Early life origins of diabetes: new ways to intervene

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Overview

- Diabetes – the extent
- What defects cause diabetes?
- Insulin action
- Early life factors and diabetes
- New ways to intervene
- The future?

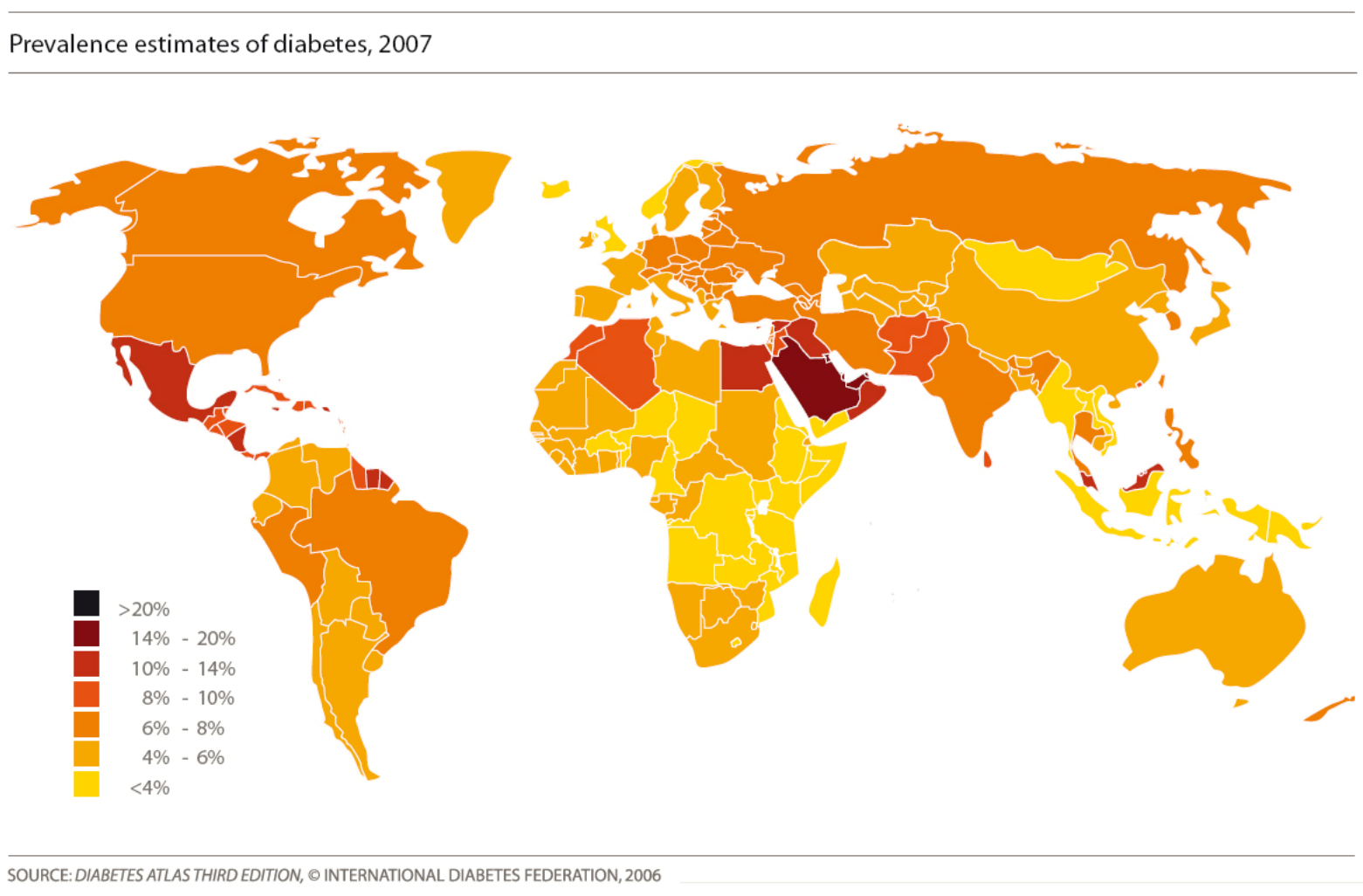
Diabetes – the extent

- Globally :
  - incidence will increase by 46% this decade
  - 300 million people with diabetes by 2025

