Developmental Western diet alters hypothalamic satiety circuit responses to Exendin-4

Investigating POMC and NPY activation in the arcuate nucleus

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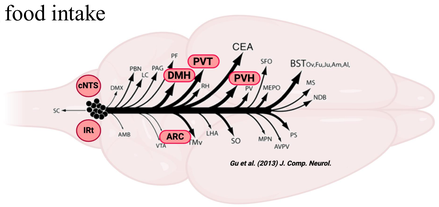
Background / Previous research

Neural regulation of feeding

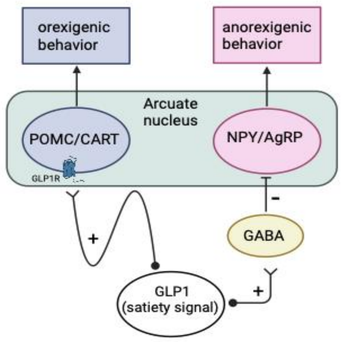
- Energy balance is regulated by hypothalamic circuits
- Glucagon-like-peptide 1 (GLP1) is a neuropeptide produced in the hindbrain that projects to subcortical nuclei across brain, regulating energy balance and reducing food intake (Brierley et al., 2021)
- Arcuate nucleus (ARC) of the hypothalamus houses 2 neuron populations controlling food intake

1. **POMC/CART** neurons induce satiety when active , and are excited by GLP1
2. **NPY/AgRP** neurons induce hunger when active , and are inhibited by GLP1
   → Balance between these neurons maintains homeostasis (Secher et al., 2014)

- GLP1 acts to regulate activity of POMC and NPY neurons to reduce food intake



GLP1 projections



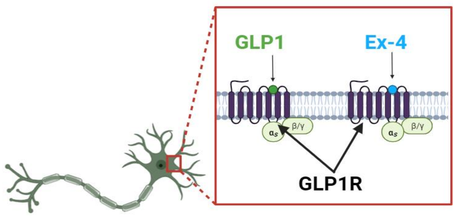
Hypothalamic feeding circuit

Satiety signaling via GLP1 / Excendin-4 (Ex4)

- GLP1 → GLP1 receptors → reduced food intake
- GLP1R plays important role in satiety
- Ex4: GLP1R agonist

→ suppresses food intake via GLP1R activation

- POMC and NPY neurons affected inversely by Ex4



Mechanism of Ex-4 (GLP1 agonist) activating GLP1 receptors

Developmental diet impact on satiety circuitry

- Maternal exposure to high fat high sugar diet (western diet; WD) caused higher risk of obesity in offspring (Ullah et al., 2023)
- Perinatal WD exposure induces obesity and altered hunger regulation circuits of developing rats
- These changes impair satiety signaling and increase food intake into adulthood (Desai et al., 2020; McNay et al., 2012)

Previous research: Developmental western diet alters neuronal activity

Developmental WD exposure reduced Ex4 induced neuronal stimulation

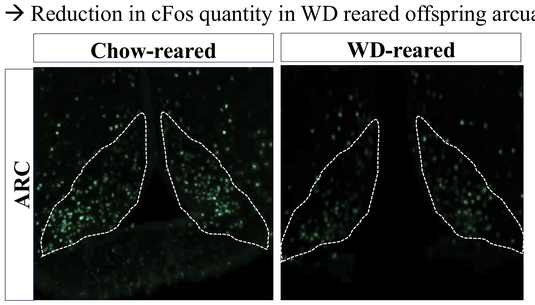
- Ex4 increased neuron activity in multiple areas of the brain involved in feeding regulation
- Offspring reared on WD showed reduced neuronal stimulation following Ex4, compared to control counterparts (chow reared animals

→ Suggests **WD exposure impaired satiety signaling**

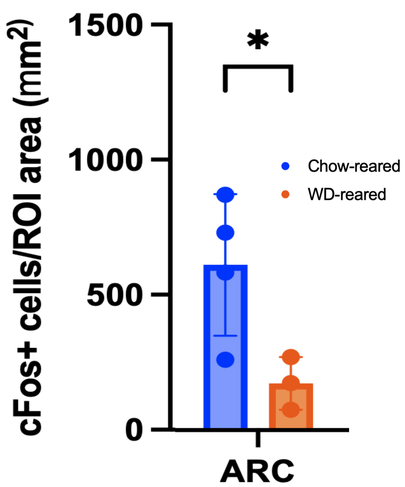
- cFos: early gene marker of general excitatory input, expressed following neuron stimulation

