Effects of Stress and Food During Prenatal Development

Presented by The Peptide Pods
Nutritional programming of hypothalamic development: critical periods and windows of opportunity

By: SG Bouret
Presented by Lara Hagopian
What is the hypothalamus?

Hypothalamus: “a critical regulator of energy balance and glucose homeostasis because it contains sets of neurons that are devoted to metabolic regulation and can directly respond to peripheral hormonal nutritional signals”

- Hypothalamic nuclei: regulation of energy balance and glucose homeostasis
  - Arcuate nucleus (ARH)
  - Ventromedial nucleus (VMH)
  - Dorsomedial nucleus (DMN)
  - Paraventricular nucleus (PVN)
  - Lateral hypothalamic area (LHA)
Perinatal Insults
- Maternal and/or postnatal overnutrition
- Maternal or postnatal undernutrition
- Maternal hypoinsulinism
- Perinatal hyper- and hypo-leptinemia

Long term Structural Effects
- Changes in hypothalamic cell numbers
- Altered development of hypothalamic neural projections
- Reduced leptin sensitivity
Critical Periods of Hypothalamic Development

- Developmental Processes for a functional hypothalamus
  - The determination of cell numbers involving neurogenesis (neuron production), neuron migration and cell death
  - The formation of functional circuits; this involves axonal growth and synaptogenesis

- In humans it has been reported that early hypothalamic development is limited to the 9th and 10th week of gestation
Maternal Obesity/ high fat diet

- When feeding pregnant mothers of rodents and non-human primates a high fat diet, the babies end up being overweight no matter what point (gestation or gestation and lactation) they gave the mothers this diet.
  - Negative Consequences for offspring: hyperphagic (abnormally increased appetite), glucose intolerance, and increased adiposity (condition of being obese)
- Even if the mothers only get the high fat diet for a short time without developing a metabolic disorder, the children are still more likely to be obese which includes having increased body weight, fat mass and food consumption.
- Therefore, even short exposures to nutritional and hormonal changes that occur during pregnancy could induce long term side effects
Maternal Obesity/ high fat diet, Continued...

- Effects a high fat diet had on the actual cell proliferation in the hypothalamus
  - It increased hypothalamic cell proliferation and ended up creating more orexigenic (appetite stimulant) neurons in the PVH and LHA
    - These neurons included galanin, enkephalin, dynorphin, melanin-concentrating hormone and orexin neurons
- This effect has been shown to occur in rodents for both periods of a high fat diet for the mother during gestation or gestation and lactation
  - This meaning that even if a baby was taken away from its obese mother once it was born and given to a healthy mother to drink milk from, they still had similar hypothalamic cell numbers compared to the babies born and fed by their obese mothers
- Also note, that if the mother is obese before she gets pregnant, she is likely to pass down this obese trait to her children
- Maternal diabetes alone can also cause long term structural changes in the hypothalamus
Prenatal malnutrition/altered growth

- Adult animals born to malnourished mothers may have normal body weight however they are hyperphagic, glucose intolerant and have increased sensitivity to diet-induced obesity.
- Reduction in orexigenic neurons in the hypothalamus (it is unclear if this decrease is because of neurogenesis and cell migration or an increase in number of cells undergoing apoptosis).
- When protein consumption is reduced in pregnant mothers, the genes involved in brain development get down regulated:
  - Astrocytogenesis is effected
  - Reduced glia to neuron ratio (and we know glia are super important!)
- Hypothalamic axonal connectivity is reduced.
- For rodents, it is possible to have a critical period of “catch up post hypothalamic grown.”
What about the father??????
Leptin, Nutrition, and the Programming of Hypothalamic Feeding Circuits

Written by: Sebastien G. Bouret
Presented by: Max Bishop
First, a lil introduction

- A lot of data suggests that adverse early environments, such as maternal obesity during pregnancy or early postnatal life, are linked to an increased prevalence of metabolic disease in the offspring of these adults.
  - These problems in offspring are prevalent throughout adult life as well.
- The mechanisms that underlie these effects are still poorly understood, but recent data from rodents has given insight into the brain in this ‘metabolic programming’
- This review paper summarizes the developmental changes that have been observed in the hypothalamus in response to changes in the early nutritional and hormonal environment.
Introduction to the review paper!