  - Adult onset, type 2 diabetes (T2DM) ~90%

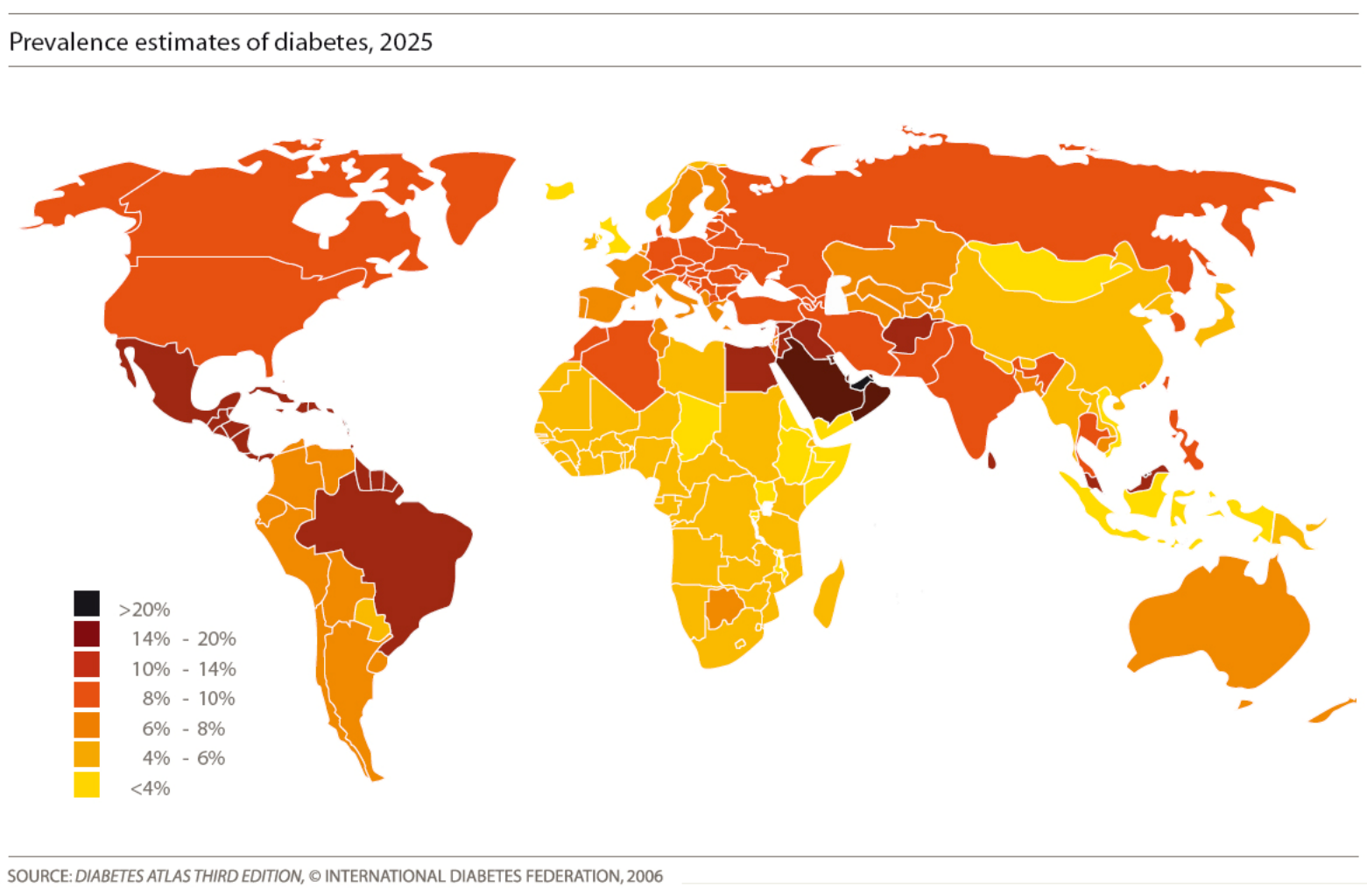
Zimmet P et al 2001 Nature 414: 782-787

Estimated prevalence of diabetes: 2007



Diabetes Atlas, 3rd edition © International Diabetes Federation, 2006

Estimated prevalence of diabetes: 2025



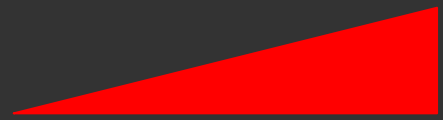
Diabetes Atlas, 3rd edition © International Diabetes Federation, 2006

What causes diabetes?

