

# The role of early metabolic imprinting in escalating obesity rates in children and the link to childhood anxiety and depression

Kevin L. Grove  
Director of Metabolic Disease  
Oregon National Primate Research Center  
Oregon Health & Science University



Childhood Obesity

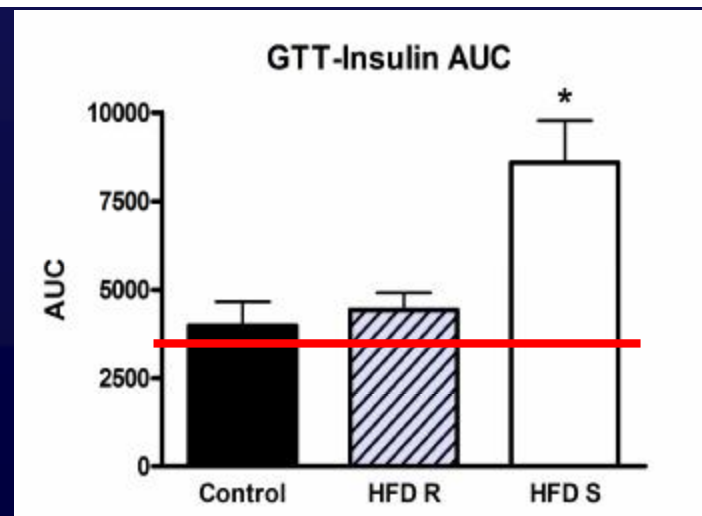
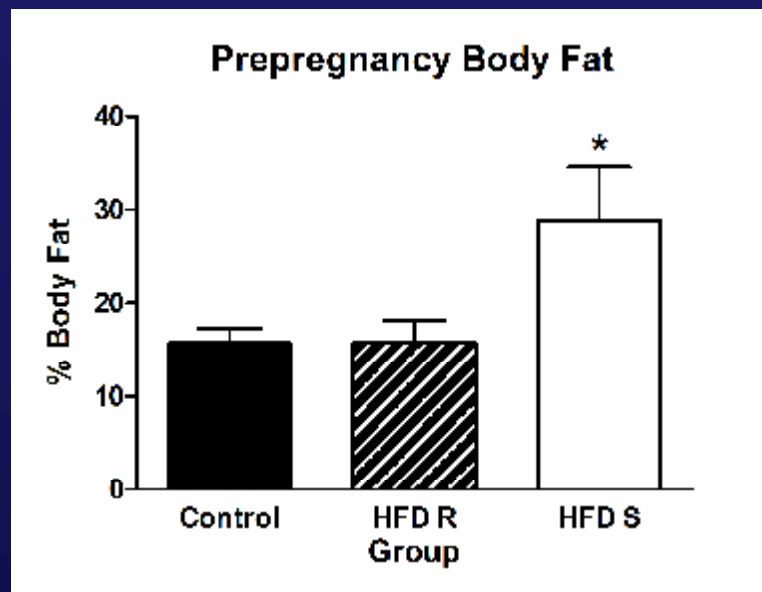
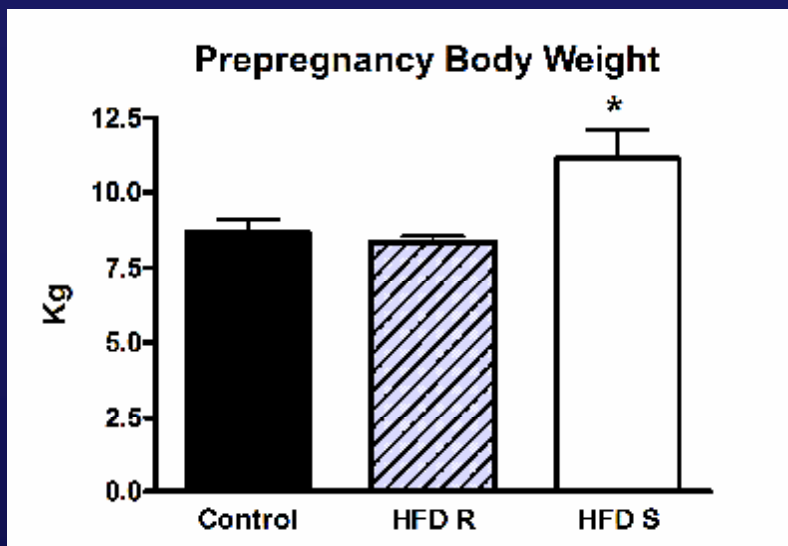


Fetal/Neonatal Imprinting?

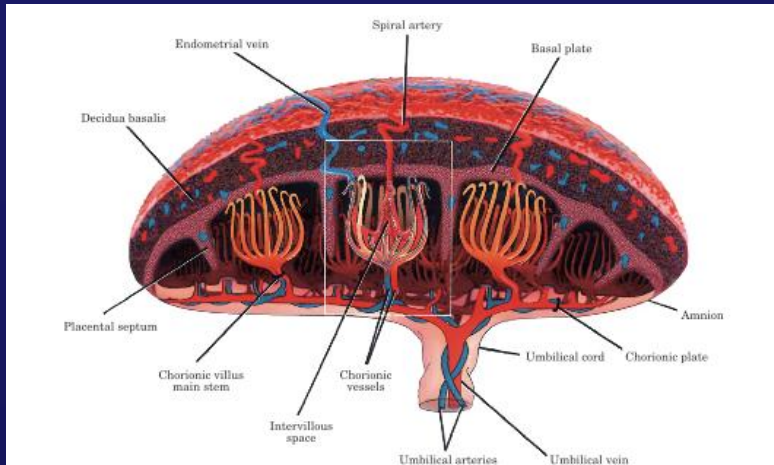
To determine whether chronic consumption of Western diet, with and without maternal obesity/GDM, leads to an altered **programming** in the fetus of non-human primates



