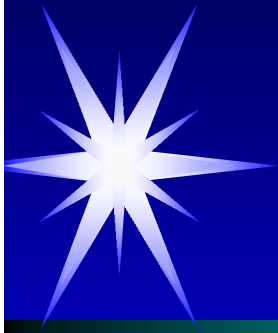




Division of  
Reproduction and Endocrinology

**KING'S**  
*College*  
**LONDON**

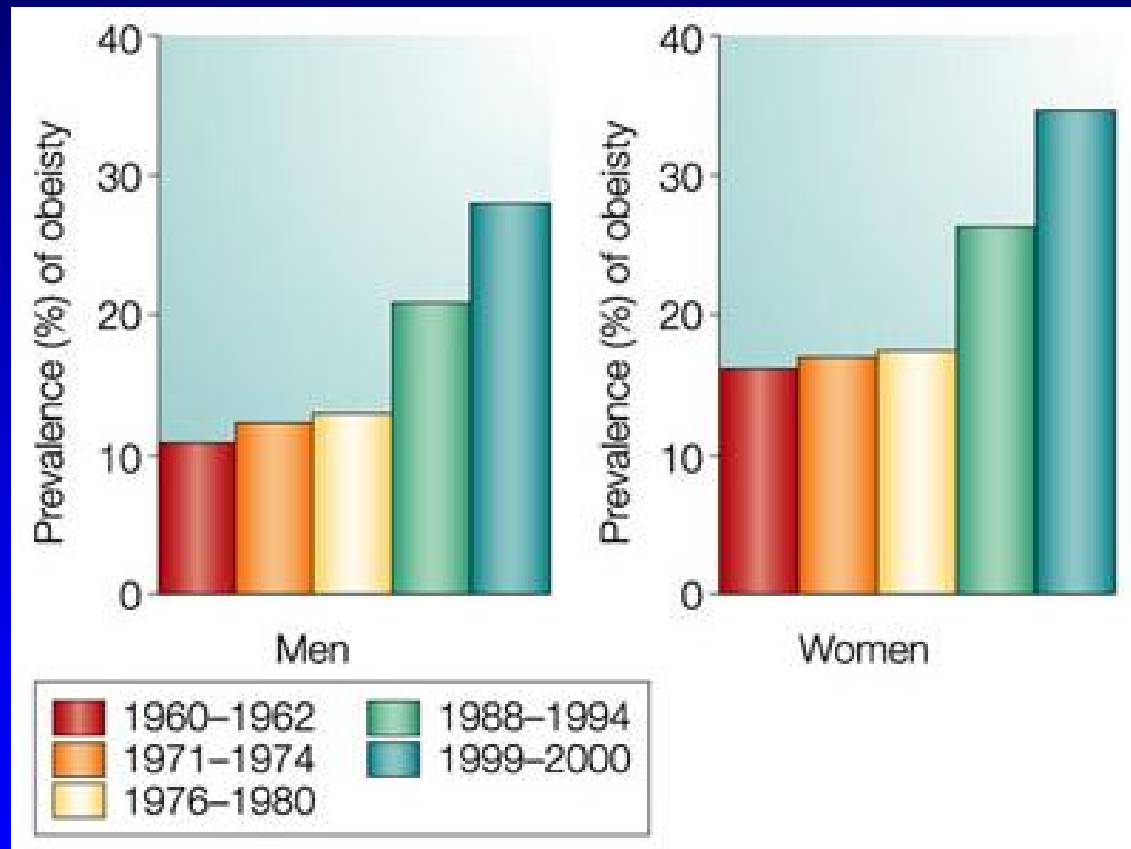


## Developmental Origins of obesity and the metabolic syndrome

Paul Taylor PhD

Maternal & Fetal Research Unit

# The Increasing Prevalence of Obesity in the USA

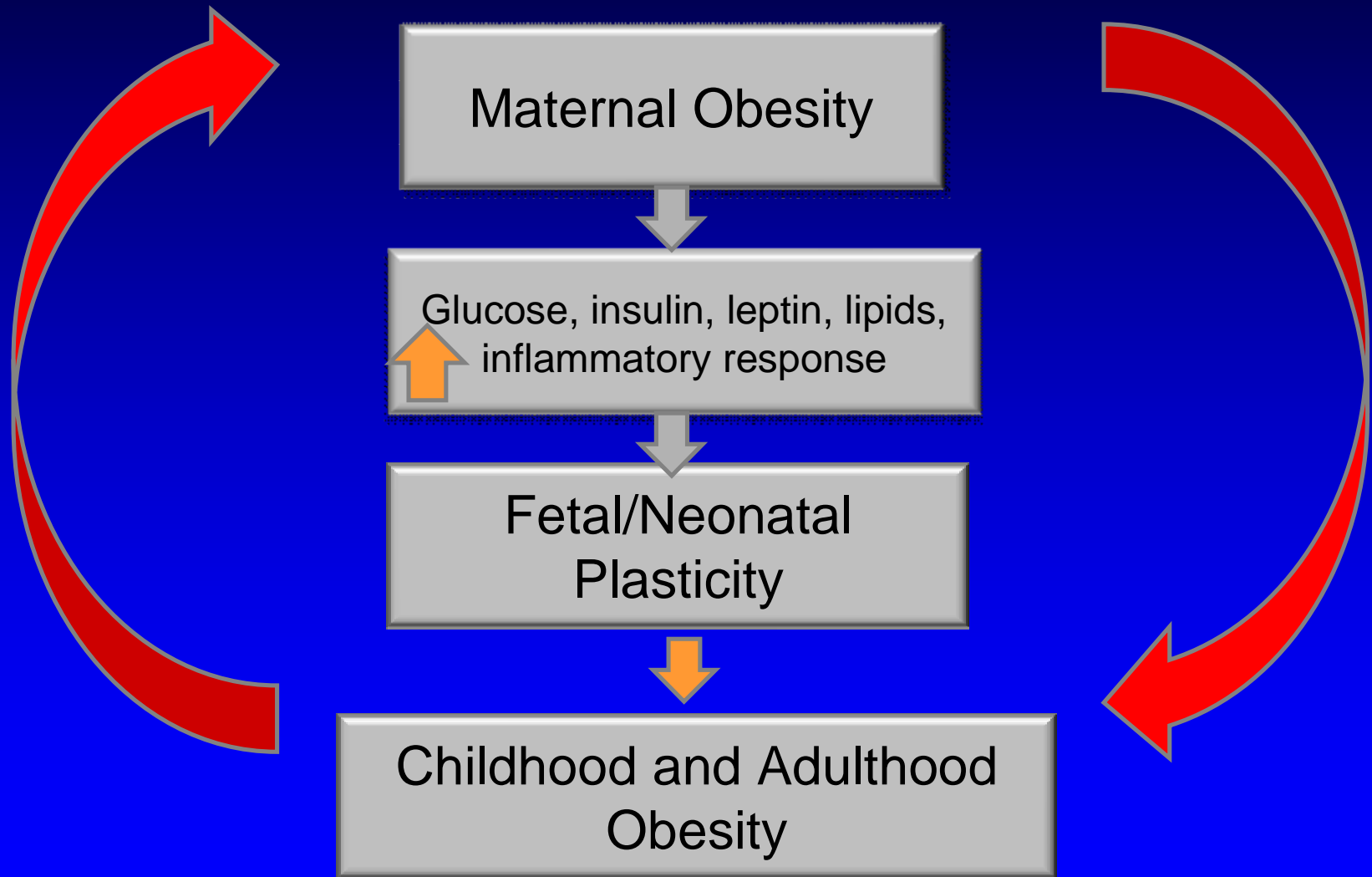


# USA statistics on maternal obesity



- NHANES Survey (1999-2002) - 29% non-pregnant women of reproductive age (20-39 years) are obese (Hedley et al., 2004).
- Excessive nutrient intake during gestation - shift to increasing gestational weight gain (Siega-Riz et al., 2006).
- Combined effect of high energy diets and maternal obesity on fetal development – predisposition to offspring obesity and T2D