- Insulin secretion

- Insulin sensitivity

- Hyperglycaemia



Impaired insulin action increases blood glucose

Insulin secretion

Insulin

- peptide hormone
- synthesised by beta cells of pancreas

- released in response to rise in blood glucose or other nutrients

- promotes glucose uptake
- inhibits production and release of glucose

by sensitive tissues

Insulin sensitivity

Insulin sensitive tissues

- Liver
- Skeletal muscle
- Adipose tissue

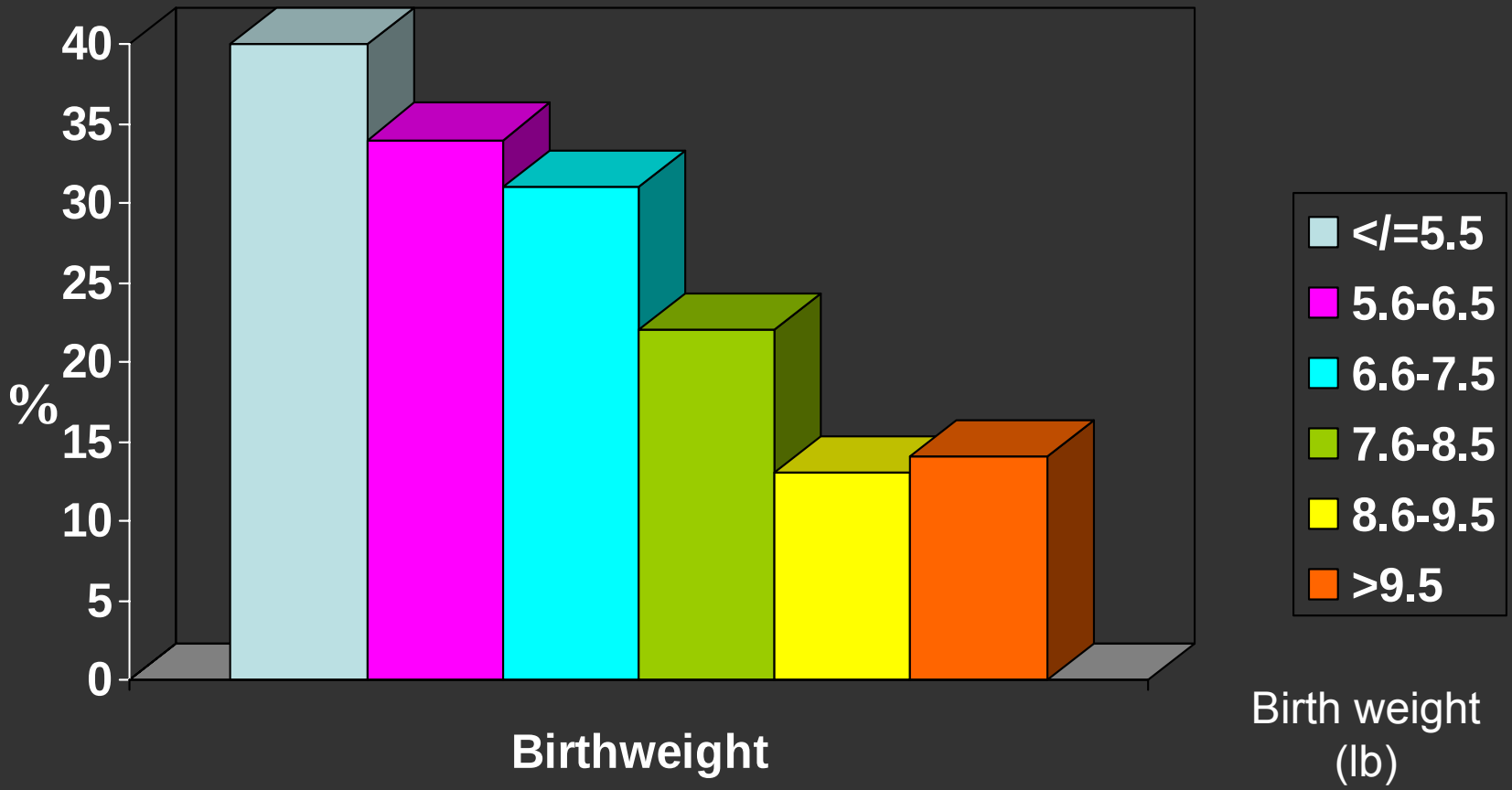
Early life factors and diabetes

Mothers in Hitchin, Hertfordshire at the turn of the 20th century

Ledger entry in 1917, Hertfordshire

Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	R	D	T
8¾ lbs	24½ lbs	B.	11	Y	-	-	4
Healthy & well developed.				Buckland School. Card to S.[illegible]			
7 lbs	15¾ lbs	B	12	N.	Y.	Y.	8
Moved to Bury Green. [illegible] Hadham.				Had measles, pneumonia & [illegible]			
8	20	Bot.	11	Y.	Y.	?	4
[illegible] in [illegible] neck opened. Ant. fontanelle still open 2 3 yrs. Abdomen very large & [illegible]							
8½	22	B.B.	9	Y	Y	Y	10
Healthy & normal.				Buckland School. Card [illegible]			

Prevalence of type 2 diabetes and impaired glucose tolerance* in men aged 59-70 years



* Plasma glucose concentration >7.8 mmol/l at two hours after challenge.

Hales et al, 1991

Diabetes and small size at birth

Population study of men aged up to 80 yrs old in Sweden

- Being <3kg at birth accounted for 18% of population risk for diabetes
- 1kg ↑ in birth weight 53% ↓ in prevalence of diabetes