# Chronic consumption of a Western style diet causes obesity in female macaques

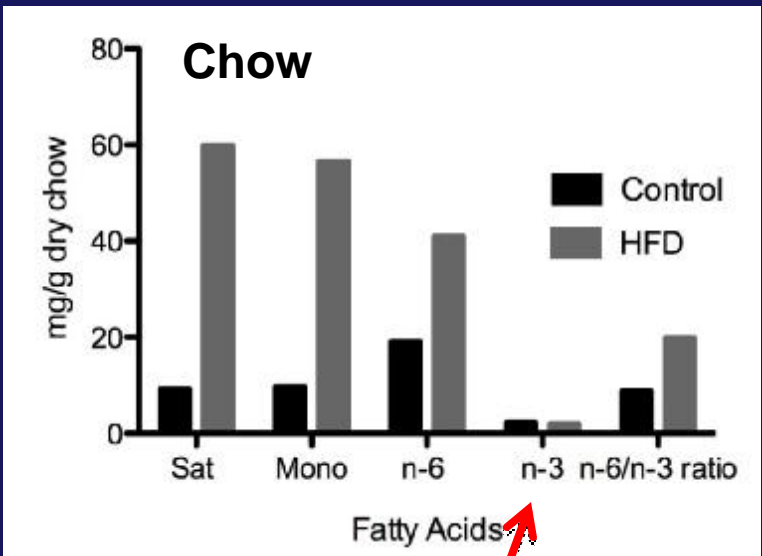


McCurdy et al, JCI, Feb 2009



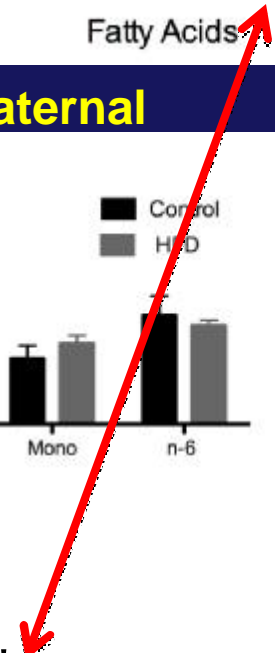
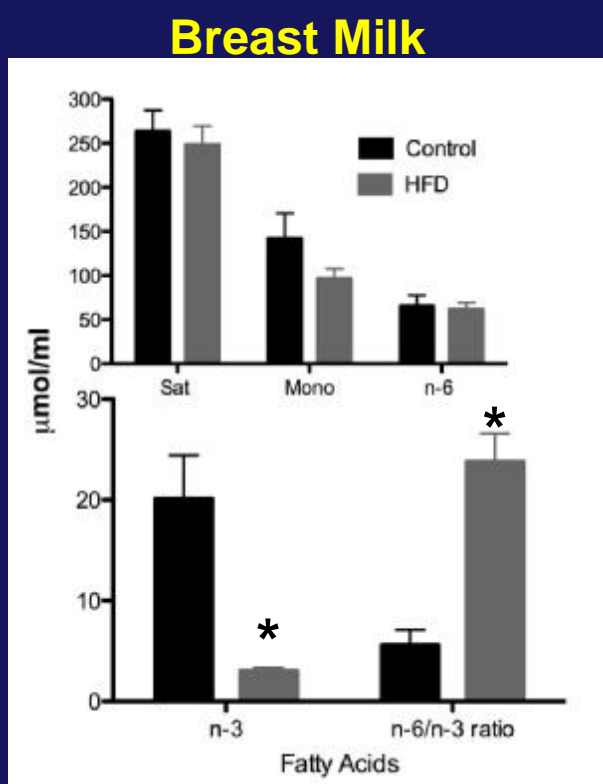
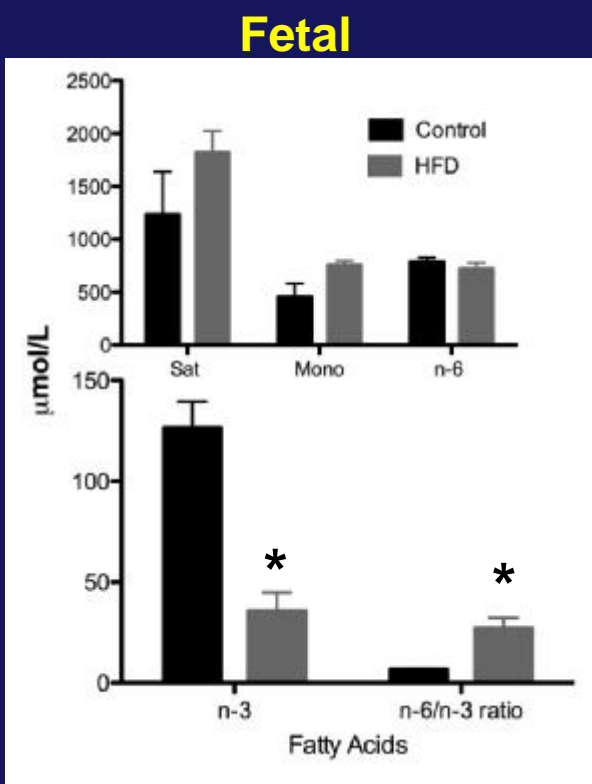
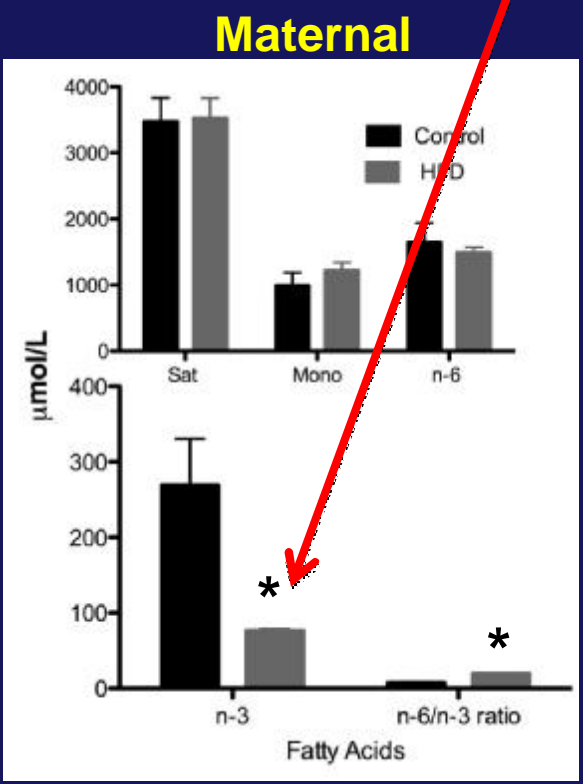
## Are lipids a good fuel source for the placenta and developing fetus?