- Obesity is increasing worldwide at an alarming rate
  - Parallels an increase in the prevalence of metabolic diseases such as Type 2 Diabetes and Metabolic Syndrome
- A number of human epidemiological and animal studies have indicated that neonatal nutrition and maternal environmental factors may also have long-term effects on obesity
  - Maternal obesity and diabetes during pregnancy \(\Rightarrow\) increase the incidence of offspring obesity and associated metabolic diseases (Type 2 Diabetes)
- A number of factors affect the development and subsequent function of the brain.
  - These include stress hormones, sex steroids and, more recently, nutrients and metabolic hormones.
Importance of the Hypothalamus in Regulating Feeding and Energy Balance

- Appetite, energy expenditure, and metabolism are carefully regulated by the central nervous system
  - New experiments, models, and methods have clarified some of the organization of neuronal pathways involved in eating and energy balance.
  - These new approaches have led to defining the circuitry in the hypothalamus that supposedly plays a role in the homeostatic regulation of energy balance.

- A primary focus in this paper is on the neurons of the Arcuate Nucleus (ARH)
  - The Arcuate nucleus has long been associated with obesity and contains neurons that respond directly to a variety of signals, including leptin, insulin, ghrelin, amino acids, and glucose
  - The arcuate nucleus expresses both orexigenic and anorexigenic neurons
    - Orexigenic = Neuropeptide Y (NPY), Agouti-related peptide (AgRP)
    - Anorexigenic = Proopiomelanocortin (POMC)
Importance of the Hypothalamus in Regulating Feeding and Energy Balance

- But why is this important?
  - Both AgRP/NPY (orexigenic) and POMC (anorexigenic) neurons send extensive projections from the Arcuate Nucleus to other parts of the hypothalamus, including the Paraventricular and Dorsomedial nuclei of the hypothalamus, as well as the lateral hypothalamic area.
  - Recent work suggests that extra-hypothalamic sites may also be crucial for homeostatic and allostatic control of energy balance.
Development of Hypothalamic Feeding Circuits

- Birthdating studies on mice showed that neurons located in these key hypothalamic nuclei are born prenatally and within distinct temporal domains
  - Neurons of the Dorsomedial nucleus and the lateral hypothalamic area are born between embryonic day 12 and 14 (E12 - E14)
  - Neurons of the Arcuate nucleus and the Ventromedial nucleus are born between embryonic day 12 and embryonic day 16 (E12 - E16)
  - Neurons of the Paraventricular nucleus are born on embryonic day 12 (E12)

- However, it is largely unknown when specific hypothalamic cell types are born
  - For example, POMC neurons express mRNA in the Arcuate nucleus on E12, but NPY cell bodies aren’t found in the Arcuate nucleus until E14
  - The expression of orexigenic and anorexigenic neurons continues to increase through postnatal development, reaching maximum levels by postnatal day 15
Development of Hypothalamic Feeding Circuits

● While neuronal proliferation occurs prenatally, the neural connectivity between these nuclei is largely immature at birth and is primarily established postnatally in rodents.
  ○ Results showed that the Arcuate nucleus innervates different hypothalamic nuclei at different times
    ■ Connections between the Arcuate nucleus and the Dorsomedial nucleus, Paraventricular nucleus, and the lateral hypothalamic area are formed on postnatal day 6, postnatal day 10, and postnatal day 12, respectively, in rats
    ■ These projections aren’t fully mature until the rat’s 3rd week of life
  ○ Interesting to point out that orexigenic and anorexigenic neurons can modulate food intake before the arcuate nucleus’ projections become mature
    ■ Suggest that pathways other than Arcuate nucleus projections are responsible for feeding regulation during early life
Factors Influencing Hypothalamic Development

- During early stages of postnatal life, leptin and its receptors are expressed and functional in the developing hypothalamus, particularly in the Arcuate nucleus.
- Observations suggest that leptin may possess different functions during neonatal brain development that are independent of energy balance regulation.
  - There is a neonatal surge in leptin that appears to coincide with the development of major hypothalamic feeding circuits.
    - This leads to the fact that neonatal leptin may influence the development of these hypothalamic circuits.
- This hypothesis was tested through neuroanatomical experiments performed on leptin-deficient, obese mice.
Factors Influencing Hypothalamic Development

- In this experiment, the experimenters focused on the differences between control mice and leptin-deficient, obese mice in regards to the circuitry of hypothalamic nuclei
  - Axonal labeling of neurons in the Arcuate nucleus axons revealed that the Arcuate nucleus projections are severely reduced in the leptin-deficient mice and that leptin deficiency causes a significant delay in the formation of projections from the Arcuate nucleus to major hypothalamic nuclei
  - Disruption of the Arcuate nucleus pathways in these mice appears to be permanent, since even on postnatal day 60, a stage considered as mature with respect to mice, a lower density of Arcuate nucleus axons innervating each of the hypothalamic sites that are involved in the control of energy homeostasis was observed.
Factors Influencing Hypothalamic Development