Eriksson et al 2004 J Internal Med 255: 236-246

Diabetes and small size at birth

Insulin resistance

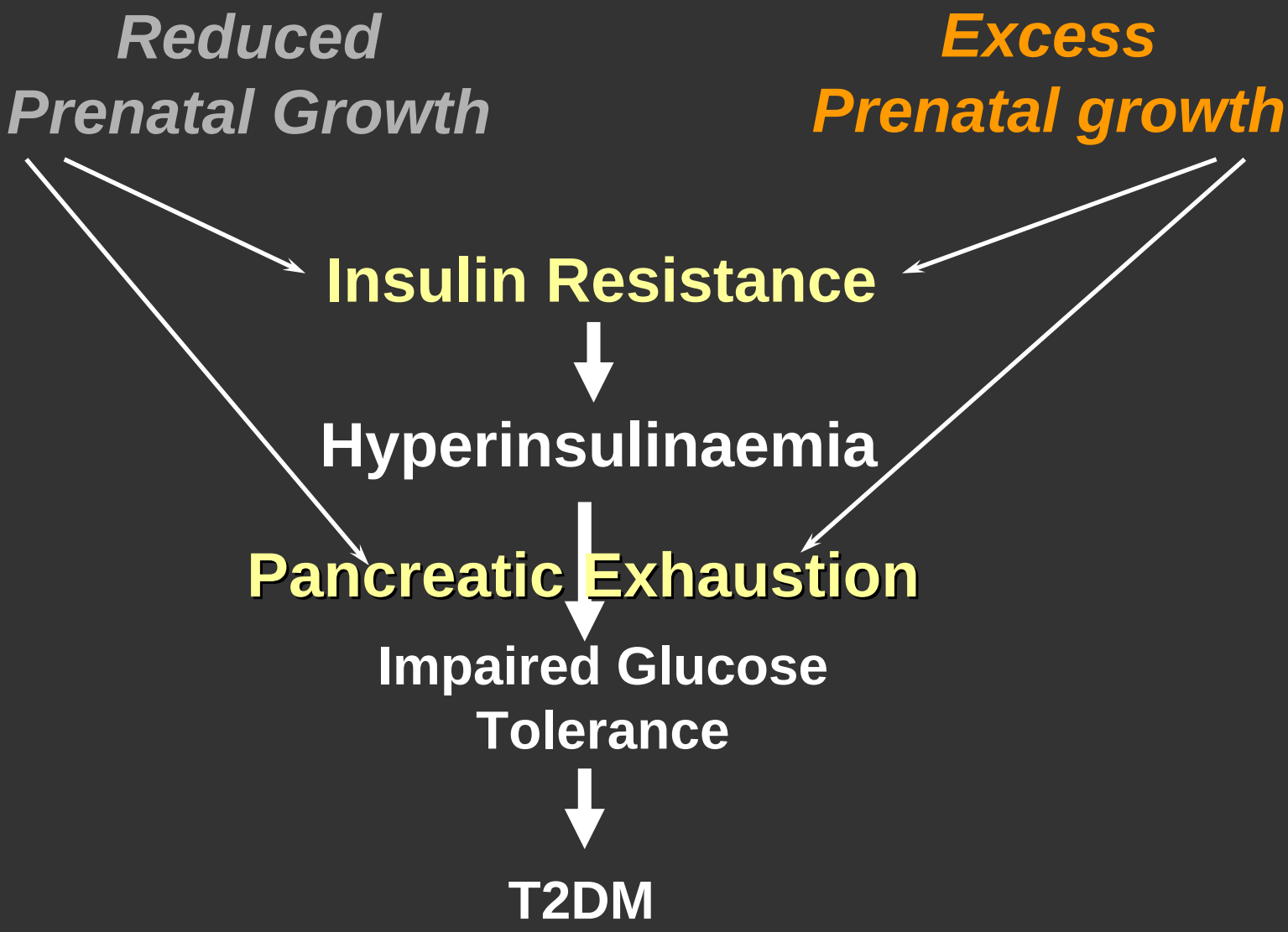
- Increased fasting plasma insulin (20/26)
- Measures of insulin resistance (17/22)

Impaired insulin secretion

- Variable insulin secretion (16/24 increased, 7/24 decreased)
- **Direct measures show insulin deficiency of early onset**

(Newsome et al 2003; Jacquet et al 2001)

Early life programming of diabetes



Early life programming

‘Disturbance of the environment in early life,

at critical stages of development of regulatory systems and their target tissues,

alters structural and functional development,

impairing functional capacity longer term,

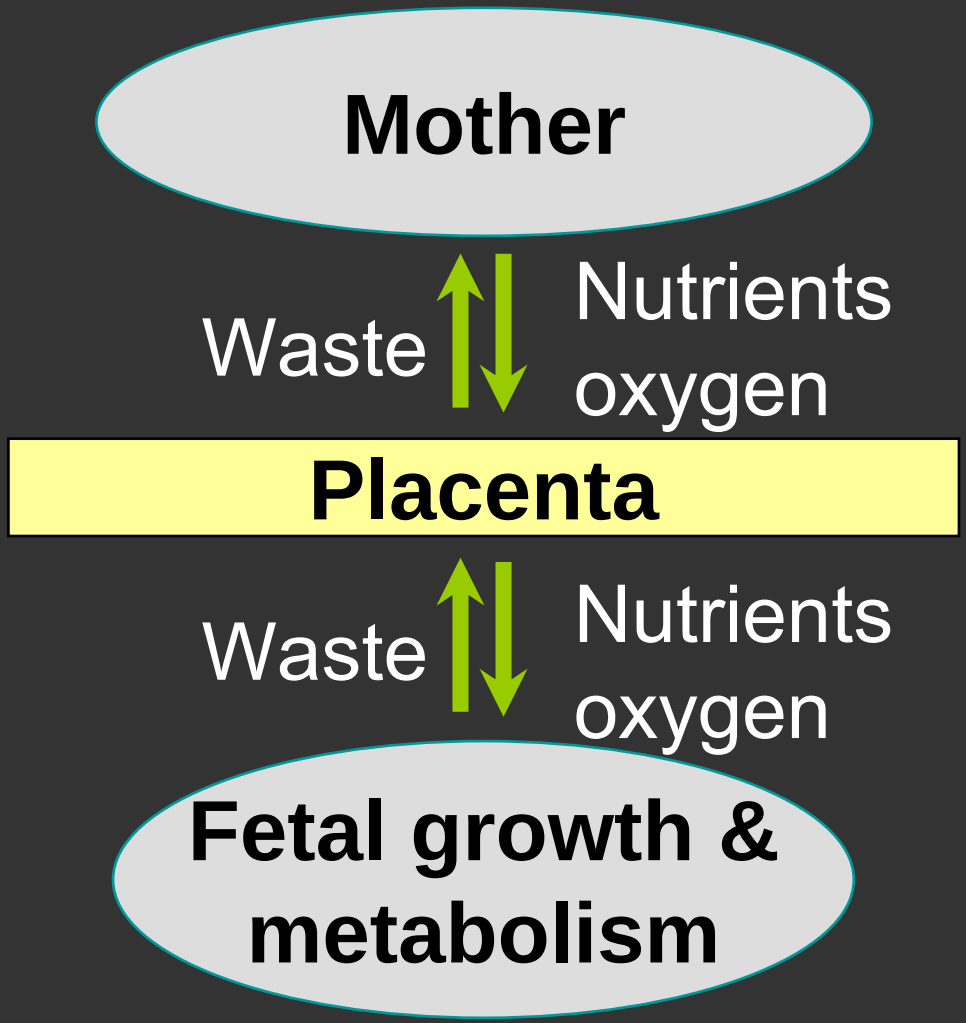
and predisposing to disease in later life’