- Placenta is glycolytic and does not use fatty acids for ATP synthesis.
- The fetus is primarily glycolytic, but can upregulate systems to oxidize fat (but at what cost?).
- Developing infants readily oxidize fat (Breast milk)



The increased n6/n3 ratio would be proinflammatory

N3s are critical for development



# Maternal Circulation

# Fetal Placenta

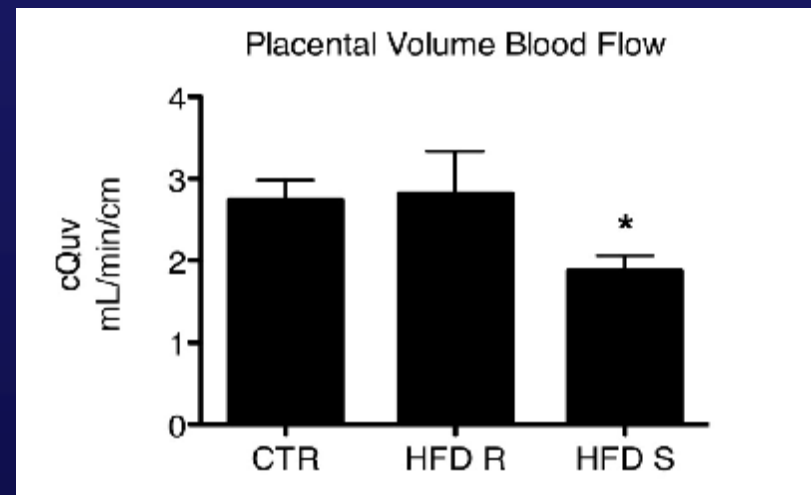
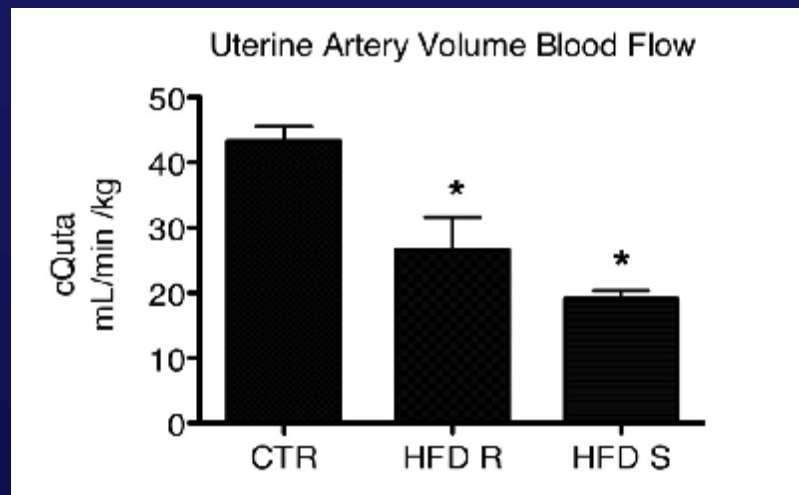
Target	Alternate	Control	HF Diet	P value
C5a		2.64 ± 1.06	2.15 ± 0.32	0.68
CD40 ligand	CD154	0.51 ± 0.31	0.57 ± 0.12	0.87
G-CSF	CSF8	1.09 ± 0.50	0.72 ± 0.13	0.52
GM-CSF	CSF $\alpha$	1.33 ± 0.47	0.64 ± 0.09	0.22
GRO $\alpha$	CXCL1	2.50 ± 0.41	0.98 ± 0.19	0.03*
I-309	CCL-1	0.84 ± 0.33	0.27 ± 0.12	0.18
sICAM-1	CD54	0.46 ± 0.23	0.14 ± 0.05	0.25
IFN $\gamma$		0.69 ± 0.14	0.16 ± 0.06	0.02*
IL-1 $\alpha$	IL-1F1	0.68 ± 0.39	0.74 ± 0.13	0.89
IL-1 $\beta$	IL-1F2	0.39 ± 0.26	0.58 ± 0.05	0.51
IL-ra	IL-1F3	2.76 ± 0.69	2.09 ± 0.28	0.42
IL-2		0.86 ± 0.31	0.38 ± 0.13	0.22
IL-4		0.55 ± 0.17	0.21 ± 0.10	0.17
IL-5		0.38 ± 0.16	0.11 ± 0.06	0.19
IL-6		0.34 ± 0.19	0.17 ± 0.05	0.45
IL-8		2.38 ± 0.26	3.17 ± 2.0	0.72
IL-10		0.49 ± 0.32	0.61 ± 0.10	0.73
IL-12p70		0.40 ± 0.28	0.58 ± 0.07	0.58
IL-13		2.89 ± 0.75	1.92 ± 0.22	0.28
IL-16		1.79 ± 0.47	0.96 ± 0.24	0.19
IL-17		0.86 ± 0.24	0.32 ± 0.15	0.13
IL-17E		0.84 ± 0.35	0.29 ± 0.13	0.21
IL-23		0.58 ± 0.26	0.32 ± 0.15	0.44
IL-27		1.17 ± 0.06	0.58 ± 0.30	0.13
IL-32 $\alpha$		1.28 ± 0.71	0.96 ± 0.06	0.68
IP-10	CXCL10	0.70 ± 0.15	0.92 ± 0.01	0.23
I-TAC	CXCL11	4.14 ± 0.78	5.28 ± 0.82	0.37
MCP-1	CCL2	0.95 ± 0.30	0.57 ± 0.26	0.40
MIF	GIF	12.37 ± 1.71	6.42 ± 1.59	0.06
MIP-1 $\alpha$	CCL3	1.05 ± 0.44	0.40 ± 0.19	0.24
MIP-1 $\beta$	CCL4	0.62 ± 0.26	0.32 ± 0.14	0.37
Serpin E1	PAI-1	9.24 ± 0.29	6.88 ± 3.84	0.57
RANTES	CCL5	20.76 ± 9.48	20.33 ± 8.55	0.98
SDF-1	CXCL12	1.72 ± 0.98	1.24 ± 0.07	0.65
TNF $\alpha$		1.16 ± 0.47	0.97 ± 0.31	0.74
sTREM-1		1.01 ± 0.43	0.56 ± 0.30	0.44