# *Transgenerational 'Acceleration' of Obesity?*

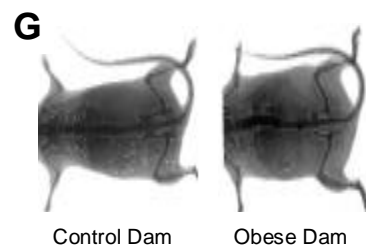
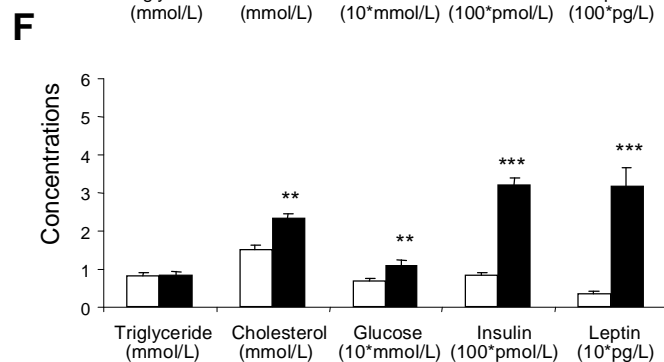
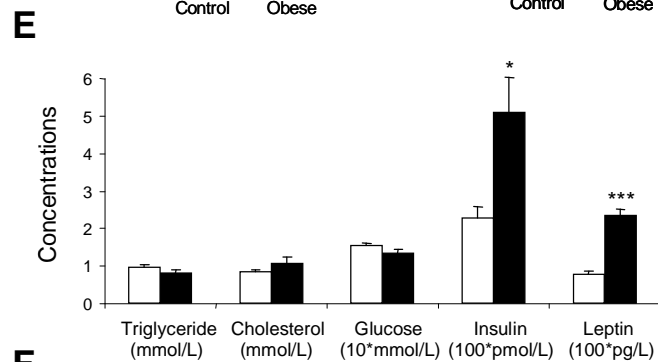
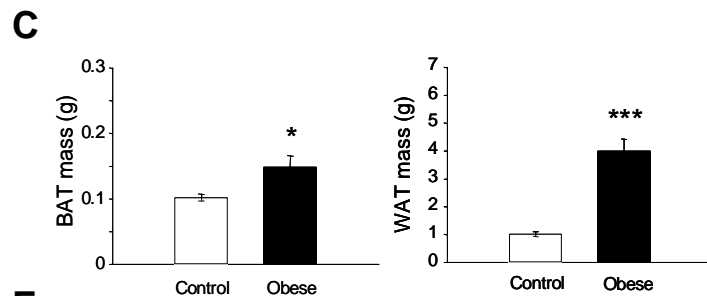
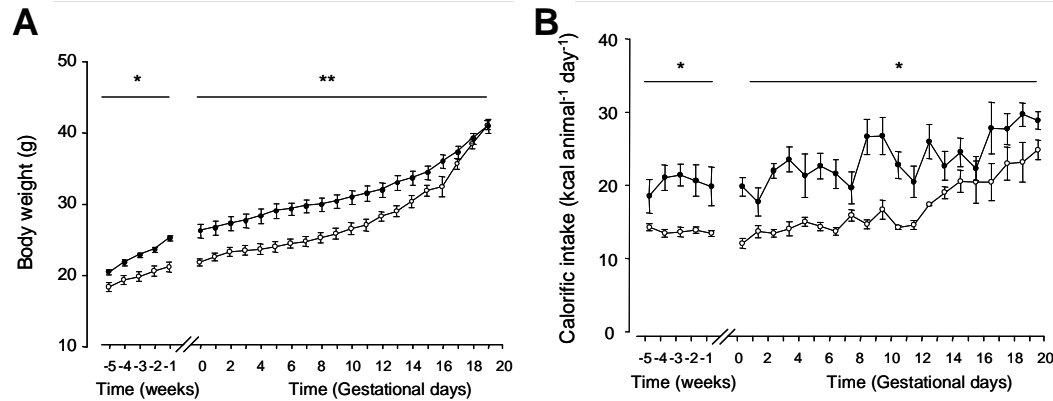


## Developmental programming studies in animals:

- Reduce possible genetic influence
- Relatively quick life cycle
- Environment can be tightly controlled
- Enable different diets to be tested