Targets

- **beta cells of pancreas**
- **liver**
- **skeletal muscle**

IUGR and insulin action in humans

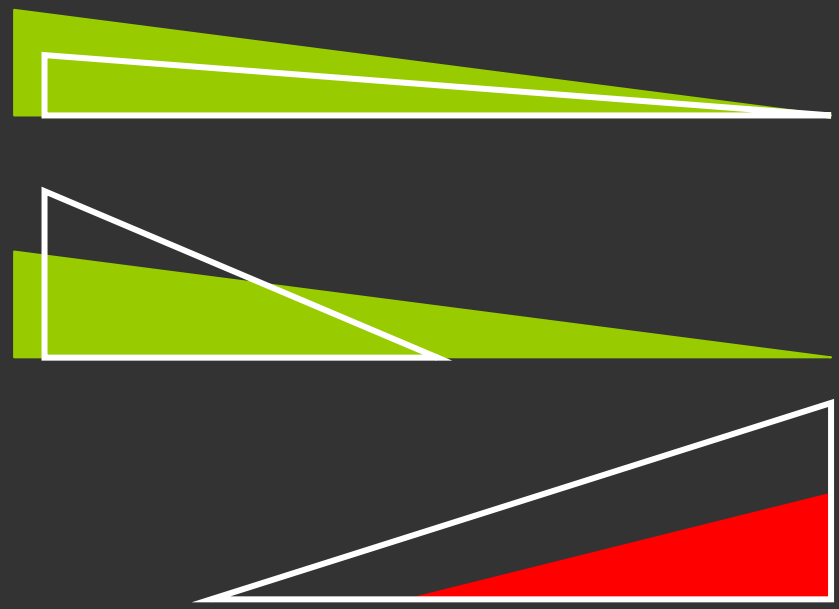
Placental insufficiency and IUGR



- ↓ oxygen
- ↓ glucose
- ↓ amino acids
- ↓ methyl groups
- ↓ insulin, IGFs, TH
- ↑ cortisol and catecholamines
- ↓ tissue energy substrates

IUGR and insulin action in humans

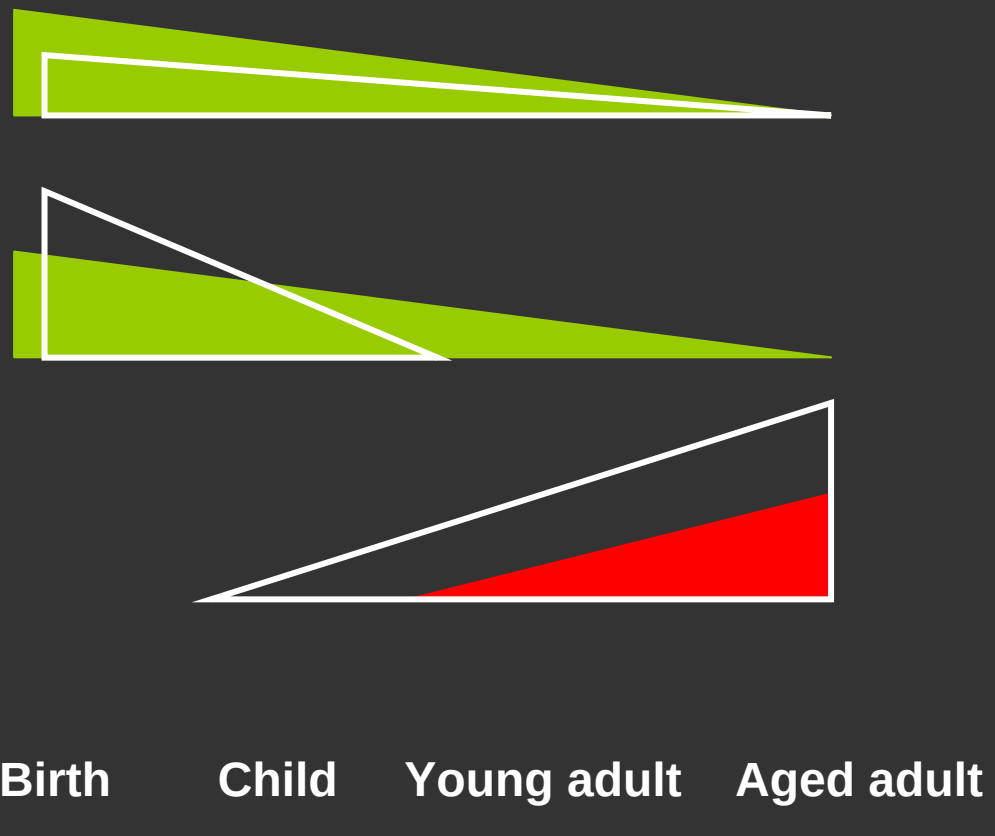
- Insulin secretion
- Insulin sensitivity
- Hyperglycaemia



Birth **Child** **Young adult** **Aged adult**

New ways to intervene in IUGR?

