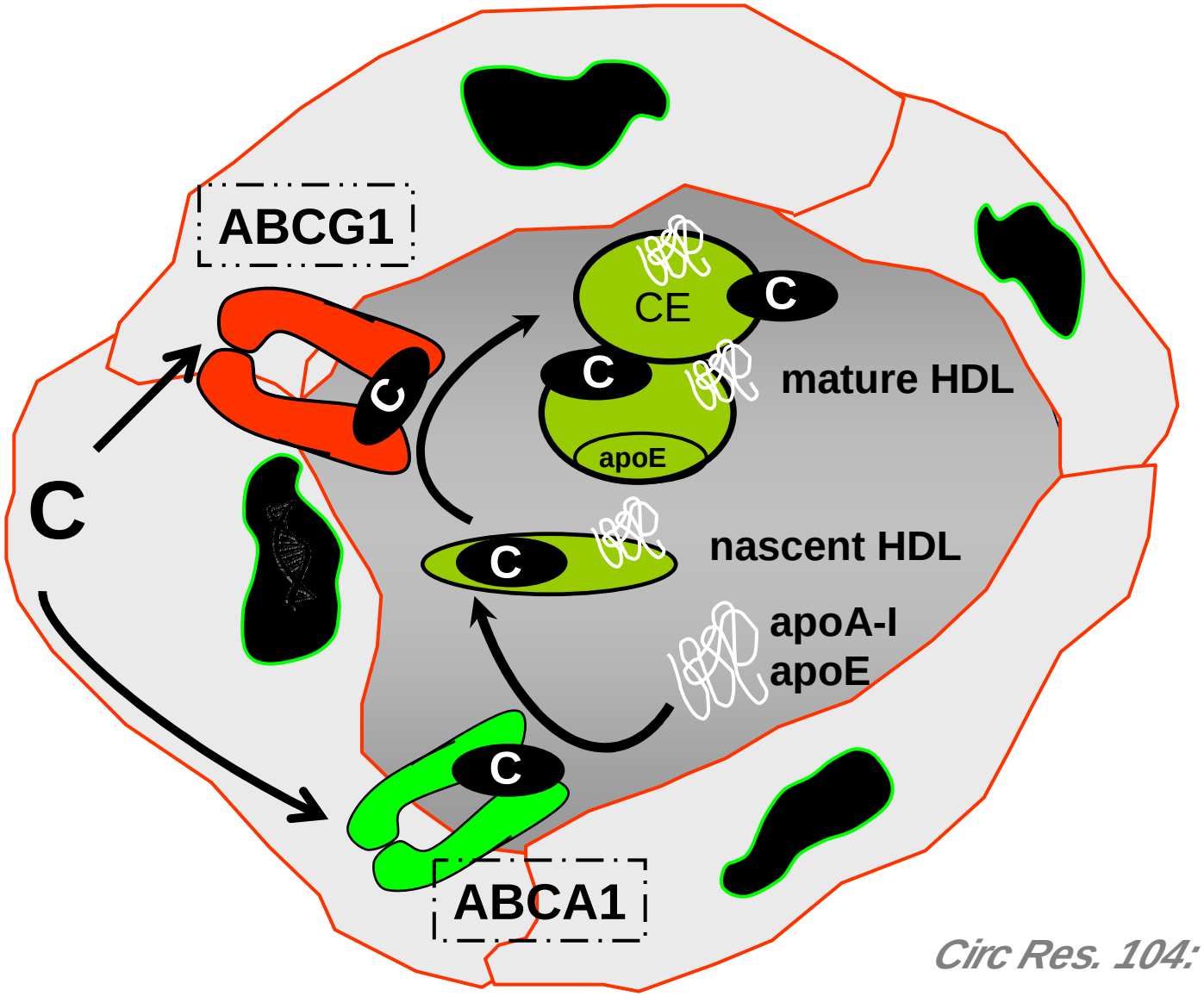
Pathways of Placental Lipid Metabolism



Pathways of Placental Lipid Metabolism



Cholesterol efflux from placental endothelial cells to the foetal circulation



Circ Res. 104: 600, 2009

Phospholipid transfer protein (PLTP)

- Mediates PL transfer between lipoproteins

  (Huuskonen et al. Biochemistry 2000)