- Investigate critical periods

# Maternal Phenotype In the Mouse

(Samuelsson et al,  
*Hypertension* 2007)



	CONTROL	OBESE
Lean mass (g)	20.5	18.8
Fat mass (g)	3.6	9.8
% Fat	14.8	34.4

A) Body weight

B) Food intake

C) Fat mass (WAT)

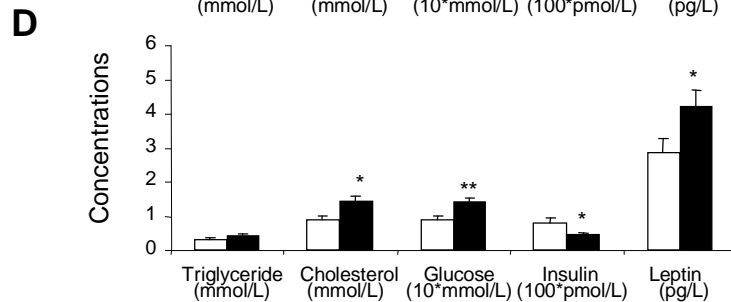
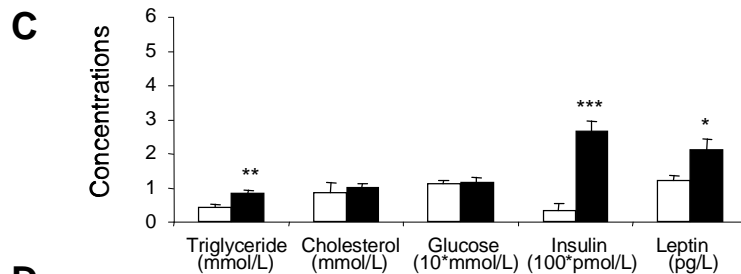
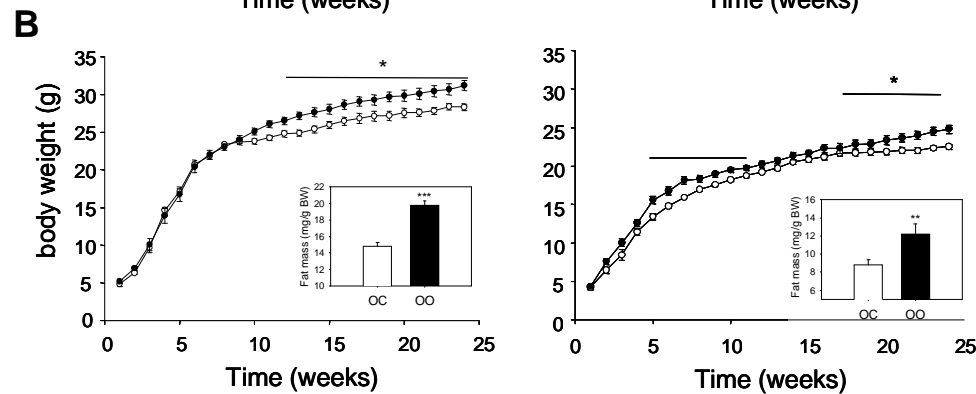
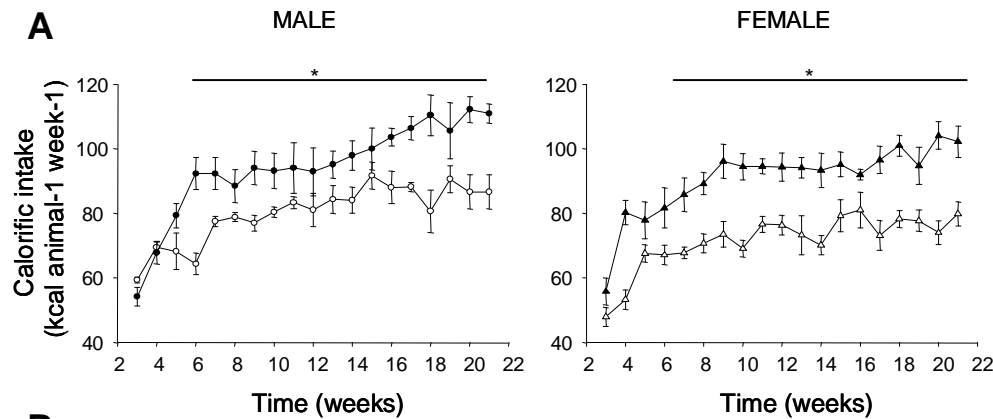
D) Fat mass (BAT)