- Insulin secretion
- Insulin sensitivity
- Hyperglycaemia



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  - Normalise placental delivery of nutrients and oxygen before birth?
  - Specific micronutrient or nutrient supplementation?

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New ways to intervene in IUGR to prevent diabetes?

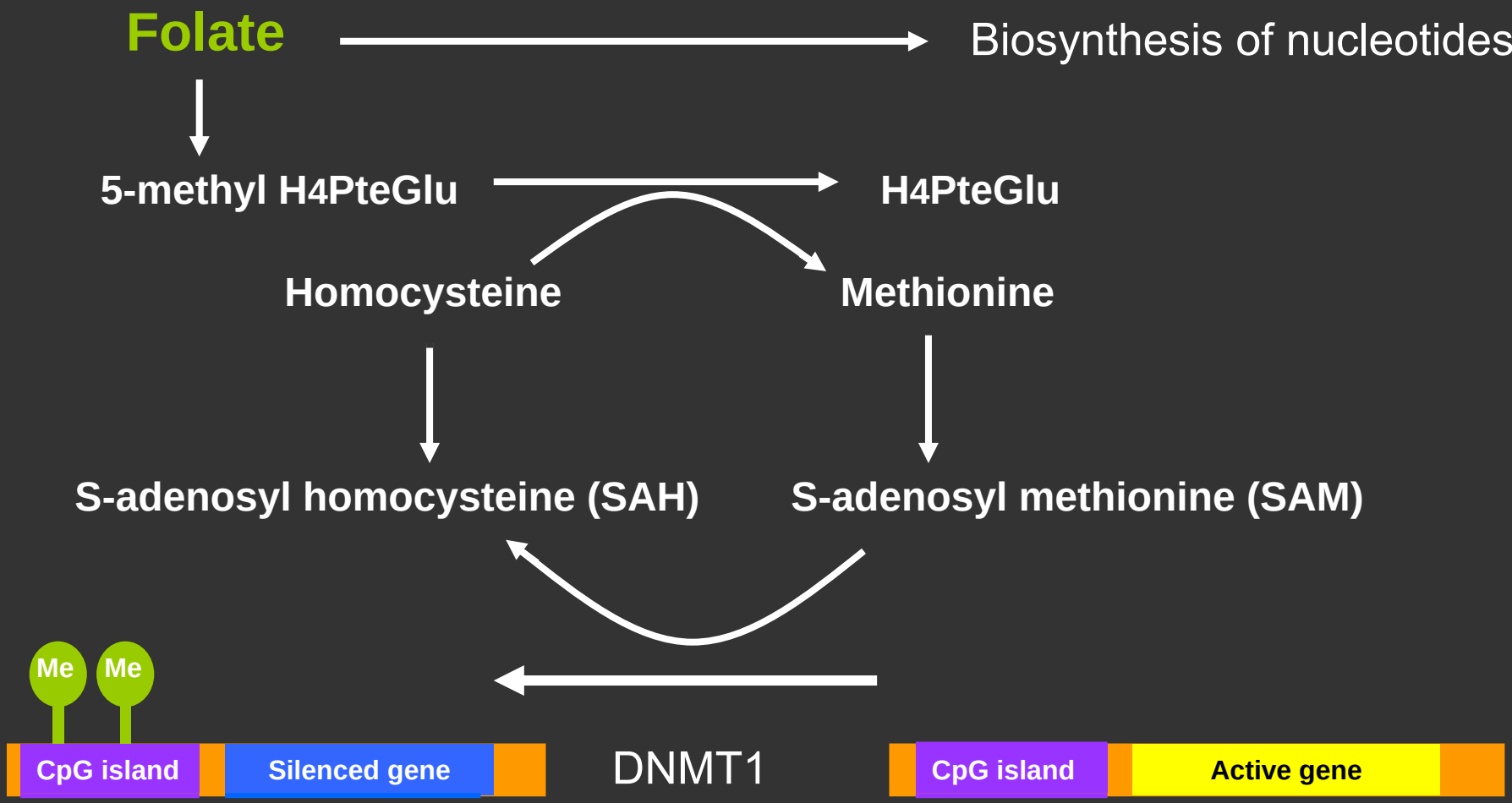
Pre-clinical testing:

- Prevention (before birth)
  - Methyl donors (folate): insulin secretion and sensitivity

DNA methylation: an epigenetic mechanism

- Epigenetics: heritable changes in gene expression potential
- Molecular mechanisms
  - encode information with no change in DNA sequence
  - Heritable through mitosis and meiosis: *persists*
  - Four types….include
    - DNA methylation