- Involved in vitamin E delivery to endothelial cells

  (Desrumaux et al. FASEB J 1999)

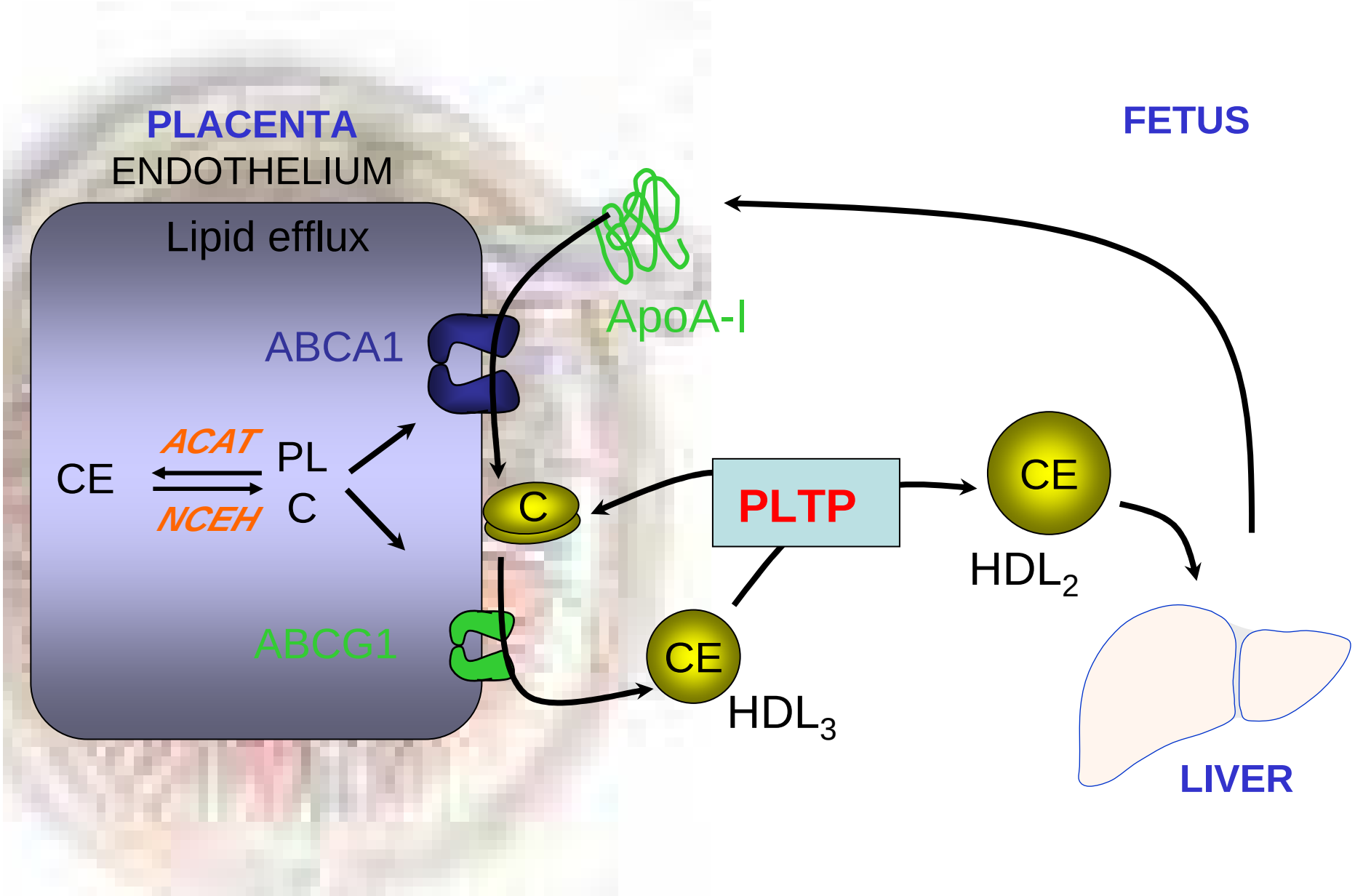
- Enhances cholesterol efflux to HDL

  (Wolfbauer et al. Biochim Biophys Act 1999, Oram et al. J Biol Chem 2003)