Target	Alternate	Control	HF Diet	P value
C5a		1.30 ± 0.45	2.27 ± 0.71	0.31
CD40 ligand	CD154	0.73 ± 0.42	1.85 ± 0.14	0.07
G-CSF	CSF8	0.81 ± 0.28	2.40 ± 0.12	0.006*
GM-CSF	CSF $\alpha$	0.68 ± 0.31	1.95 ± 0.13	0.02*
GRO $\alpha$	CXCL1	1.06 ± 0.22	2.50 ± 0.32	0.02*
I-309	CCL-1	0.75 ± 0.10	1.54 ± 0.33	0.09
sICAM-1	CD54	0.36 ± 0.11	0.97 ± 0.23	0.08
IFN $\gamma$		0.32 ± 0.11	0.69 ± 0.28	0.29
IL-1 $\alpha$	IL-1F1	0.61 ± 0.42	1.83 ± 0.12	0.05*
IL-1 $\beta$	IL-1F2	0.30 ± 0.39	1.55 ± 0.16	0.04*
IL-ra	IL-1F3	2.24 ± 0.37	4.00 ± 0.63	0.07
IL-2		0.75 ± 0.15	1.80 ± 0.13	0.006*
IL-4		0.58 ± 0.12	1.58 ± 0.24	0.02*
IL-5		0.53 ± 0.10	1.26 ± 0.37	0.13
IL-6		0.46 ± 0.15	0.10 ± 0.37	0.25
IL-8		0.87 ± 0.15	1.51 ± 0.56	0.33
IL-10		0.40 ± 0.41	1.34 ± 0.08	0.09
IL-12p70		0.24 ± 0.35	1.37 ± 0.22	0.05
IL-13		1.64 ± 0.36	4.44 ± 0.37	0.005*
IL-16		1.21 ± 0.19	3.09 ± 0.26	0.004*
IL-17		0.86 ± 0.19	2.07 ± 0.32	0.03*
IL-17E		0.85 ± 0.16	1.87 ± 0.44	0.09
IL-23		0.61 ± 0.15	1.35 ± 0.50	0.23
IL-27		0.46 ± 0.04	1.05 ± 0.28	0.10
IL-32 $\alpha$		0.62 ± 0.46	2.20 ± 0.34	0.05
IP-10	CXCL10	0.52 ± 0.41	1.74 ± 0.17	0.05
I-TAC	CXCL11	0.98 ± 0.44	3.09 ± 0.19	0.01*
MCP-1	CCL2	0.74 ± 0.27	2.13 ± 0.15	0.01*
MIF	GIF	13.50 ± 2.33	23.04 ± 3.58	0.09
MIP-1 $\alpha$	CCL3	1.24 ± 0.04	1.83 ± 0.39	0.20
MIP-1 $\beta$	CCL4	0.54 ± 0.09	1.26 ± 0.45	0.19
Serpin E1	PAI-1	4.66 ± 0.96	8.13 ± 1.76	0.16
RANTES	CCL5	13.91 ± 5.79	27.14 ± 3.15	0.12
SDF-1	CXCL12	0.93 ± 0.61	2.18 ± 0.27	0.13
TNF $\alpha$		0.49 ± 0.40	1.76 ± 0.13	0.04*
sTREM-1		0.75 ± 0.25	1.55 ± 0.09	0.04*

HFD vs CTR (n = 3 per group)

Frias et al, Submitted

# Chronic consumption of a High Fat Diet Decreases Placental Blood Flow

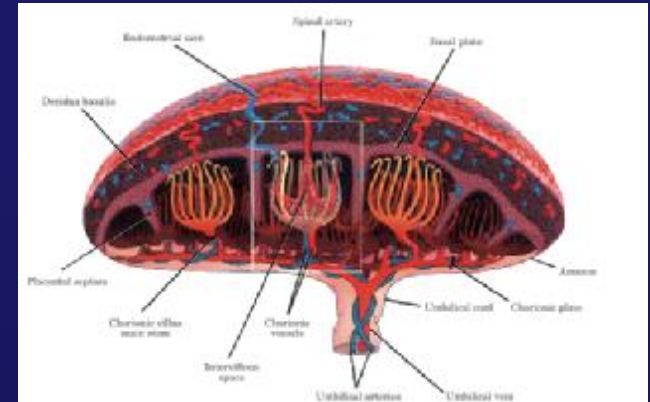


**HFD Sensitive animals have decreased placental blood flow on both the Maternal and Fetal sides of the placenta.**

**HFD Sensitive and resistant animals have placental pathology showing extensive necrosis and vascular disruption – preeclampsia**