E) Plasma Profile in  
Gestation

F) Plasma Profile in  
lactation

# Offspring Phenotype In the Mouse

(Samuelsson et al,  
*Hypertension* 2007)



A) Energy intake

B) Body weight

C) Plasma profiles at 3;

D) and 6 months

# Summary (1): Maternal Obesity in rodents

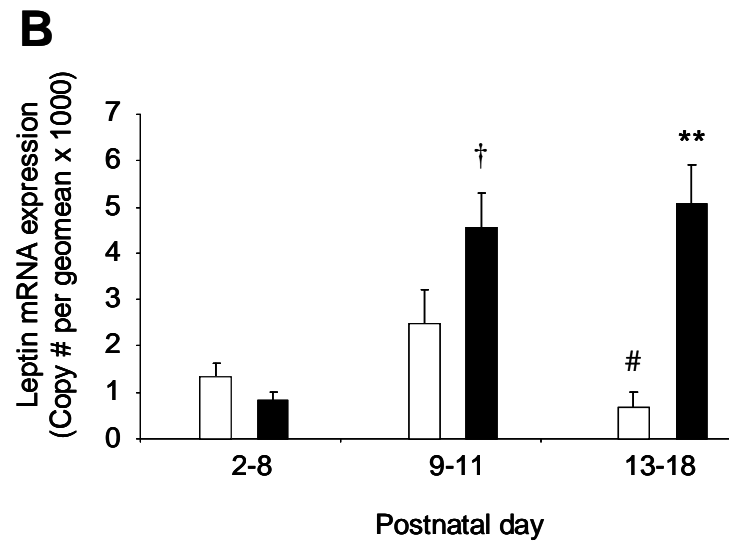
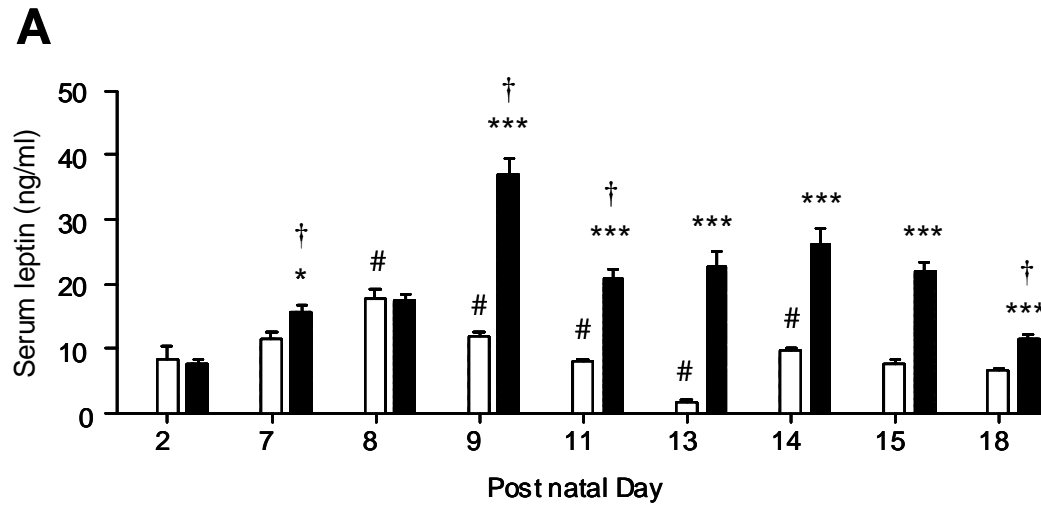
## Maternal Phenotype

- ä High-fat high-sugar diet leads to hypercalorific intake & maternal obesity.
- ä **Hyperleptinaemia**, Hyperinsulinaemia
- ä Hyperglycaemia, Dyslipidaemia.