- There are several reasons for why this surge in leptin is important when mice are born
  - In the mice that are obese and leptin-deficient, neonatal leptin treatment causes a long term reduction in food intake
  - Inhibition of this surge of leptin in normal rats results in an increased susceptibility to the development of diet-induced obesity
  - These all indicate that the correct timing and amplitude of the postnatal leptin surge appears to be required for normal energy balance regulation. Any alterations in leptin levels during critical periods of postnatal development may have long-term effects on feeding and metabolism due to disturbances in hypothalamic circuitry, specifically in the Arcuate nucleus
Postnatal Nutrition

● Animal studies have confirmed the importance of early postnatal nutrition on later metabolism
  ○ Postnatal overfeeding can influence the determination of hypothalamic cell numbers and neuronal connectivity.
    ■ For example, rats display higher numbers of neurons that produce the orexigenic neuropeptide galanin in the Paraventricular nucleus

● Postnatal overnutrition not only influences neuronal activity. It also affects the architecture of the neural circuitry involved in energy balance regulation.
  ○ When compared to normally nourished animals, diet-induced obese mice raised displayed a reduced density of Arcuate nucleus axons innervating the paraventricular nucleus.
    ■ This is due to alterations in axon growth as opposed to a reduction in cell number
Genetic Factors

- Rodent models of diet-induced obesity (DIO) is particularly suitable for this area of research, as DIO rats share various features with human obesity
  - Animals born to diet-induced obese mothers display marked differences in the development of hypothalamic neural circuits that normally distribute leptin signals in the brain and are known to regulate energy homeostasis.
    - In vitro data suggest that the abnormalities observed in these rats are due to a reduced responsiveness of hypothalamic neurons to the actions of leptin that normally occurs during postnatal life.

- Exercise in rats genetically predisposed to diet induced obesity alleviates weight gain, adiposity gain, and leptin sensitivity
  - Even up to 10 weeks after exercise cessation!
Conclusions

- Altogether, these studies from the review paper indicate that hypothalamic systems may acquire their unique properties during restricted developmental periods under the influence of both genetic and environmental factors.
  - Very clear evidence that nutritional changes during critical periods of life can impact hypothalamic development and function, with lasting effects on feeding and metabolism.
  - One of the key mechanisms for metabolic programming of the brain is leptin signaling during critical periods of fetal and postnatal development.
  - It is likely that other environmental factors, such as exercise or stress, may also influence the development and function of neural systems involved in energy balance regulation.
Developmental programming of hypothalamic neuronal circuits: impact on energy balance control

Ramamoorthy et al.
Overall focus of the paper

The effects of maternal nutrition on programming permanent changes in the offspring’s hypothalamic neuronal circuits located in the arcuate nucleus (ARC)
Fetal programming of adult disease

- Both epidemiological studies and animal models indicate that adult obesity and associated metabolic disorders can be programmed by intrauterine and early postnatal environment.

- The hypothalamic neuronal circuits located in the arcuate nucleus (ARC) controlling appetite and energy expenditure are set early in life and are perturbed by maternal nutritional insults.

- The fetus will adapt to adverse changes in the intrauterine environment such as maternal undernutrition/overnutrition.
Quick Review

- Anorexigenic ARC neuropeptides and peripheral hormones
  - POMC
  - CART
  - α-MSII neuropeptide
    - Agonist to melanocortin 3 receptors (MC3R) and melanocortin 4 receptors (MC4R)
  - Leptin
  - Insulin

- Orexigenic ARC neuropeptides and peripheral hormones
  - NPY
  - AgRP
  - GABA
  - Ghrelin
Maternal undernutrition & its effects on the offspring

Recognized as being a cause of fetal programming leading to offspring having increased propensity to develop hypertension, type 2 diabetes and cardiovascular disease

Human Model

- Dutch famine
  - Longitudinal analysis of this cohort revealed that ~50 years of age the maternally-programmed offspring had compromised glucose tolerance and higher insulin concentrations
  - The precise mechanisms governing these changes are difficult to elucidate due to the restrictions of using human models ⇒ Animal models used to characterize the potential pathways involved
Maternal undernutrition & its effects on the offspring

In rodents, the hypothalamus is immature at birth and development continues during the first 2 weeks of postnatal life when neurons send axonal projections to their target site and functional synapses are formed.