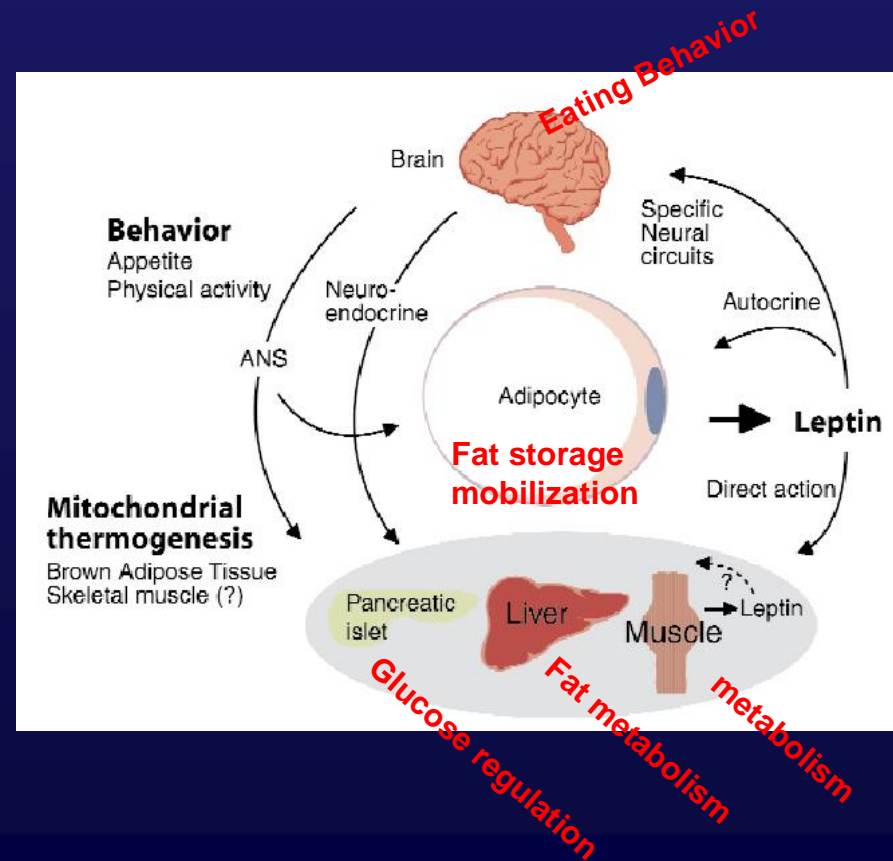
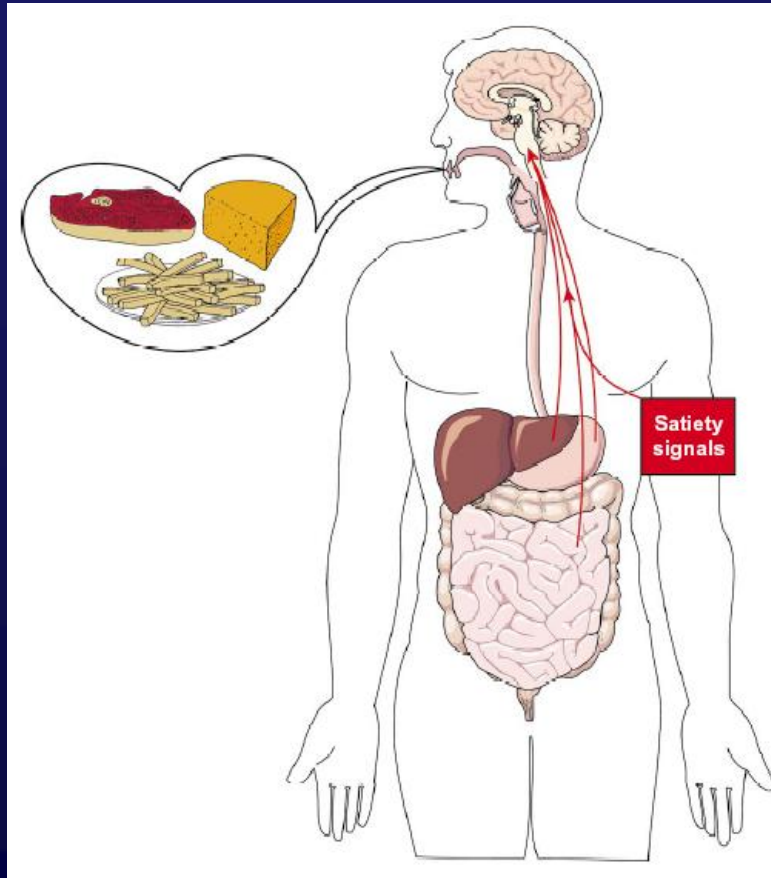
**HFD Sensitive animals have a higher rate of stillbirth**

# Conclusions

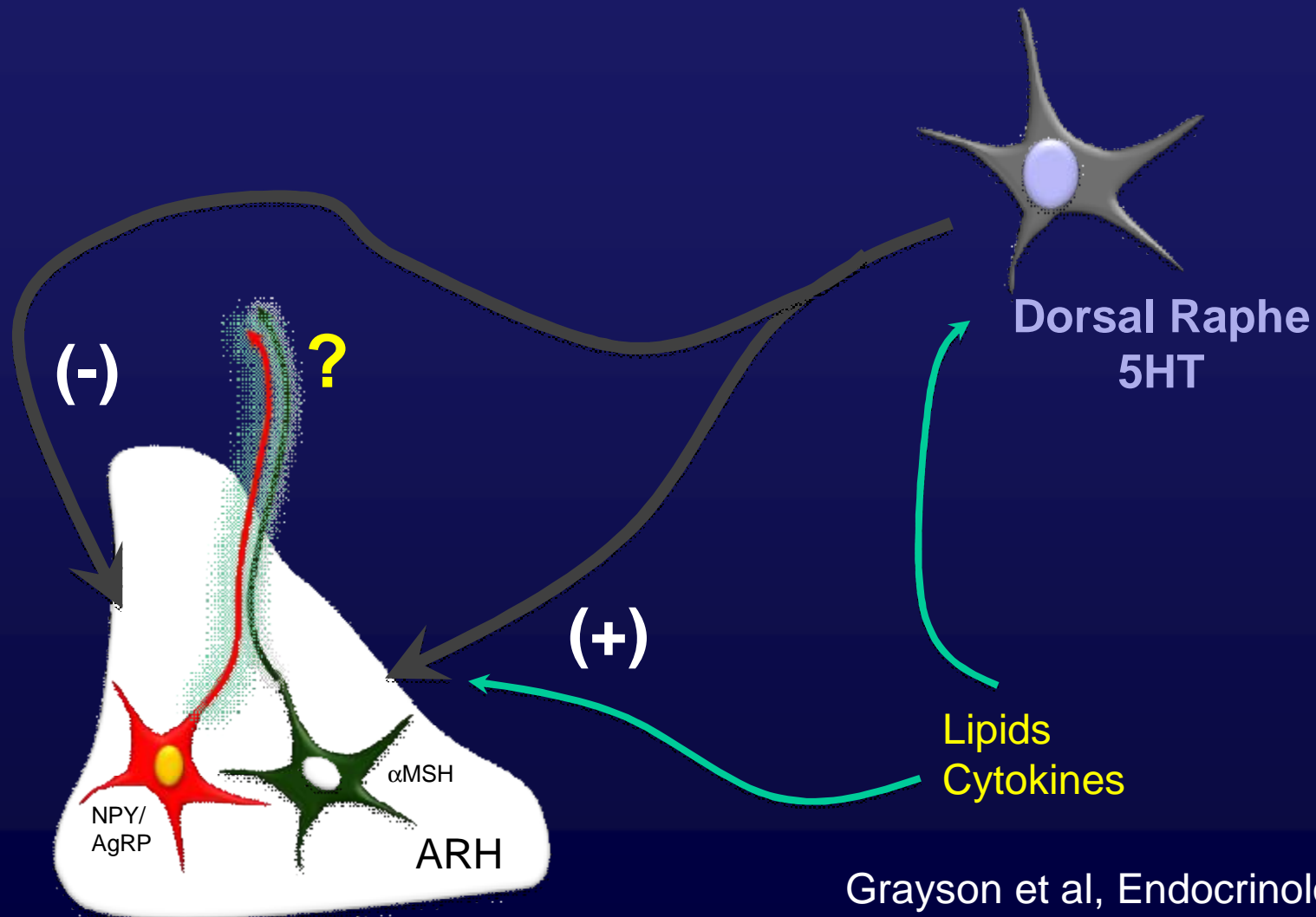


- Placental functional abnormalities and pathologies – primarily in HFD-Sensitive
- Placental deficiency is associated with numerous health risks in offspring.
  - Small for gestation age – catch up growth and obesity
  - Increased risk of cardiovascular disease: humans, sheep and rodents
  - Maternal metabolic phenotype vs HFD?