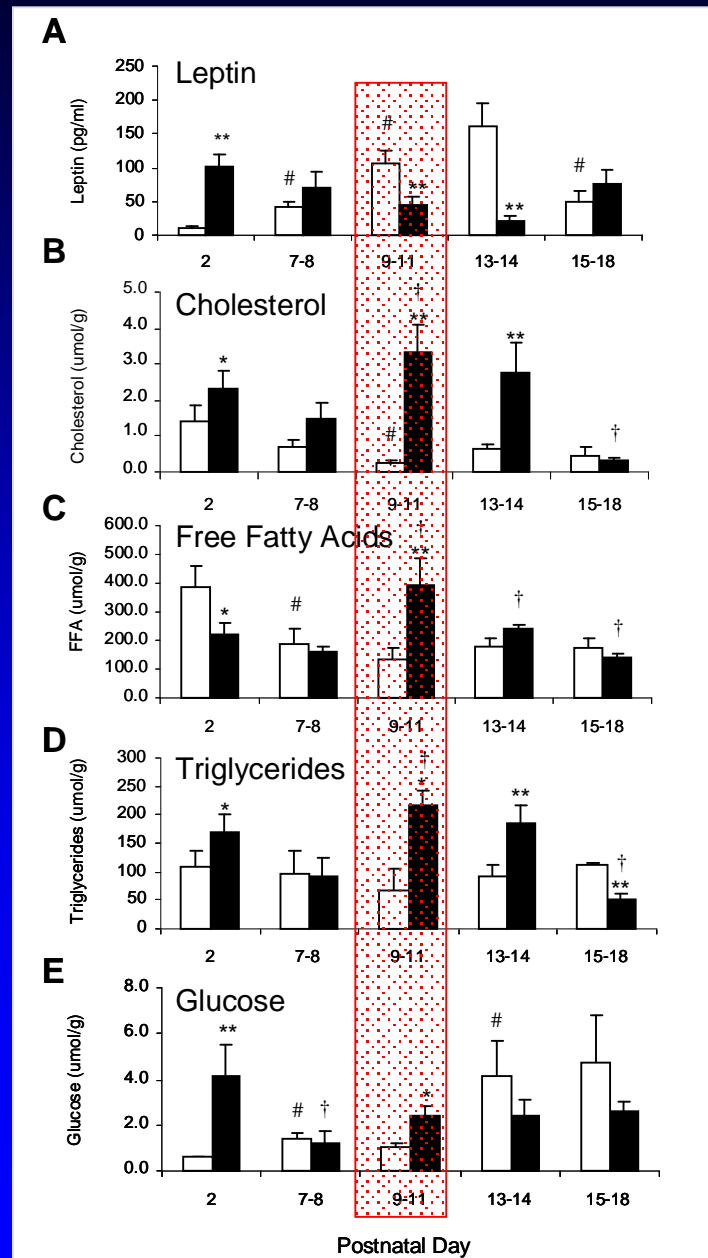
## OffOb Phenotype

- ä Offspring of Obese rodents are **Hyperphagic** from weaning
- ä Increased Birthweight & weight at weaning
- ä Increased body weight & significant abdominal obesity by 10-12 weeks, reduced muscle mass.
- ä Dyslipidaemia, hyperinsulinaemia and hyperleptinaemia at 3 mo
- ä Hyperglycaemic at 6 mo