- As a result, the rodent hypothalamus is not fully formed until after weaning. Any changes in the maternal nutritional environment during these critical periods will severely impact on this system potentially altering the offspring’s developmental trajectory.
- Results of maternal undernutrition:
  - Offspring have low birth weight, exhibit hyperphagia in postnatal life and develop obesity and insulin resistance in adulthood.
  - Hyperphagia exacerbated when offsprings are fed high caloric diet in the post-weaning period.
  - Alterations in hypothalamic cell proliferation and impaired axonal elongation.
    - These changes modify the density of the NPY and POMC neurons which could have direct consequences on the animal’s food intake and energy expenditure and depending on which neurons are affected it could increase food consumption and body weight.
Maternal overnutrition & its effects on the offspring

The number of epidemiological studies establishing a clear link between increased maternal body mass index and the offspring’s susceptibility to disease in adulthood are extensive.

- Rodent models used to detail the effects of maternal high fat diet on offspring
  - Outcome of these studies has been the development of obesity in the offspring accompanied by impaired insulin and glucose homeostasis, as well as many other outcomes such as cardiovascular diseases.
  - Unlike maternal undernutrition, the findings from the maternal overnutrition studies have been conflicting and therefore, more difficult to interpret.
    - While some studies are in agreement that there are impaired anorexigenic and orexigenic nerve fiber projections from the ARC to the PVN, the levels of neuropeptide expression are extremely diverse.
Maternal overnutrition & its effects on the offspring

- In Vogt et al. (2014), a possible underlying mechanism suggested to induce modified fiber projections was altered insulin signaling
  - When the insulin receptor on POMC neurons was ablated in offspring from mothers fed a high fat diet, this led to a rescue in the previously distorted nerve projections
    - As a result, this was the first study to demonstrate a clear link between altered insulin signaling in the hypothalamus and perturbations in the hypothalamic energy regulating pathways in a maternally programmed paradigm
    - Since in humans, ARC neuronal projections arise during the third trimester, these results indicate that changes in maternal glucose metabolism during this critical window may have metabolic effects on the offspring throughout life
    - This investigation did not rule out the possibility of other mechanisms affecting the structure of the hypothalamus and other studies have suggested that changes in hypothalamic connections may also be associated with altered leptin resistance
Maternal nutrition & its effects on the offspring

- Taken together, these results demonstrate that exposure to prenatal or postnatal undernutrition AND overnutrition in rodents results in substantial changes in the development of the hypothalamic architecture
  - Increases susceptibility to develop metabolic disorders, cardiovascular disease, hypertension, obesity
Developmental Programming of Feeding Pathways

Sexual Dimorphism:
- Male offspring of undernourished mothers had a higher chance for reduced insulin levels (Todd et al., 2009)
  - Male brain shown to be more sensitive to changes in leptin and insulin associated with nutritional imbalance (Clegg et al., 2003)
  - These changes in leptin and insulin result in lower central regulation of food intake (Delahaye et al., 2008; Vogt et al., 2014)
  - Result: Lower POMC Expression and Increased Food Intake
- Why not Females?
  - Hypothesized that estrogen may regulate levels of insulin and leptin and this could serve to balance out the dysregulation from maternal undernutrition

Maternal Undernutrition → Dysregulation of Central Leptin and Insulin Signaling → Males: Increased fat mass, lowered insulin
Females:...estrogen compensation for dysregulation of insulin and leptin?
Molecular Mechanisms Implicated in Programmed Obesity

Epigenetics: the study of stable alterations in gene activity without changes in the DNA sequence (Delage and Dashwood, 2008); “marks” are established during fetal development and early postnatal life (Jaenisch and Bird, 2003)

DNA Methylation: The process of adding a methyl group to either cytosine (majority at C5) or adenine to repress gene expression (Jones, 2012)

Histone Modifications: Acetylation, Methylation, Phosphorylation, Ubiquitination, Sumoylation to “open and close” the sites of gene expression; key enzymes: HAT and HDAC (Kouzarides, 2007)
Molecular Mechanisms Implicated in Programmed Obesity

CpG Islands: DNA Methylation at the C5 position of cytosine residues that are adjacent to guanine residues which results in a Cytosine-Guanine Dinucleotide (CpG Island)