→ visual representation of neuron stimulation after Ex4 administration

→ Reduction in cFos quantity in WD reared offspring arcuate nucleus



Fluorescent micrographs of cFos (green dots) Reduction in quantity of cFos in WD condition compared to chow diet animals Outline represents ARC



Graph showing significant cFos quantity differences between WD and chow offspring following Ex4 dose

Knowledge gap: Reduced cFos is evidence for WD causing decreased GLP1R recruitment by Ex4 and disrupted satiety signaling
how blunted GLP1R expression impacts specific satiety neurons and circuits remained incompletely understood

Current project

Effects of perinatal western diet exposure on the development and function of satiety circuits in the arcuate nucleus of rat offspring

- GLP1 directly binds to GLP1 receptors on POMC neurons exciting them and indirectly inhibits NPY neurons (Nilsson et al., 2013)
- Does developmental exposure to WD alter activation of POMC neurons following Ex4 administration?
- Does developmental exposure to WD alter activation of NPY neurons following Ex4 administration?

rats developmentally exposed to WD will show reduced POMC activation and altered NPY activity in response to Ex4.

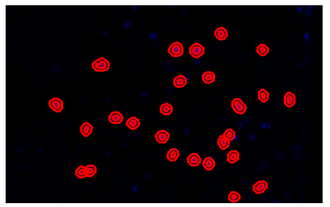
- Changes in these neuronal populations may contribute to impaired appetite suppression and increased susceptibility for obesity

Methods

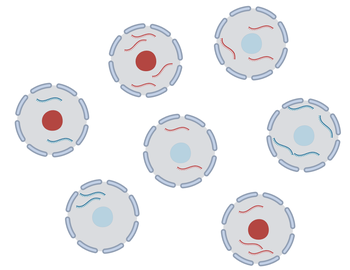
- Diet condition (WD/Chow) exposure prior to breeding and maintained throughout experiment
- Offspring reared and exposed to diet condition of dam
- Offspring perfused at post natal day 14 and post natal day 21 (2 points of analysis during development)
- Brains sectioned and stored for analysis
- RNAscope *in situ* hybridization to identify neurons that express the genes encoding POMC and NPY
- Immunohistochemical labeling to identify Cfos

→ cFos presence represents neuronal stimulation

- Fluorescent cFos identifies POMC and NPY neurons with excitatory input following Ex4



cFos labeling highlighted by quantification software used to obtain cFos positive cell counts



Representation of cFos positive cells (red nucleus) and cFos negative cells (blue nucleus) with POMC and NPY mRNA transcripts in cell body

→ Quantification

- Total POMC neuron
- Total NPY neurons
- Active POMC neurons
- Active NPY neurons
- % stimulated neurons in each subpopulation

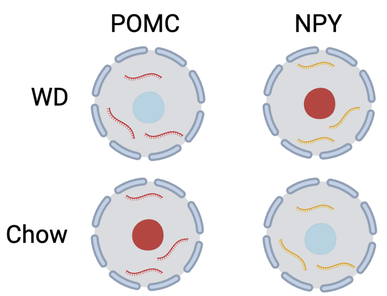
Expected results

- WD blunts cellular stimulation after GLP1R agonist administration
- Blunted GLP1R recruitment by WD exposure may decrease POMC stimulation and increase NPY stimulation

Potential outcomes

- ↓ neurons with POMC and cFos (stimulated POMC neurons)
- ↓ POMC neurons
- ↑ neurons with NPY and cFos (stimulated NPY neurons)
- ↑ NPY neurons

These changes would support impaired hypothalamic satiety signaling caused by western diet during development



Hypothesized stimulation and gene expression by diet condition for NPY and POMC neurons

Significance

Previous work frames the developmental period as critical for healthy regulation of hunger and satiety signals. My research suggests that WD plays a role in reducing response to signals that convey satiation. If early life exposure to WD decreases activity of circuits in place to regulate food intake, then this exposure could increase susceptibility for overeating.

This study investigates how neuronal populations involved in energy regulation and food intake are impacted by WD during development. Potential alterations in activity and cell count for either POMC or NPY populations in the ARC would provide insight into WD and its impact on hunger regulation. These changes would suggest a mechanism for impaired energy balance signals caused by high fat and sugar diets. This would contribute to a better understanding of the developmental origins of obesity. Understanding these origins will provide us with a foundation to combat the rising rates of obesity that is harming youth around the world

References

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