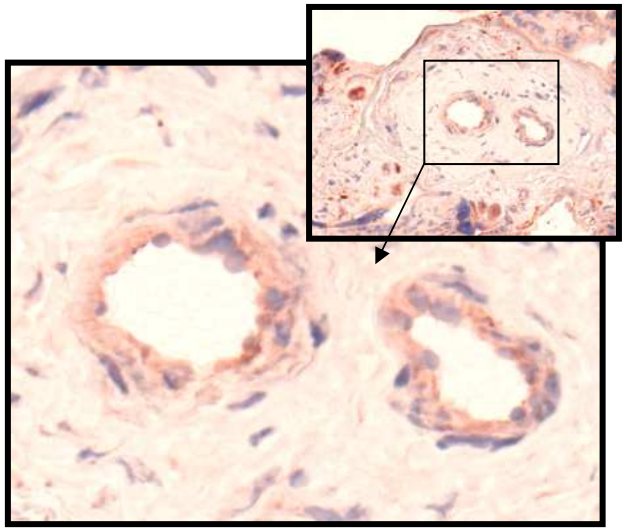
- Contributes to the remodeling of HDL_3 → generation of large HDL_2 and nascent HDL particles

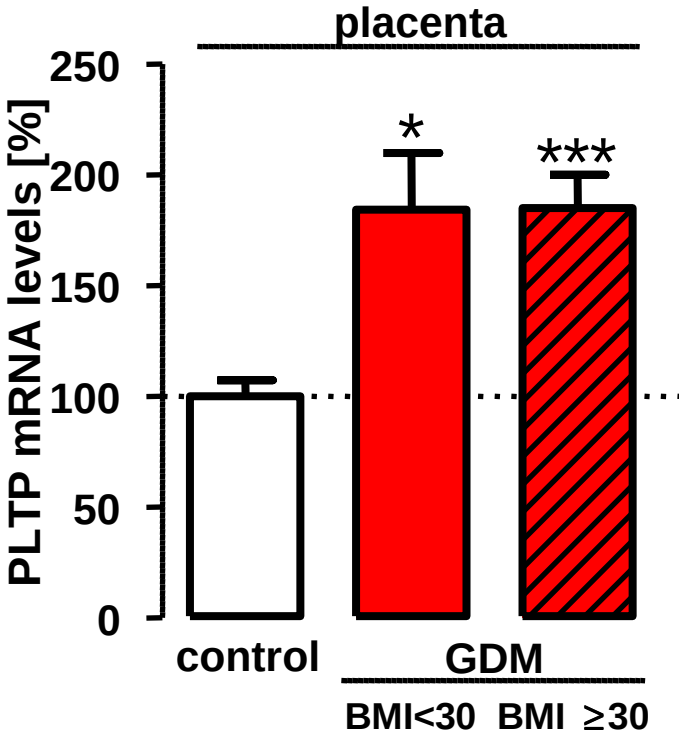
  (Jauhiainen et al. J Biol Chem 1993)