Role of Folate in DNA methylation

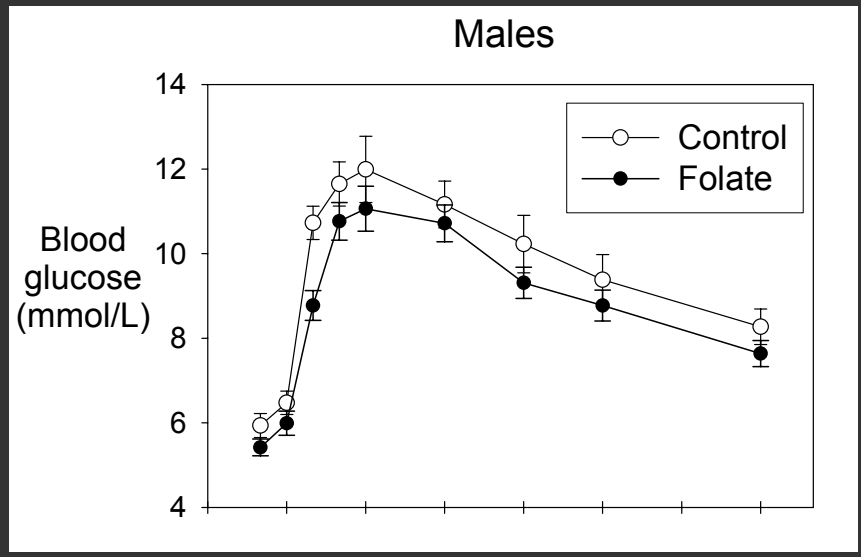


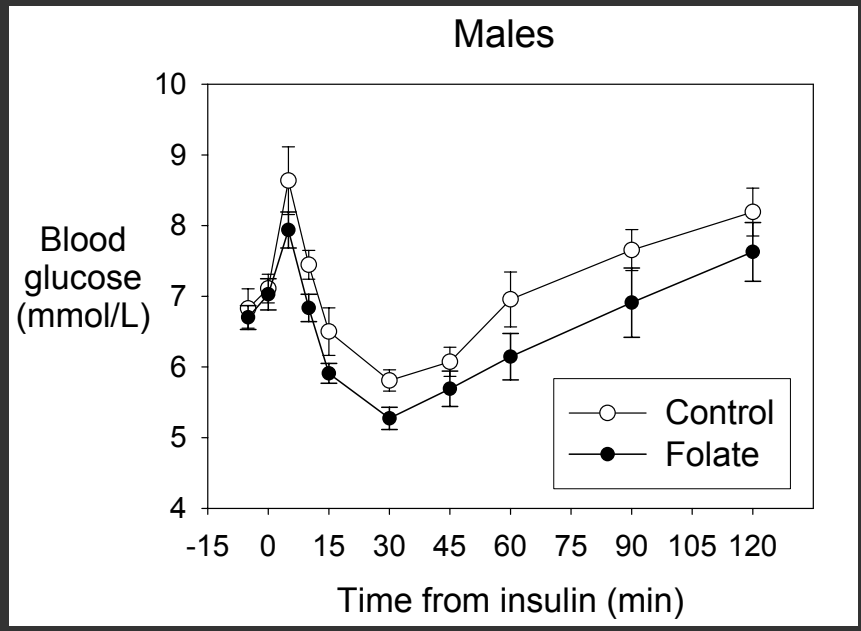
(Lucock, 2000)

Maternal folic acid supplementation

- improves glucose tolerance
- does not alter insulin secretion
- improves insulin sensitivity

in young adult male offspring





New ways to intervene in IUGR to prevent diabetes?

Intervention (after birth)

- Restore insulin secretion and/or sensitivity

New ways to intervene in IUGR

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    - Direct hormonal treatment to restore beta cell numbers and function (pdx-1)
    - Exercise