- DNA Methyltransferases (DNMTs) catalyze methylation using S-adenosylmethionine (SAM)
- Methylation preserved across replication of DNA
- Two methods of action:
  - Directly prevents transcriptional proteins from binding (Watt and Molloy, 1988)
  - Silence gene expression with methyl-CpG-binding proteins which attract co-repressor complexes containing histone deacetylases (Boyes and Bird, 1991; Jones et al., 1998; Nan et al., 1998)
Molecular Mechanisms Implicated in Programmed Obesity

Hypothalamic POMC Neurons:

- POMC gene has two CpG islands which can be modified by maternal over-/under-nutrition
  - CpG Island in promoter region and between intron 2/exon 3 boundary
  - Hypothalamic POMC Expression also regulated by upstream neuronal enhancers nPE1 and nPE2 (Newell-Price, 2003; Kuehnen et al., 2012)

- Maternal undernourishment in sheep showed hypomethylation of the nPE1 and nPE2 regions (Stevens et al., 2010, 2011)

- Maternal overnourishment in rats showed hypermethylation of CpG-sites associated with insulin and leptin mediated expression of POMC in the hypothalamus (Plagemann et al., 2009)

- Both of the above patterns yielded an obese phenotype

- In human children, hypermethylation of the intron 2/exon 3 CpG island was found in peripheral blood cells of obese children as opposed to normal weight children (Kuehnen et al., 2012)
  - This hypermethylation was associated with reduced binding of the p300 histone acetyltransferase and decreased POMC expression in the peripheral blood cells
  - *Most epigenetic changes are tissue specific*
Glucocorticoid Receptor (GR):

- Maternal undernourishment in sheep showed decreased GR promoter methylation and alterations in histone modifications that lead to increased GR mRNA expression in the fetal hypothalamus (Stevens et al., 2010; Begum et al., 2012)
  - These changes persisted up to five years of age in the sheep and were associated in decreased POMC expression
- Epigenetic GR changes observed in the liver and hippocampus as well (Lillycrop et al., 2005, 2007; Ke et al., 2011)
  - Folic Acid supplementation to a protein-restricted diet prevented these epigenetic changes (Lillycrop et al., 2005)
Molecular Mechanisms Implicated in Programmed Obesity

Other Genes:

- **NPY** (Mahmood et al., 2013)
  - Newborn rats fed with high-carb milk had higher mRNA expression of NPY
  - This was associated with a hypomethylation of CpG sites and increased H3K9 acetylation in the promoter region of NPY
  - These changes led to adult obesity in the rats
- **Insulin Receptor** (Plagemann et al., 2010)
  - Overfeeding during neonatal life has been shown to lead to hypermethylation in the promoter of the hypothalamic insulin receptor
- **Hypothalamic Dopamine and Opioid-Related Genes** (Vucetic et al., 2010)
  - High fat diet during pregnancy and lactation resulted in global and promoter hypomethylation and therefore higher expression of these genes
  - Resulted in raised preference for palatable foods rich in sucrose and fat
Molecular Mechanisms Implicated in Programmed Obesity

Mechanisms of Epigenetic Changes:

- Levels of methyl-group donors
  - SAM is the universal methyl donor for DNA methylation, so levels of folate, choline, methionine, and other vitamins which contribute to the making of SAM can influence epigenetics
  - Methyl donor supplement has been shown to prevent the adverse effects of maternal over-/under-nutrition (Carlin et al., 2013)

- DNMT Modulation
  - Methyl-group donors such as folic acid have been shown to alter the expression of DNMTs and MBPs which are used for epigenetic silencing (Ghoshal et al., 2006; Lillycrop et al., 2007)

- Other Epigenetic Enzymes
  - Histone acetyltransferases (HATs) and Histone Deacetylases (HDACs) are susceptible to the levels of their cofactors such as acetyl-CoA, NAD, FAD, and alpha-ketoglutarate (Kaelin and McKnight, 2013)

- Timing/Intensity Dependence
  - The timing and intensity of the nutritional insults are important but are poorly understood
Molecular Mechanisms Implicated in Programmed Obesity

Transgenerational Effects:

- These epigenetic changes have been shown to persist across generations, either inherited paternally or maternally (Vickers, 2014)
  - *DNMT1 is a maintenance DNMT that preserves the methylation patterns across replication* (Hermann et al., 2004)
- The inheritance has been shown to occur regardless of adverse conditions (i.e. maternal over-/under-nutrition) (Aiken and Ozanne, 2014)
- Glucose metabolism, cardiovascular system, and HPA axis dysregulation have been implicated in transgenerational inheritance (Martin et al., 2000; Benyshek et al., 2004; Gniuli et al., 2008; Pinheiro et al., 2008; Jimenez-Chillaron et al., 2009; Bertram et al., 2008)
Effects of Premature Birth on Offspring Metabolism
Effects of Premature Birth on Offspring Metabolism