PLTP modifies HDL



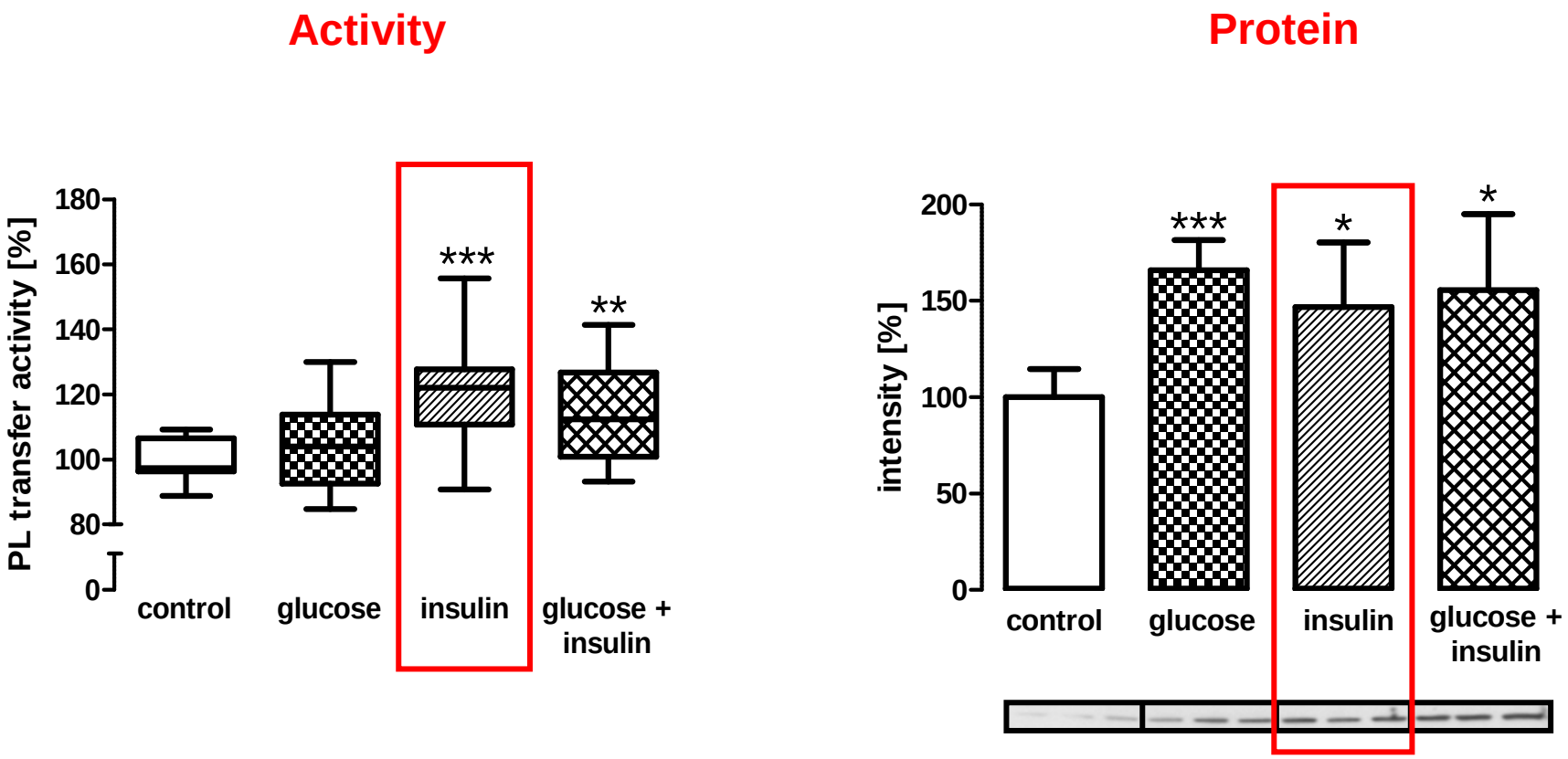
Placental PLTP is expressed foeto-placental endothelium and up-regulated in GDM