# Neonatal Serum Leptin & Adipose Leptin mRNA Expression

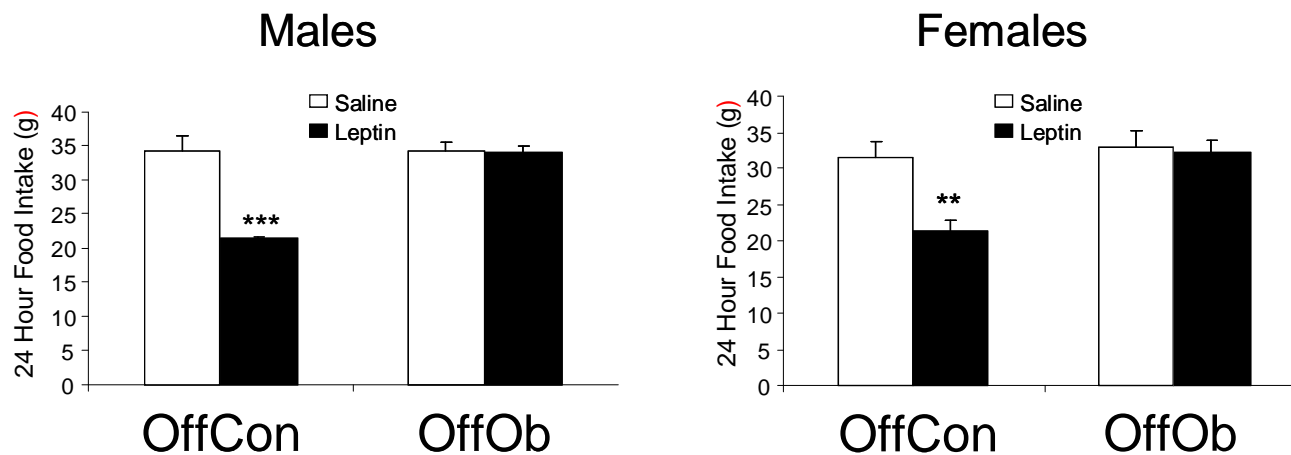


# Milk Contents (Pre-weaning Stomach Contents)

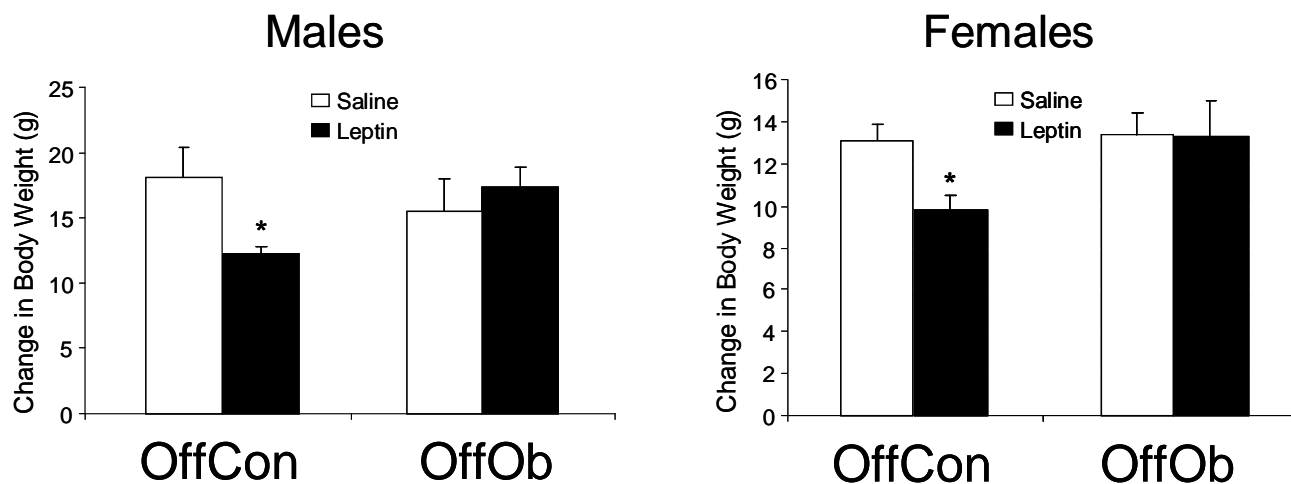


# Leptin Challenge in Day 30 Offspring

## 24 hr Food Intake



## $\Delta$ Body Weight



## Conclusions (1)

- Maternal obesity has adverse consequences for offspring energy balance including leptin resistance and hyperphagia.
- We hypothesise that leptin resistance in the ARC is acquired during a critical period due to an amplified and prolonged neonatal leptin surge.
- Deficits in leptin-signalling may impair leptin's neurotrophic effects on AgRP projections to the PVH.
- Abnormal neuronal development in the appetite regulatory centres of the brain may permanently programme hyperphagia and therefore obesity in adult life.