Barker’s Hypothesis:

“A hypothesis proposed in 1990 by the British epidemiologist David Barker (b. 1939) that intrauterine growth retardation, low birth weight, and premature birth have a causal relationship to the origins of hypertension, coronary heart disease, and non-insulin-dependent diabetes, in middle age”

Potential Reasons for Barker’s Causal Relationship:

- NICU Stress: Premature infants exposed to temperature differences, pain, sleep disruption, excessive noise and light levels, and frequent handling (Montirosso R, Provenzi L., 2015)
Stress Effects on Premature Infant Metabolism (Tsigos C, Chrousos GP, 2002):

- As shown, the glucocorticoid receptor can influence NPY production
  - Orexigenic effects, food-seeking behavior leading to adiposity
- Cortisol induces insulin resistance in the Liver and skeletal muscle
  - Raised cortisol levels in early life could lead to lifelong insulin insensitivity in these tissues
- Cortisol and Insulin work together to up-regulate Leptin
  - This up-regulation in early life could lead to leptin insensitivity

Leptin levels in adults born preterm vs those born at term (Sarah Mathai et al, 2013)
Epigenetic Implications on Premature Metabolism:

- Ex. SLC6A4 methylation has been shown to result in increased adiposity (by twin studies) (Zhao J, Goldberg J, Vaccarino V., 2013)
  - NICU pain-related stress has been implicated in the methylation of SLC6A4
- More research needs to be done on other genetics implications of premature birth, as well as the environmental factors surrounding premature infants that may lead to epigenetic changes

### Effects of Premature Birth on Offspring Metabolism

<table>
<thead>
<tr>
<th>Anthropometry</th>
<th>Adults born preterm</th>
<th>Adults born at term</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>170.0 (167.1–172.9)</td>
<td>171.5 (167.9–175.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight (kg)†</td>
<td>88.0 (81.2–95.4)</td>
<td>82.9 (75.1–91.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>BMI (kg/m²)†</td>
<td>30.5 (28.3–32.9)</td>
<td>28.3 (25.8–31.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>35.4 (32.0–38.8)</td>
<td>29.4 (25.2–33.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Truncal fat (%)</td>
<td>38.3 (34.1–42.5)</td>
<td>30.1 (25.0–35.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Android fat to gynoid fat ratio</td>
<td>1.09 (1.01–1.16)</td>
<td>0.93 (0.83–1.02)</td>
<td>0.004</td>
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*Fat Levels in Preterm Adults vs Term Adults (Sarah Mathai et al, 2013)*
Effects of Premature Birth and Sexual Dimorphism (Sarah Mathai et al, 2013):

- Overall preterm and full term adults had non-significant differences in obesity.
- But when preterm adults and full term adults are analyzed by sex, men are more likely to have an obese phenotype.
- Phenotypically familiar to sexual dimorphism in offspring of undernourished mothers.
Transgenerational Effects (Sarah Mathai et al, 2013):

- Children of Adults born preterm are at greater risk of an adverse phenotype
  - Although fatter parents have fatter kids regardless of term-length, the stereotypical distribution of fat in preterm adults carried over to their children
- Mothers born preterm are more likely to give birth preterm themselves
  - Fathers born preterm also affect this but to a lesser degree

Effects of Premature Birth on Offspring Metabolism

| Inherited Phenotype in Children of Preterm Adults (Sarah Mathai et al, 2013) |
|------------------|------------------|------------------|------------------|------------------|
| **Anthropometry** | **Height SDS**    | **BMI SDS**      | **Total body fat (%)** | **Truncal fat (%)** |
|                  | 0.51 (0.01–1.01) | 0.26 (-0.22–0.75) | 19.3 (16.3–22.8) | 15.8 (13.6–18.4) |
|                  | 0.54 (0.02–1.07) | 0.38 (-0.13–0.90) | 17.2 (14.3–20.7) | 12.3 (10.1–15.1) |
| **p-value**      | 0.90             | 0.65             | 0.22             | 0.048            |

<table>
<thead>
<tr>
<th><strong>Android fat to gynoid fat ratio</strong></th>
<th><strong>Baseline cortisol (nmol/l)</strong></th>
</tr>
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<tbody>
<tr>
<td>0.71 (0.63–0.81)</td>
<td>220 (177–273)</td>
</tr>
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</table>
| 0.60 (0.52–0.68)                    | 173 (137–219) | 0.009 0.048
Metabolic Syndrome, Alzheimer Disease, Schizophrenia, and Depression: Role for Leptin, Melatonin, Kynurenine Pathways, and Neuropeptides

Anderson et al
Focus

- There are overlaps between Alzheimer’s disease and schizophrenia in biological and metabolic processes.