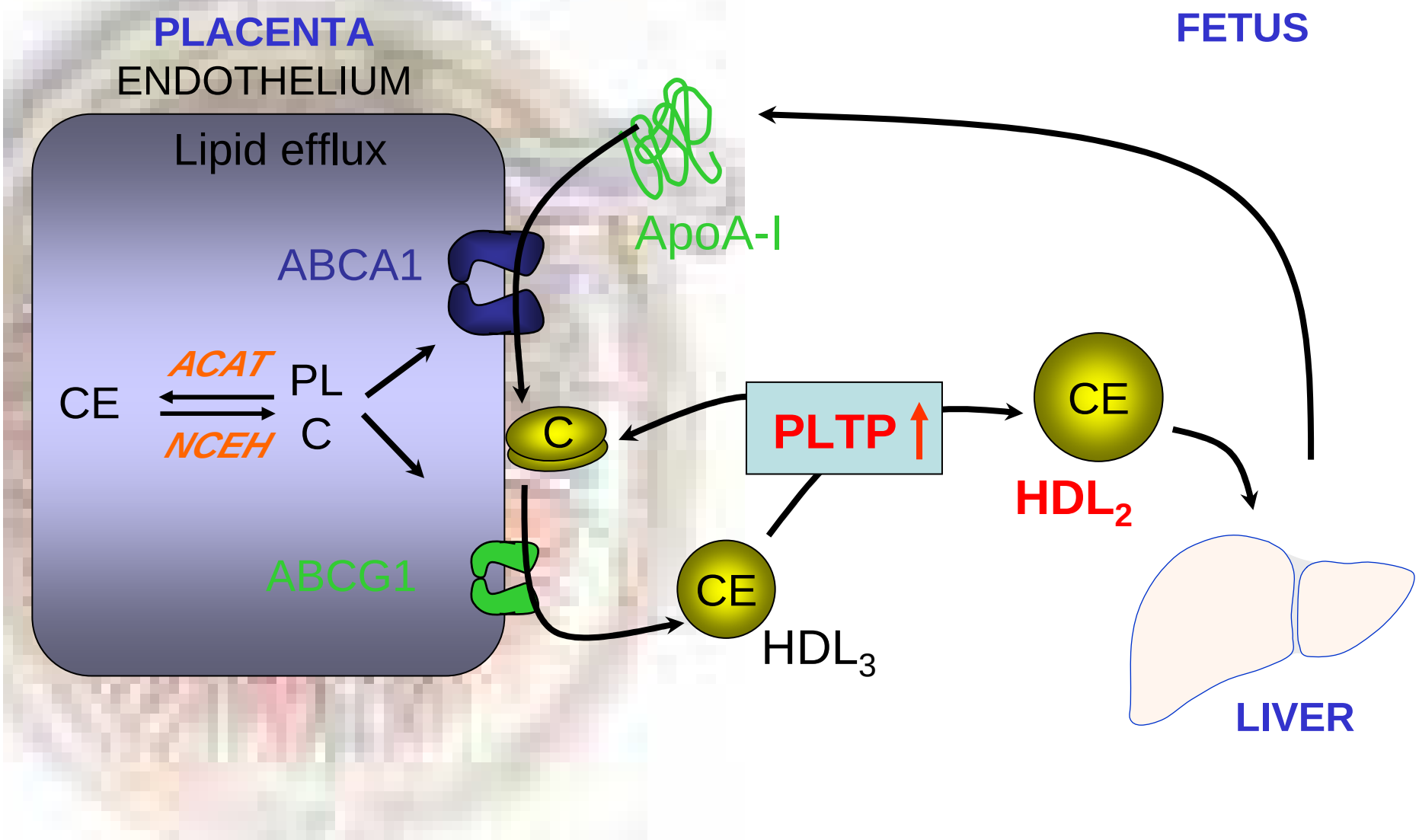
Scholler et al. J Clin Endo Metab, 2011

Insulin increases endothelial PLTP

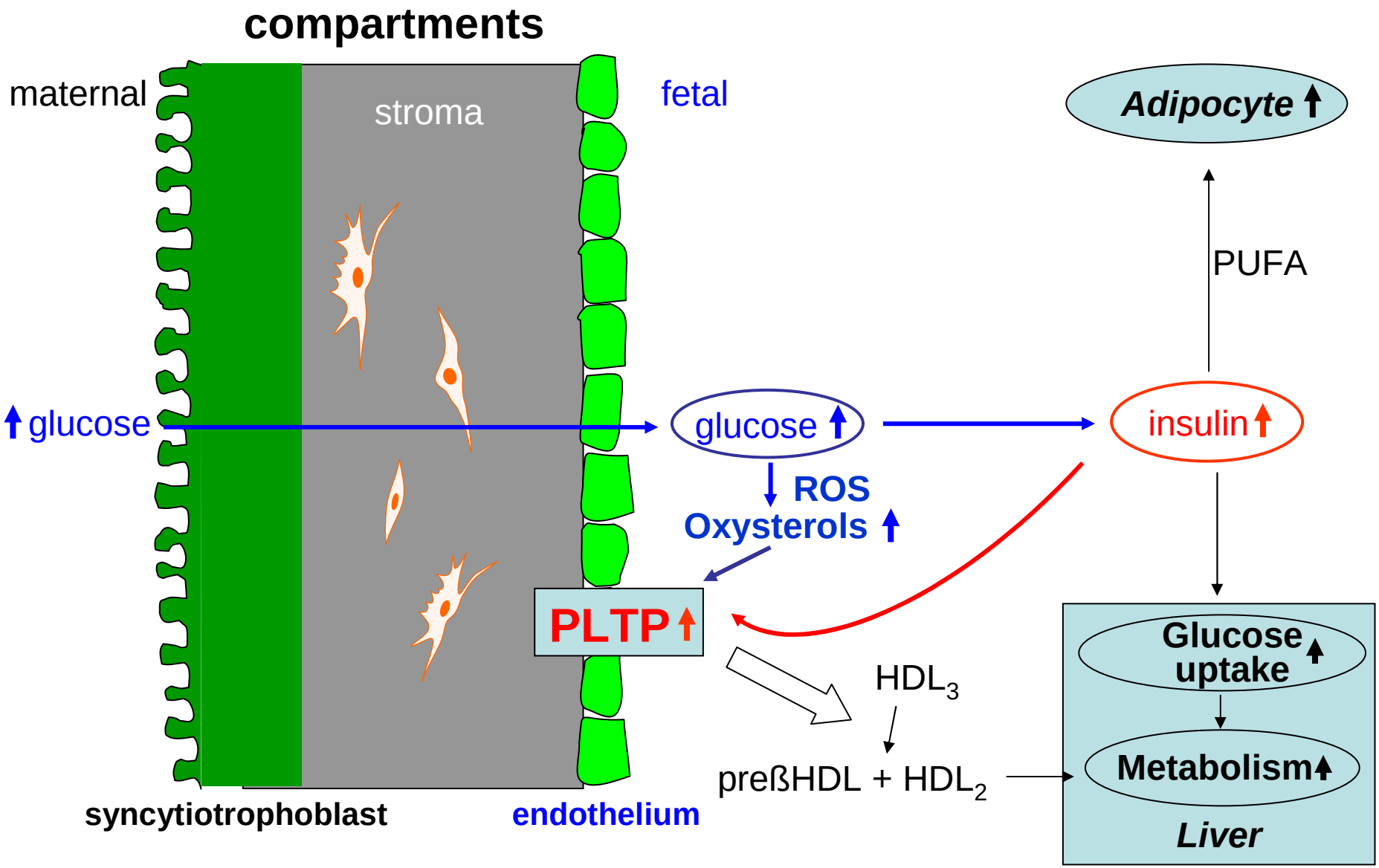