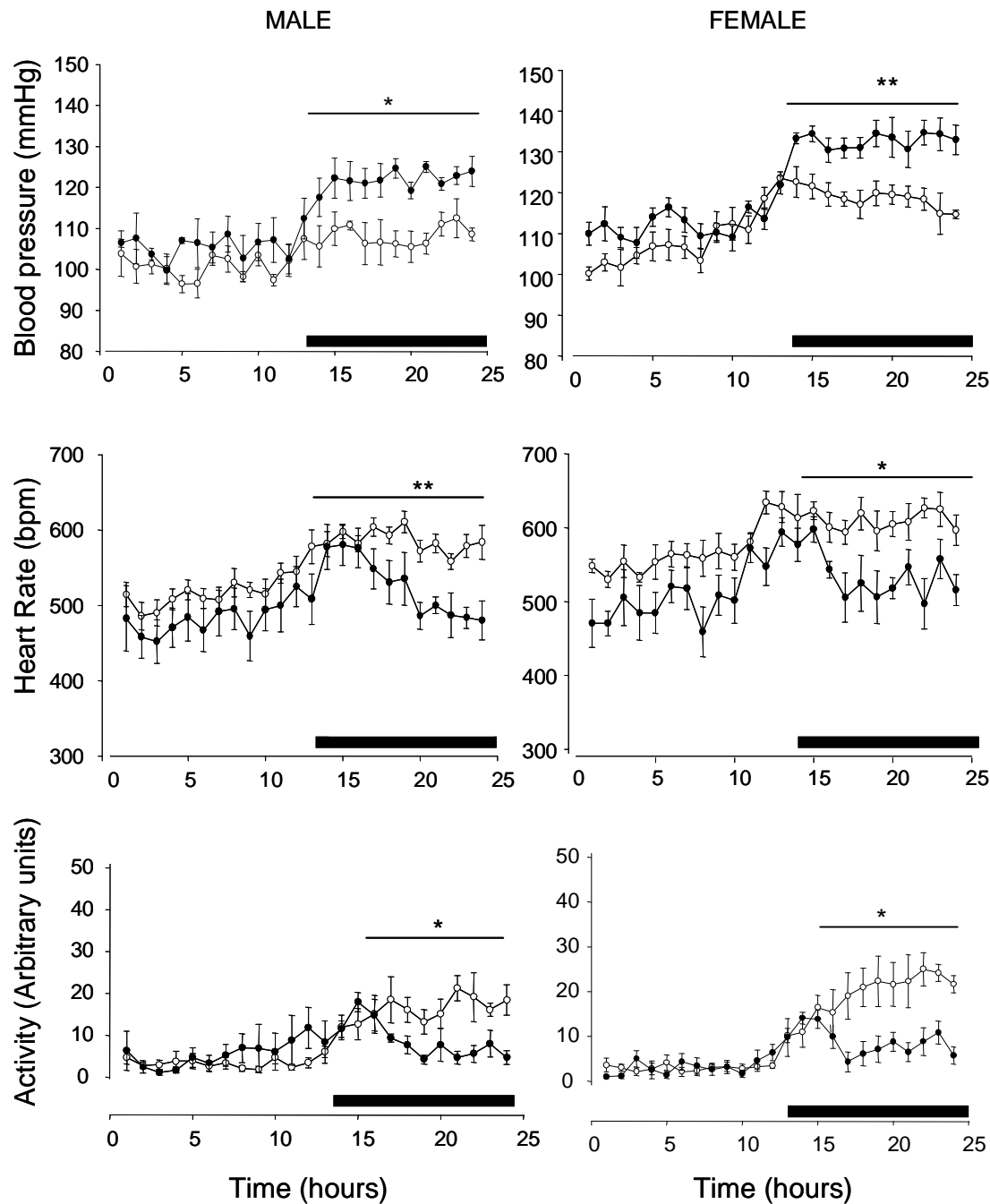
# Cardiovascular Radio-telemetry in 3 month offspring of Obese mice

