

Background:

Overnutrition (i.e. excessive food intake) causes cellular dysfunction throughout the body, including in the brain that leads to the development of metabolic disease and weight gain. One key brain region of interest in this process is the arcuate nucleus (ARC) of the hypothalamus. The ARC contains at least two neuronal populations that can inhibit or induce feeding (POMC neurons and AgRP/NPY neurons, respectively), and signaling via the ARC is crucial for regulation of feeding and energy balance. While many other regions of the hypothalamus contribute to energy balance, the ARC is considered a “first responder” to homeostatic challenges because, similar to other circumventricular organs such as the area postrema, it lacks a full blood brain barrier; the ARC therefore has preferential access to circulating signals, including nutrients, hormones and other mediators. *The mechanisms and cellular targets, however, by which overnutrition/diet regulate the ARC to impact energy balance remain unclear.*

A recent report¹ suggests that overnutrition is associated with *brain injury* in the ARC and these changes may underlie the development of obesity. Consumption of an overnutritive diet (e.g. high-fat diet, HFD) increased inflammatory markers, the appearance of reactive astrocytes and microglia (e.g. gliosis) and selective neuronal loss in the ARC of rodents. Gliosis may also be present in the hypothalamus of obese humans. The authors of this study, however, do not posit a mechanism for the observed changes and they state that “It remains to be determined whether this finding is causally linked to obesity pathogenesis or is simply a marker of the obese state.”

Your Task:

Develop a hypothesis that mechanistically examines if/how overnutrition injures the ARC and the relevance of this mechanism to energy balance. Develop a 12 page NRSA-like proposal that addresses your hypothesis. (Page limit of proposal does not include references.)

In forming your hypothesis you may consider the following questions amongst others:

- What component of overnutrition could promote injury in the ARC?
- How could overnutrition induce changes in specific cell types?
- Does overnutrition permanently alter the ARC and energy balance? In colloquial terms, will a month of McDonalds meals doom your brain (and weight) for life?
- How could overnutrition produce inflammation and how might it be mediated in the ARC?
- Does overnutrition cause ARC injury in animals that are resistant to obesity?

Suggested Reading List

- 1) Thaler JP et al (2012). “Obesity is associated with hypothalamic injury in rodents and humans.” *Journal of Clinical Investigation*, 122(1): 153-62
- 2) Yi C-H, Tscöhp MH, Woods SC and Hoffman SM (2012). “High-fat-diet exposure induced IgG accumulation in hypothalamic microglia.” *Disease Models and Mechanisms*, 5:686-690.

- 3) Cai D (2013). "Neuroinflammation and neurodegeneration in overnutrition-induced diseases." *Trends in Endocrinology and Metabolism*, 24(1):40-45
- 4) Abizaid A and Horvath TL (2008). "Brain circuits regulating energy homeostasis." *Regulatory Peptides*, 149:3-10.
- 5) Horvath TL et al (2010). "Synaptic input organization of the melanocortin system predicts diet-induced hypothalamic reactive gliosis and obesity." *PNAS*, 107:14875-14880.
- 6) McNay DEG et al (2012): "Remodeling of the arcuate nucleus energy balance circuit is inhibited in obese mice." *Journal of Clinical Investigation* 122(1): 142-152
- 7) Araújo EP, Torsoni MA and Velloso LA (2010). "Hypothalamic Inflammation and Obesity." *Vitamins and Hormones*, 82:129-143

Sections of Your Proposal:

- Specific Aims (1 Page, single spaced). Should include:
 - A brief background of the research question and why it is important.
 - Your hypothesis to mechanistically study overnutrition-induced changes in the ARC
 - 2-3 aims that will test your hypothesis. Note that these should address different levels of neuroscience (i.e. molecular, cellular, systems/circuits, organismal, behavioral.)
- Background and Significance (2- 3 pages, double spaced):
 - Explain the scientific issue and why it is important
 - Set up the rationale for your hypothesis, including relevant citations
- Research Plan (6-7 pages, double spaced):
 - This section will describe the experiments that test your hypothesis.
 - For each aim or sub-aim, include the rationale for the experiment, description of research design and proposed statistical tests, expected outcomes as well as potential pitfalls. How would the outcome of your experiment support or falsify your hypothesis?
- References:
 - List of the primary literature cited within your proposal.

Specific Formatting Requirements for Proposal:

Font: Arial, no smaller than 11 pt.

Margins: At least 0.5" margins on all sides.

Spacing: Specific Aims and References may be single-spaced. The rest of the proposal must be double-spaced.

Page Limit: 12 Pages (not including references.)

Header: Title of your proposal on each page

Footer: Page number

Figures / Legends: Figure font may be less than 11pt, but must be readable. Your reviewers' eyes may not be as young as yours, so be kind.