- TRYCAT PATHWAY

- Leptin and Melatonin have a role in the mediation of metabolic processes underlying these disorders.
Alzheimer’s and Schizophrenia have similar attributes

Alzheimer’s and Schizophrenia have overlaps both in gene expressions and neuronal atrophy
  - Genes associated with dementia in Alzheimer’s like ApoE, and FGF-1 are hereditary in schizophrenia

Maternal prenatal Infection causes immuno-inflammatory changes in early development as well as increases in amyloid B

Both are neurodegenerative and driven by oxidative and nitrosative stress (O&NS)

Both have high levels of comorbid depression

Both share associations with metabolic dysregulation
  - Maternal obesity has effects on obstetric complications
  - O&NS and immuno-inflammatory processes mediate effects via TRYCAT pathway
TRYCAT Pathway

Pathway of tryptophan and its catabolites that enact certain effects on the body, typically activated from immune response

Tryptophan catabolites (TRYCATs): kynurenine (kyn), kynurenic acid (KYNA) and quinolinic acid (QUIN)

- Produced from indoleamine 2,3-dioxygenase (IDO) from O&NS and immuno-inflammatory activity
- Produced from tryptophan 2,3-dioxygenase (TDO) from cortisol and cAMP

Leptin has a inadvertent role in TRYCATs
Leptin’s Role in TDO

Leptin’s receptors evident in CNS regions, frontal cortex, and hippocampus

- Increases cell survival via induction of anti-apoptotic bcl-2
  - Caused by activation of intracellular pathways
- Decreases cortisol’s effects
  - Caused by inhibition of nuclear transport of cortisol’s receptor by increasing BAG-1
- Decreases levels of cAMP

Leptin inhibits TDO and the catabolites kyn and KYNA

- KYNA inhibits release of frontal cortex glutamate, dopamine and ACh by inhibiting a7nAChr
  - KYNA found in schizophrenia and mild cognitive impairment (MCI)
Leptin’s Role in IDO

AMPK and sirtuin-1 have a tandem ability to decrease levels of hyperphosphorylated tau and amyloid beta

Leptin is associated with the activation of AMPK as well as increasing levels of sirtuin-1 which can delay appearance of alzheimer’s

- AMPK increased by cAMP

IDO activation increases sirtuin-1 suggesting leptin having a role in the delicate balance of TRYCAT products and metabolic regulation
Leptin Resistance and Low Leptin Levels

- Decreased leptin transport over the blood brain barrier
- Occurs in obesity and metabolic syndrome
- Occurs in later stages of life

Effects of leptin resistance

- cAMP levels rise which increase TRYCAT production
- Cortisol effects proliferate and chronic unpredictable mild stress (CUMS) occurs
  - CUMS increases QUIN and KYNA
  - Increases in neuronal degeneration and emergence of seizures

Leptin activation inhibits glycogen synthase kinase 3-beta (GSK-3b)

- GSK-3b inhibition prevents glucose dysregulation and decreases levels of tau and amyloid beta production
Leptin, Leptin Resistance, and Melatonin

- Melatonin is decreased in many neurodegenerative, metabolic, and psychiatric disorders (mediated by increased levels of IDO and TDO driving tryptophan down the TRYCAT pathways and away from serotonin and melatonin production)

- Melatonin decreases levels of diet-induced obesity and leptin in cases of leptin resistance => suggests mutual regulatory interactions between leptin and melatonin

- Melatonin increases levels of mitochondrial oxidative phosphorylation -> enhancing metabolic activity, and favoring the differentiation of mesenchymal stem cells into osteoblasts (bone cells), strengthening bone and decreasing adipocyte (fat cells) differentiation (BAG-1-> Vitamin D3->bone enhancement)

Requires investigation to test effects of co-administration of leptin and melatonin in the treatment of metabolic dysregulation association with neurodegenerative and neuroprogressive disorders or whether sequential use of melatonin and leptin would be efficacious in cases of leptin resistance

Note: mesenchymal stem cells: multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells which give rise to marrow adipose tissue).