Blood pressure

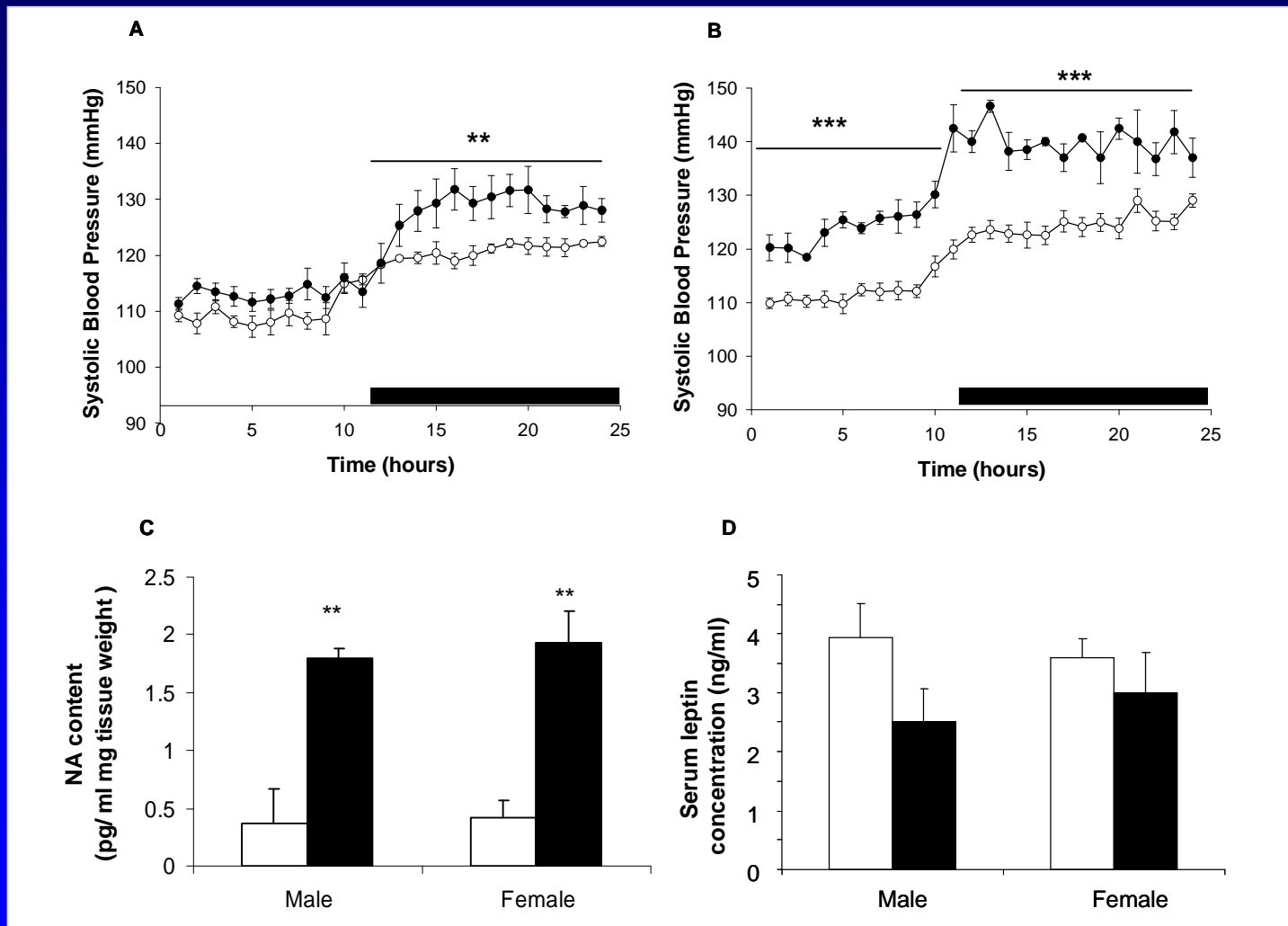
Heart Rate

Physical Activity

(Samuelsson et al,  
*Hypertension* 2007)



# Radio-telemetry in 30 day offspring of obese rats using carotid artery placement of mouse probes



## Summary (3): Offspring of Obese Rats at 30 days of age (prior to the development of obesity).

- ä Elevated systolic blood pressure
- ä Increased renal sympathetic outflow
  - ä (indirect by renal noradrenaline content)
- ä Increased reactivity to stress.
- ä Increased sympathetic component of HRV
- ä Increased pressor response to Leptin
- ä **Renal Sympathetic hypertension- is a primary programmed event in offspring of obese rats**

## Conclusions (2)

- ä Diet induced obesity in pregnant rats leads to a state of leptin resistance in the offspring in relation to appetite control but an exaggerated pressor response to leptin.
- ä Diet induced obesity in pregnant rats programmes a *selective leptin resistance* in the developing hypothalamus.
- ä Neonatal exposure to leptin secondary to maternal obesity may 'hardwire' the neonatal hypothalamus for a *hyperphagic* and *hypertensive* phenotype.

# Developmental origin of selective leptin resistance

*Fetal/neonatal  
Hyperleptinaemia  
Hyperinsulinaemia?*

**Excessive Weight Gain &  
Adiposity**

**Pregnancy  
& Lactation**



**Selective leptin resistance**

*Altered Leptin  
Signalling  
Hypothalamus  
NTS?*

↓ **Metabolic  
action**

↑ **SNS  
activity**

**Offspring  
Phenotype**

**Hyperphagia  
& Obesity**

**Hypertension**

*Schematic: mechanisms in fetal programming of obesity and hypertension.*

# Questions

- ä What are the determinants of the neonatal leptin surge in rodents? The maternal nutritional status clearly influences the neonatal leptin profile. An understanding of the factors mediating the effects of nutritional status on neonatal leptin could inform interventions to reduce the risk of obesity and metabolic disease.
- ä Relevance to human obesity ? High cord blood neonatal leptin concentration in infants which falls rapidly post-partum and is related to birthweight. The relative maturity between the human brain and that of the rodent post-partum requires consideration. Studies of the human brain are understandably few. However, continued hypothalamic development is probable in the post-partum human infant thus susceptibility to the neurotrophic influences of leptin could also occur in both ante-natal and post-partum periods.

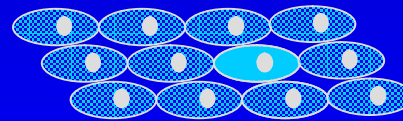
# Mechanisms of Programming?



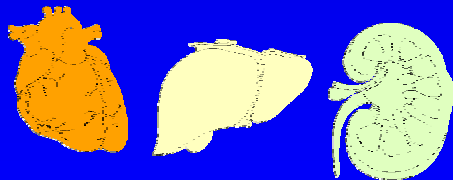
Nutritional & Humoral  
Influence

Epigenetic factors?  
Insulin/leptin/CORT  
Oxidative stress?

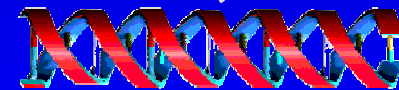
Altered Cell Number or  
intracellular organization



Reorganisation of  
organ structure



Altered morphology?



Altered DNA expression?  
(altered cell specific gene regulation)

DNA Environment?

(altered DNA binding proteins)

Altered DNA methylation?

## Overall Summary: Overnutrition in pregnancy

- ä Epidemiological studies and animal models now indicate that the origins of obesity & CVD lie not only in the interaction between genes and traditional adult risk factors, such as diet and physical inactivity, but also in the interplay between genes and the embryonic, fetal and early postnatal environment
- ä Increase public awareness of importance of a balanced diet in pregnancy and risks of obesity in pregnancy and neonatal life.
- ä Preconception counselling for obesity (UK Guidelines).
- ä More effective management of obesity and GDM in pregnancy
- ä Screening and intervention in early life?