Scholler et al. J Clin Endo Metab, 2011

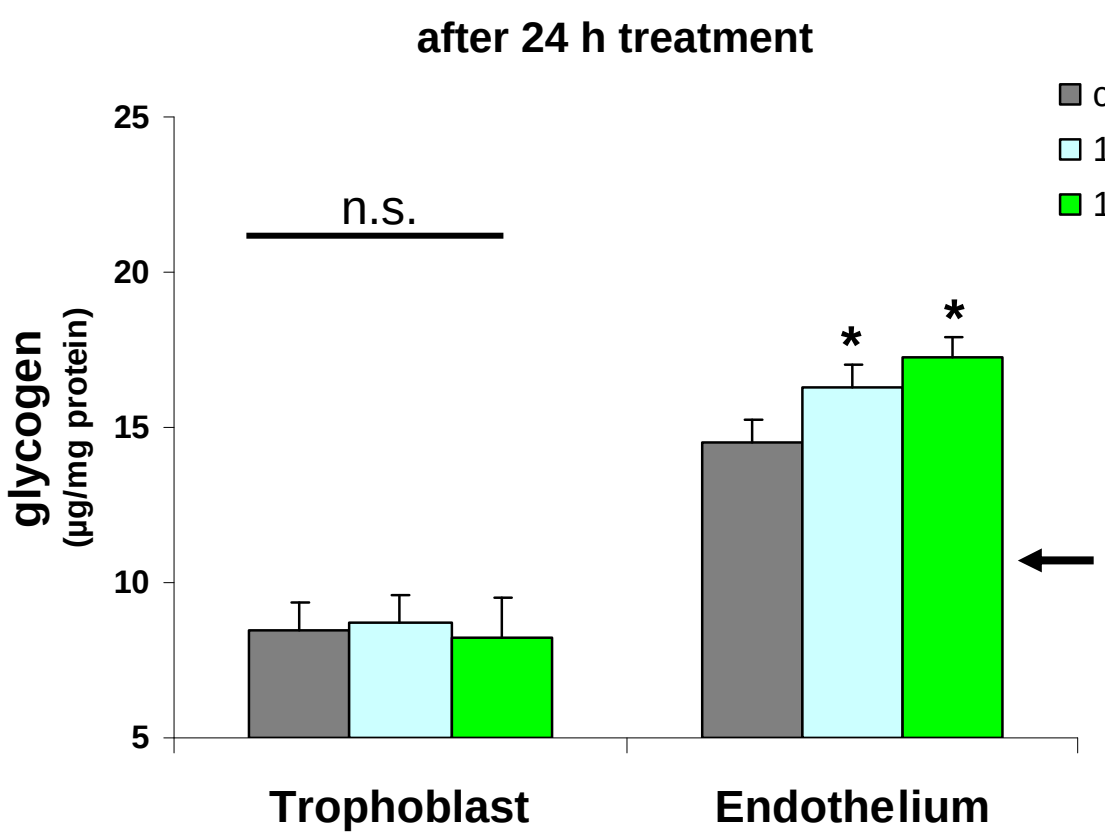
PLTP modifies HDL to reduce atherogenic risk