Note: mitochondrial oxidative phosphorylation: the synthesis of ATP by phosphorylation of ADP for which energy is obtained by electron transport and takes place in the mitochondria.
Wider Interactions (IDF-1, Neurogenesis, SubP, Opioids)

- Insulin-like growth factor-1 (IGF-1) decreases levels of amyloid B production and tau hyperphosphorylation.  
  => Amyloid B inhibits production of leptin

- Leptin increases proliferation of neuronal progenitors  
  -> neuroprotection afforded in depression and Alzheimer disease  
  (increase in BAG-1 by leptin and melatonin via decreased cortisol Gcr activation, will inhibit cortisol suppression of neurogenesis -> enhancement of neurogenesis will inhibit the course of schizophrenia)

- Stress increases release of Substance P -> increase of SubP associated with depression

- As modulating levels of stress associated cortisol production, leptin and melatonin will inhibit SubP effects via inhibition of AC/cAMP pathway

- Inhibition of SubP and NK1r (receptor) are clinical targets for anti-depressant treatment  
  (SubP activation of NK-1r increases cAMP -> increases levels of TDO-induced kyn and KYNA -> contributing to alternations in cognition and mood)
Variations in placental leptin and melatonin production (altered in obstetric complications ex: preeclampsia) -> impact on the etiological biochemical underpinnings of later neuroprogressive and neurodegenerative disorders

Maternal high-fat diet (mHFD) during pregnancy increases the levels of the mu-opioid receptor (and endogenous ligand enkephalin) -> increasing levels of dopamine transporter at specific points in the offspring

mHFD would interact with immuno-inflammatory activation, modulating metabolic dysregulation in the offspring, and susceptibility to adult onset disorders

Alterations in u-opioid receptor in amygdala subregions
-> increase fat palatability and modulate developmental influence of maturing amygdala on the development of other brain regions
=> changes in amygdala activity associated with mood disorders (early developmental link to priming for depression in neurodegenerative and neuroprogressive disorders)

Note: preeclampsia: A potentially dangerous pregnancy complication characterized by high blood pressure.
Treatment Implications

Acetylcholinesterase inhibitors

- Acetylcholinesterase inhibitors (AChEi) increases arousal-associated cognition via increased availability of ACh
- AChEi (e.g. donepezil) will compensate increased KYNA inhibition of a7nAChr, improving cognition.
- Used in treatment of schizophrenia, contributed to metabolic regulation and neuronal survival
- Treatment questioned because of weight loss and decreased leptin with progression of Alzheimer disease

Metformin

- Metabolic dysregulation-> increased risk of type 2 diabetes-> increased risk of Alzheimer disease
- Metabolic dysregulation is associated with increased levels of amyloid B and hyperphosphorylated tau (also associated with Alzheimer disease)
- Metformin decreased these levels improving prefrontal cortex connectivity

Note: AChEi: chemical or a drug that inhibits the acetylcholinesterase enzyme from breaking down acetylcholine
Leptin

- Likely to modulate cognitive functioning by inhibition of cAMP and cortisol induction of TDO and KYNA
- Increase neuronal survival by enhancing anti-apoptotic bcl-2 and its phosphorylation and inhibiting glycogen synthase kinase 3 beta GSK3b
- Induce sirtuin-1, decreased in Alzheimer disease and schizophrenia will contribute to its neuroprotective and metabolic benefits
- Inhibition of cAMP pathway is likely to decrease depression and pain-enhancing effects of SubP

Melatonin

- anti-oxidant, anti-inflammatory and immune regulator
- Decreases leptin resistance, may allow subsequent use of leptin, providing metabolic benefits
Alzheimer and schizophrenia susceptibility genes interact with maternal infection, preeclampsia, to drive changes in metabolic regulation, increasing obesity and mitochondrial dysfunction. This leads to increased oxidative and nitrosative stress (O&NS), pro-inflammatory cytokines, and leptin. Leptin has a number of neuroprotective effects, increasing pro-survival proteins. However, an increase in cAMP drives increased leptin resistance, contributing to increased TDO and removal of tryptophan from serotonin and melatonin production while increasing tryptophan catabolites (TRYCATs), such as kynurenic acid (KYNA) and quinolinic acid (QUIN). This is concurrent to altered immune regulation.

This combines to decrease neurogenesis and contribute to decrements in cognition while increasing excitotoxicity, depression (MDD), somatization, and blood–brain barrier (BBB) permeability.