# Where are the metabolic disturbances in the offspring?



# The 5HT system regulates the melanocortin system



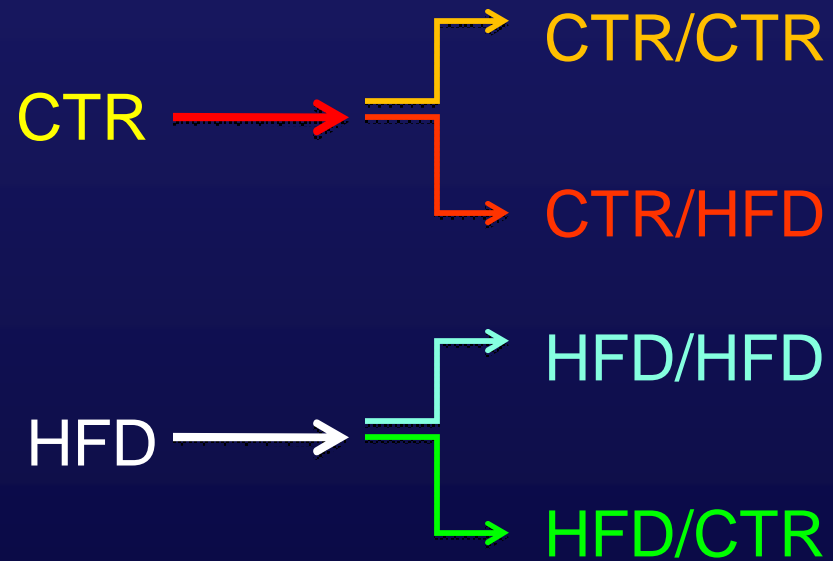
Grayson et al, Endocrinology, 2010  
Sullivan et al, J. Neurosci. 2010

# What are the long-term effects of fetal lipotoxicity?

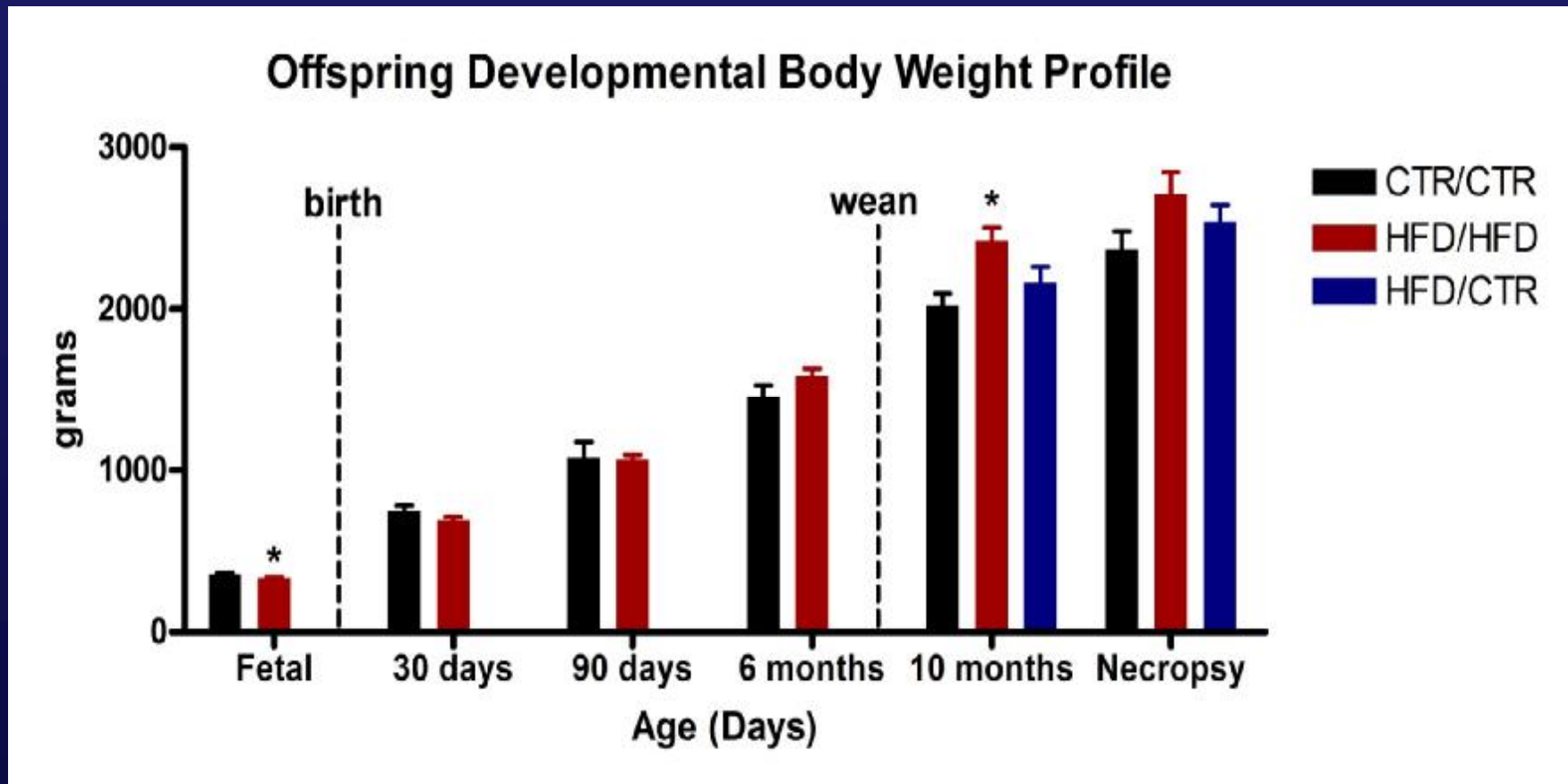
- Abnormal development of the melanocortin system (Grayson et al., 2010)
  - Predictive effects on body weight homeostasis
  - Stress responsiveness (HPA)
- Abnormal development of 5HT system (Sullivan et al., 2010)
  - Increased risk of stress/anxiety disorders
  - Predictive effects on body weight homeostasis (through the melanocortin system)