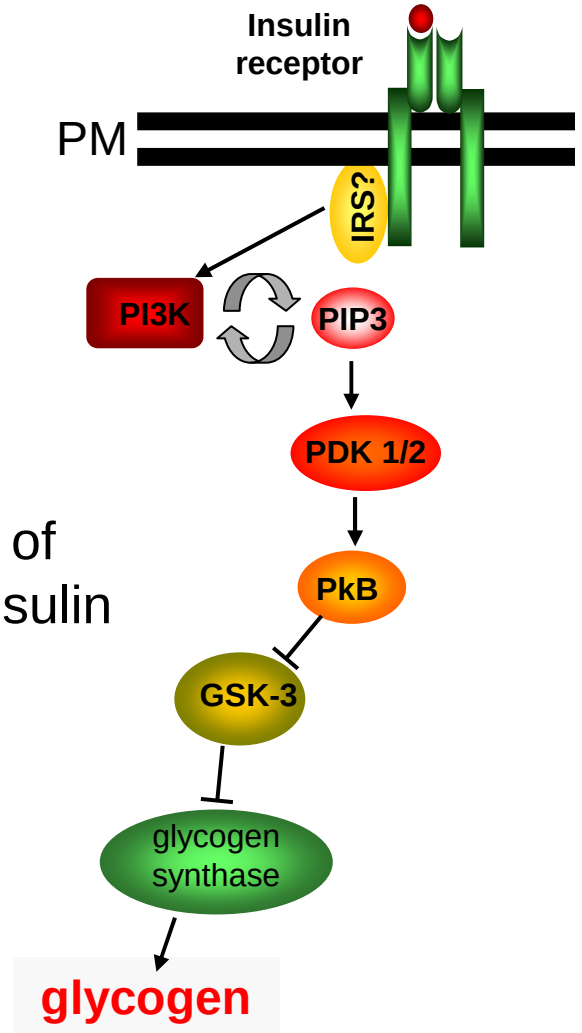
Foetal glucose & insulin lead to multiple effects on metabolism at feto-placental interface