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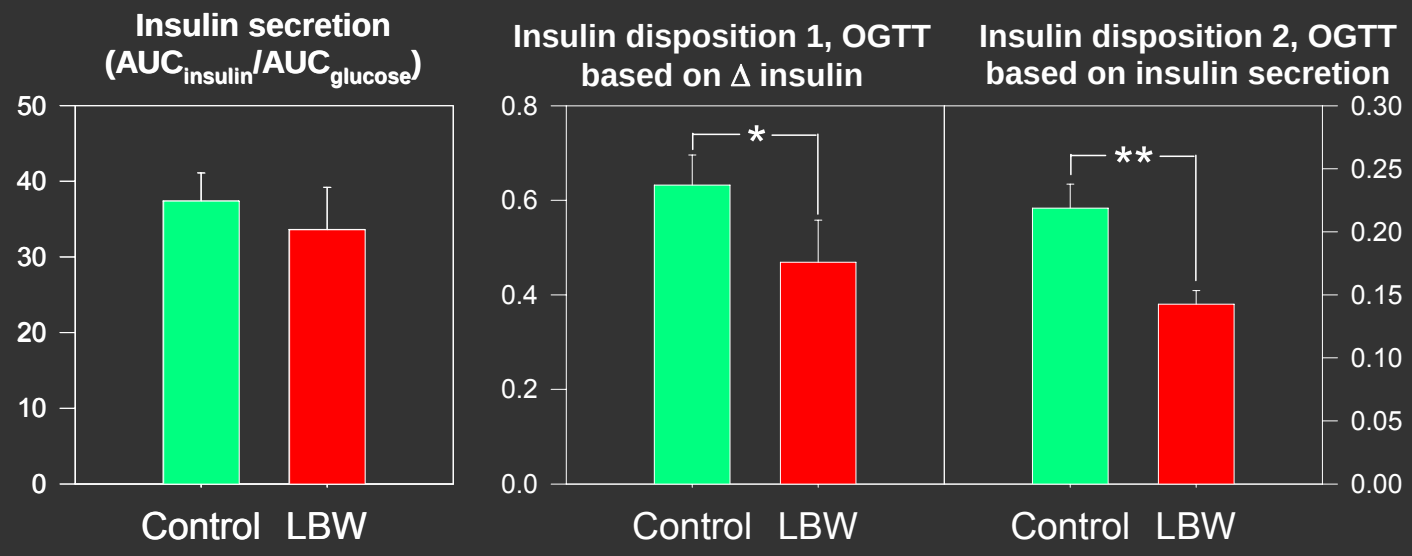
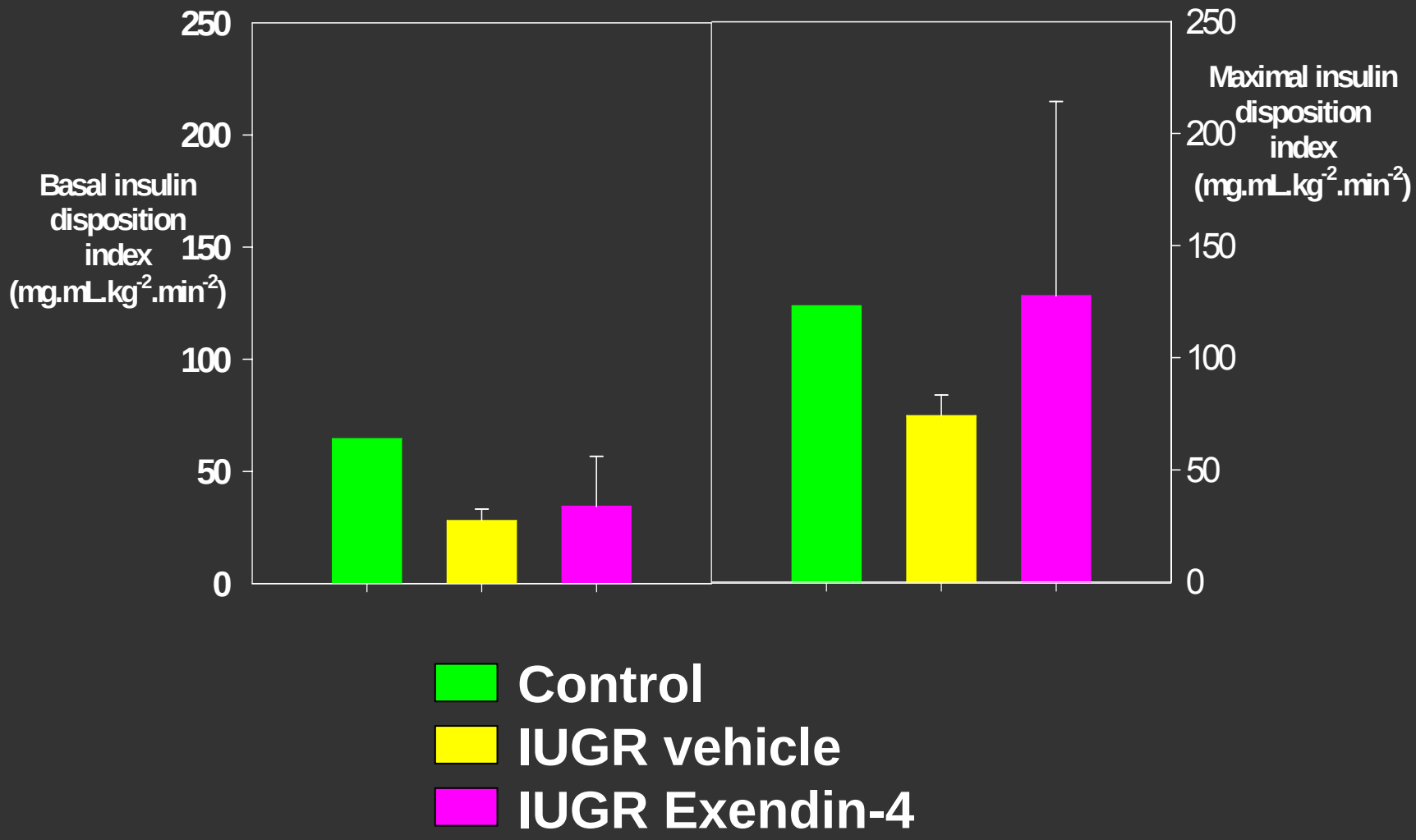
Early Differential Defects of Insulin Secretion and Action in 19-Year-Old Caucasian Men Who Had Low Birth Weight

Christine B. Jensen,[1] Heidi Storgaard,[1] Flemming Dela,[2,3] Jens Juul Holst,[4] Sten Madsbad,[1] and Allan A. Vaag[1,5]



Jensen CB et al Diabetes 2002 51:1271-1280

Exendin-4 (GLP-1) restores insulin action in juvenile lambs following IUGR



Macrosomia and insulin action in humans

Common risk factors for macrosomia

- Maternal diabetes
- Gestational diabetes
- Maternal overweight and obesity

New ways to intervene to limit macrosomia

- Maternal diabetes
  - Metformin (Dr Hague and colleagues, WCH and University of Adelaide)
- Gestational diabetes
  - intensive treatment (ACHOIS) (Prof Crowther and colleagues, University of Adelaide)
- Maternal overweight and obesity
  - limit weight gain (LIMIT) (Dr Dodd and colleagues, University of Adelaide)

New ways to intervene to limit diabetes?

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The future: *optimal early life environment for better health outcomes?*

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