# Postnatal Groups

Weaned at approximately 7 months

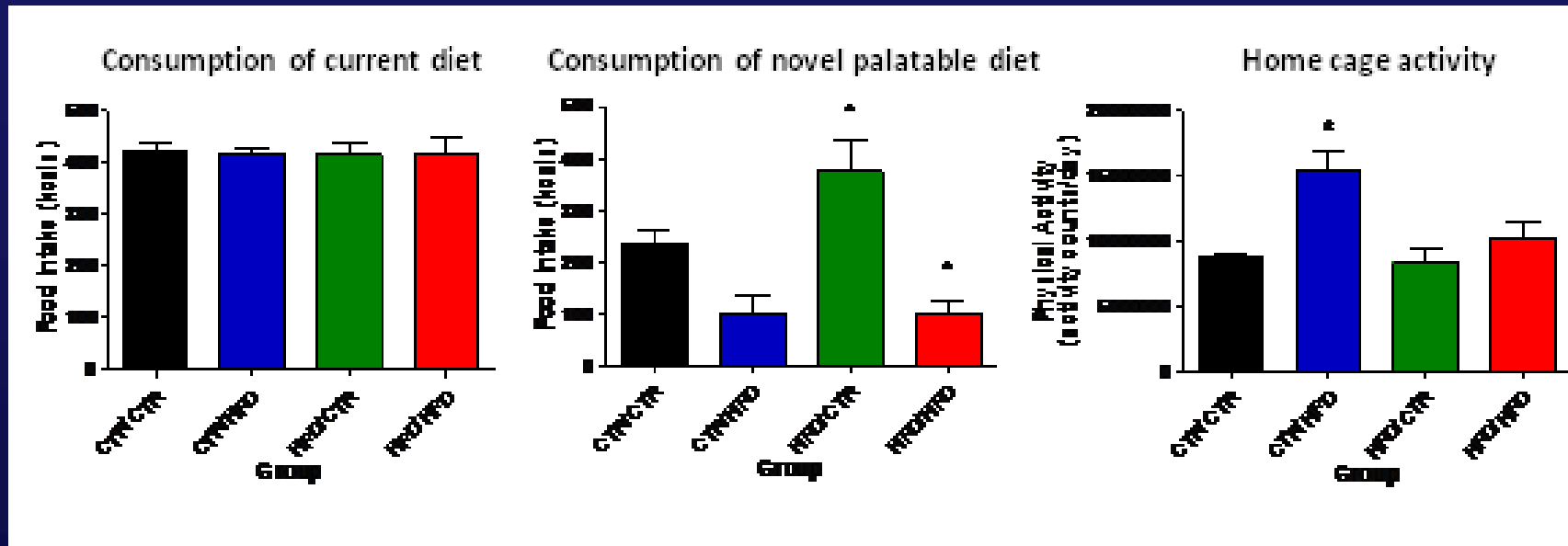


# Persistent effects of body weight and adiposity

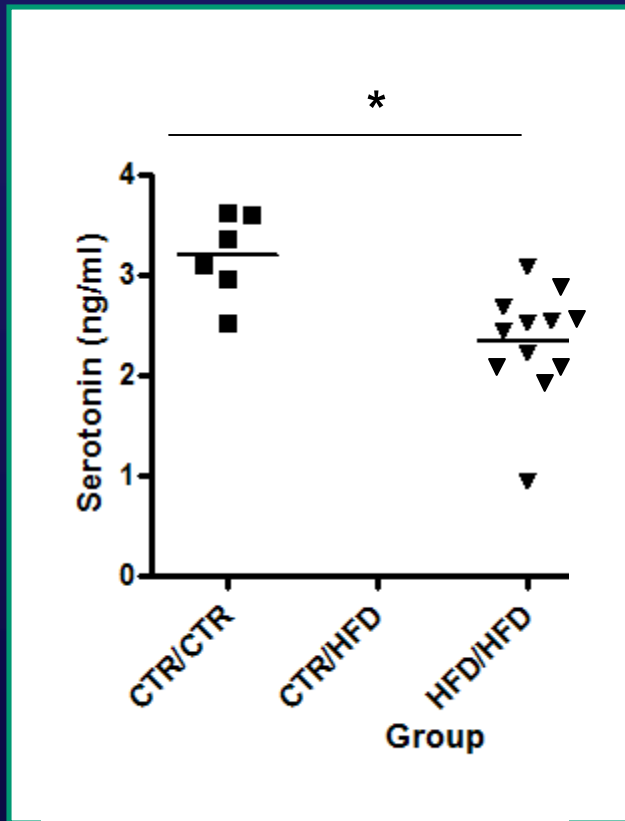


Effects on food intake? Other Behavior?