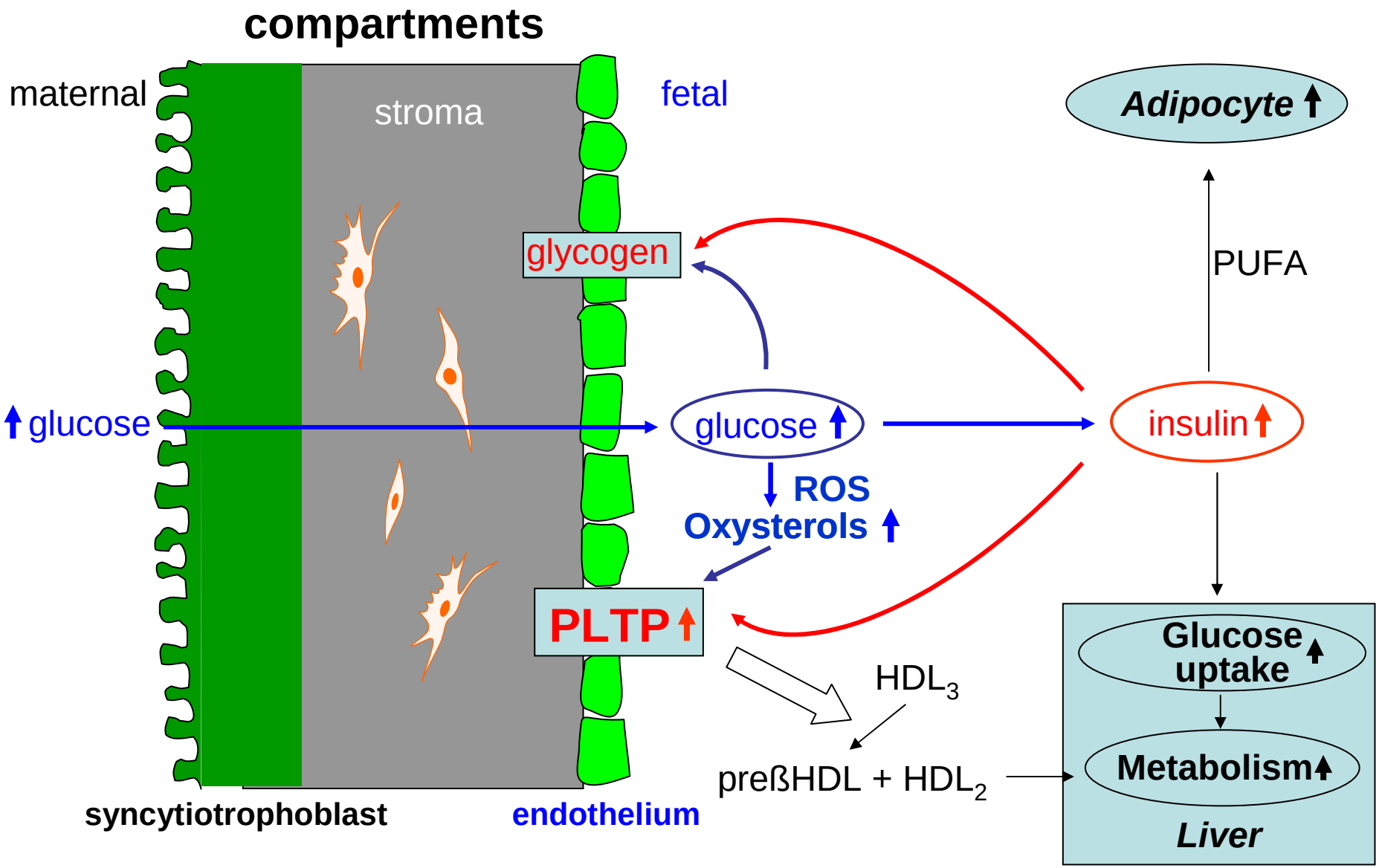
Insulin Upregulates Glycogen only in the Endothelium of Term Human Placenta



Result of fetal insulin



Foetal glucose & insulin lead to multiple effects on metabolism at feto-placental interface



Take home messages

The human placenta does not appear to limit maternal-to-foetal flux of glucose (and fatty acids)

The rate limiting step for maternal-to-foetal fatty acid transport is unknown

LCPUFAs are selectively transferred across placenta and extracted in foetus

Take home messages (cont'd)

The foetal glucose insulin axis is an important driver for maternal-foetal transport as well as for regulating foetal fat deposition

The intrauterine environment of the first trimester of gestation may already play a key role in determining foetal growth

Note of caution

- A-V difference
- Effect of foetal sex
- Third trimester/term of gestation vs earlier stages

Aachen:

Peter Kaufmann

Gabi Kohnen

Amsterdam:

Mireille van Poppel

Brisbane:

David McIntyre

Buenos Aires:

Alicia Jawerbaum

Veronica White

Cleveland, OH/Paris:

Sylvie Hauguel-de Mouzon

Jerusalem:

Eleazar Shafrir

Madrid:

Emilio Herrera

Iliana Lopez-Soldado

Henar Ortega

Manchester:

Carolyn Jones

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Martha Lappas

Padma Murthi

Richard Saffery

Nottingham:

Lopa Leach

Milano:

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Silvia Tabano

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Mario Klingler

Bert Koletzko

Rome:

Giorgio Sesti

Zagreb:

Josip Djelmis

Marina Ivanisevic

Christian Wadsack

Ursula Hiden

Thank you for your attention!