# HFD Offspring have increased consumption of palatable diets.

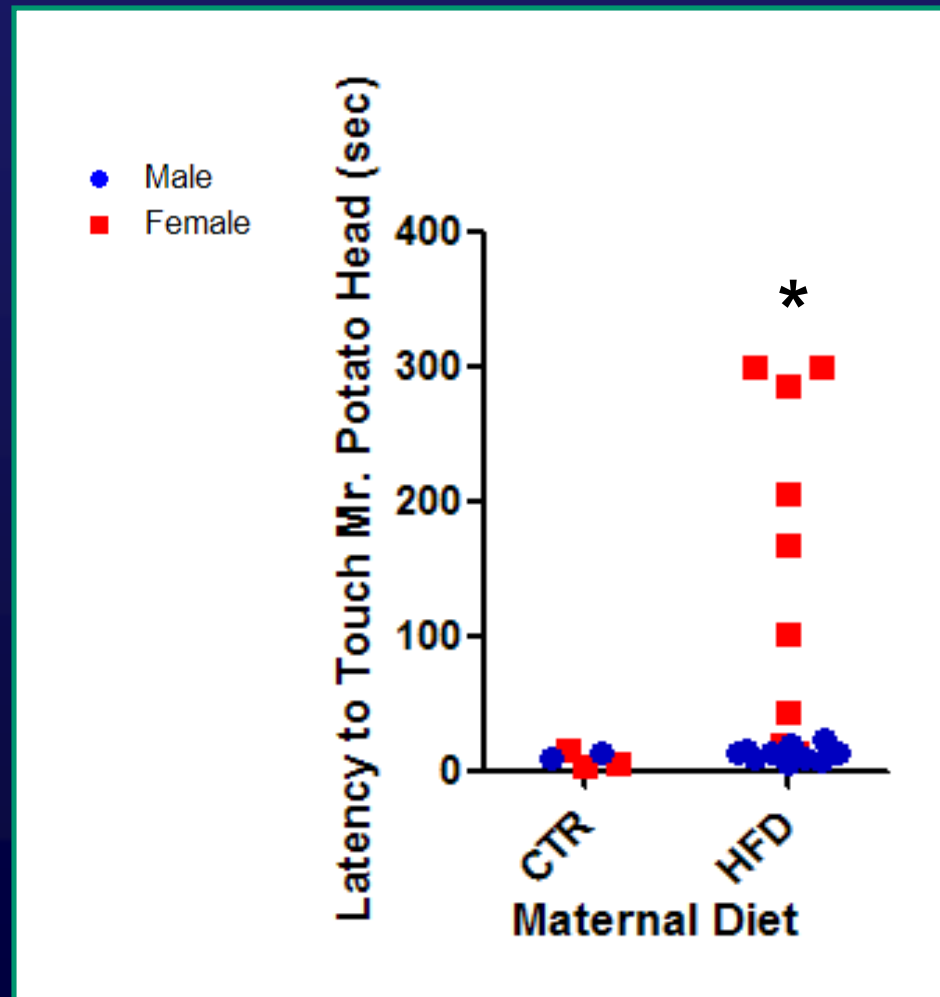


# Serotonin is Decreased in Juvenile Offspring from Mothers Consuming a HFD



Decreased serotonin levels are associated with anxiety, depression and aggression.

Female Offspring from HFD fed mothers exhibit *increased* latency to explore novel objects suggesting *increased anxiety*

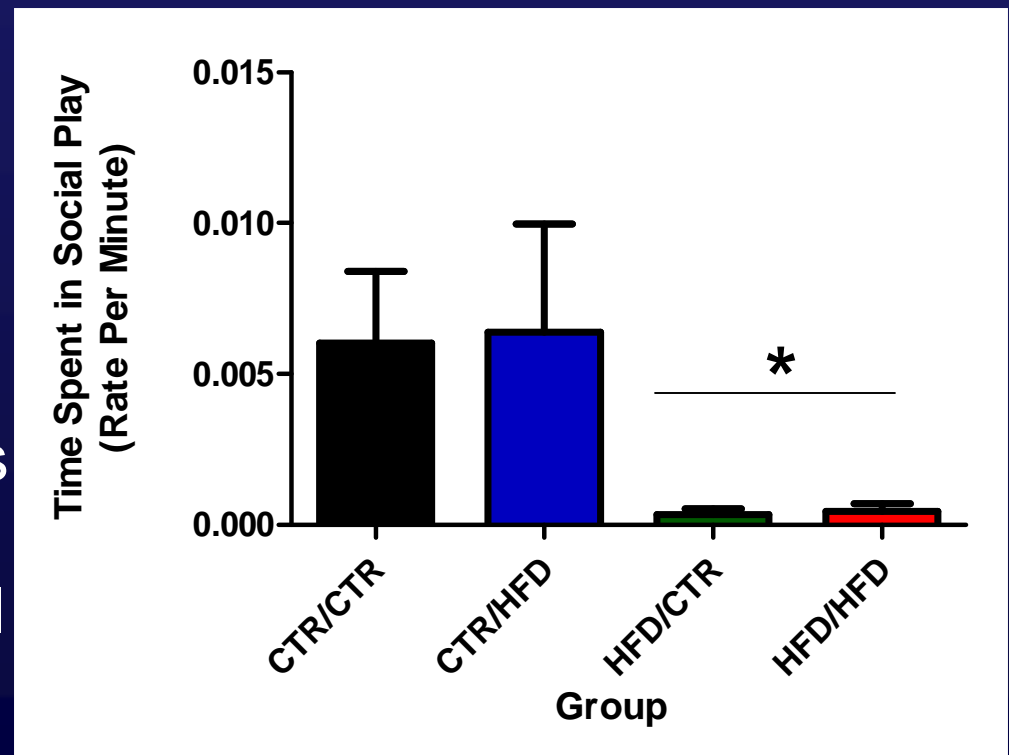


80% of females

## Male and Female Offspring from HFD fed mothers exhibit *antisocial behavior*

### In social housing settings:

- Spend more time alone
- Spend less time in play
- Initiate fewer social contacts
- More frequently avoid social contacts initiated by others



# Summary: Maternal HFD

- Significant impact on placental function & development
  - Cytokine production – released into developing fetus
  - Decreased placental function – exacerbated in HFD-S mothers
- **Increased adiposity and glucose intolerance**
  - Abnormalities in the melanocortin system
  - Fatty liver disease
  - Pancreatic islet hyperplasia
  - Hyperphagia of palatable diets
  - Social Behavior
    - Decreased Serotonin
    - Female Offspring – increased anxiety
    - Male offspring – increased aggressive behavior
    - Both sexes display decreases in social behavior
- Is NOT dependent on maternal obesity

Chronic maternal HFD (Western-style diet) consumption  
with and without maternal obesity/GDM can lead to an  
altered **programming** in the fetus

Childhood Obesity



Fetal/Neonatal Imprinting?



## Grove/Smith Group

Dr. M. Susan Smith

Dr. Bernadette Grayson

Dr. Elinor Sullivan

Dr. Paul Kievit

Dr. Li Fan

Dr. Antonio Frias

Sarah Williams

Diana Takahashi

Lindsay Pranger

Anne Evans

Rene Lindsley

Ashley Kostbra

Dr. Jed Friedman and Lab (UC Denver)

Dr. Carrie McCurdy – **fatty liver studies**

Dr. Daniel Marks (OHSU) – **inflammatory system**

Dr. Kris Coleman (ONPRC) – **Behavior testing**

**Epigenetic Modification**

Dr. Robert Lane (Univ. Utah)

Dr. Kjersti Tillery-Aagaard (Baylor)

**Placental/Cardiovascular Function**

Dr. Michael Cowley (Monash, Australia)

Dr. Kent Thornburg (OSHU)

Dr. Sanjiv Kaul

**Respiratory Dysfunction**

Dr. Eliot Spindel

Funding: DK060685, DK079194, DK078590,

DK079219, HD34430 **ONPRC Pilot Project**