The Neurodevelopmental Effects of Western Diet on the Central GLP-1 System

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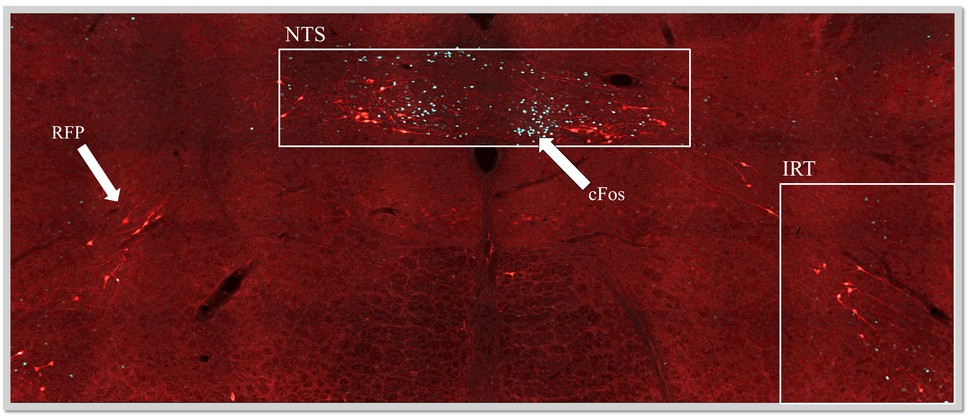
Introduction

- Maternal consumption of the Western diet (mWD) has many negative health consequences in offspring, and the underlying mechanism linking the two is not fully understood.
- GLP-1 is a neurotransmitter that regulates many of the behaviors and outcomes related to the mWD, such as appetite regulation, glucose metabolism, insulin sensitivity, and energy balance.
- There has been no prior investigation into whether mWD influences development of GLP-1 circuitry.
- To investigate this, we used Gcg-Cre/td-Tomato offspring and fed rat dams either WD or chow throughout pregnancy and lactation.
- GLP-1 is actively produced in two hindbrain nuclei: Nucleus of the Solitary Tract (NTS) and Intermediate Reticular nucleus (IRt)
- GLP-1 neuron anatomy and GLP-1 receptor neuron responsiveness were investigated within these two hindbrain regions
- The outcome of this research will reveal the effects of mWD on the development of the central GLP-1 system.

Methods

- Homozygous female Gcg-Cre rats were crossed with homozygous male tdTomato rat to produce heterozygous Gcg-cre/tdTomato offspring used in this study. These offspring express red fluorescent proteins (RFP) in all GLP-1-producing neurons.
- Introduced female rats to WD or chow before pregnancy and keep them on chosen diet throughout lactation. On postnatal day 21 (P21), all pups are weaned onto a chow diet.
- On P60, peptide Exendin-4 is administered through IP injection two hours before sacrifice. Exendin-4 binds to GLP-1 receptors, activating GLP-1R neurons.
- RFP expression allows for visualization and tracking of GLP-1 neurons, facilitating a detailed examination of their structure and where they are found in the brain.
- Visualized activated GLP-1 receptor neurons through cFos expression.
- Imaged P60 brains in 20x magnification (seen below).
- Used FIJI to analyze the number of GLP-1 neurons and amount of Ex-4-induced cFos expression.



Results

Figure 1

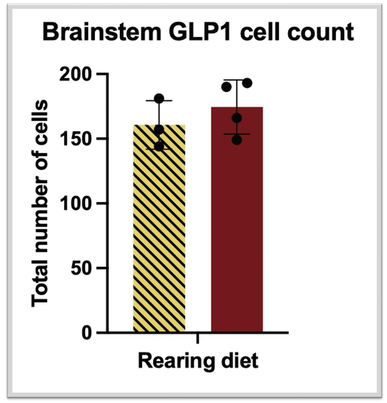
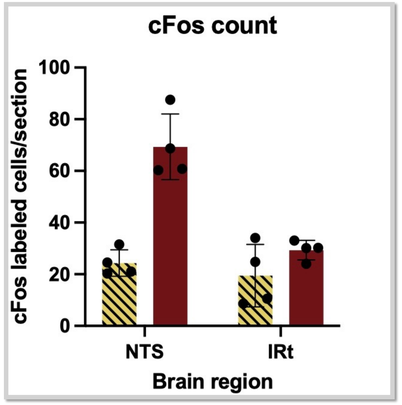


Figure 2



- The level of cFos examined in the western diet offspring was much lower than the level of cFos observed in the chow diet offspring.
- There was no observed difference in RFP expression in hindbrain GLP-1 neurons between dietary conditions.
- This data is preliminary, and trends may change once more subjects are added.

Conclusion

- If subsequent data follows this trend, it will suggest that maternal Western diet causes dysregulation of the GLP-1 system, which has significant implications for our understanding of early life environments and metabolic health.
- Although our data is preliminary, a decrease in cFos suggests that there is a decrease in reactivity of the GLP-1R neurons within GLP-1 producing nuclei of mWD hindbrains.
  - Reduced responsiveness of GLP-1 receptors suggests that mWD can blunt GLP-1 signaling in offspring.
  - GLP-1 plays a huge role in appetite regulation and glucose metabolism by providing a feeling of fullness after eating and enhancing insulin sensitivity.
- This data arouses speculation that consuming mWD during the gestation and lactation period may contribute to a decline in metabolic health. Blunted GLP-1 signaling may contribute negatively to overall metabolic health.
  - Poor metabolic health can lead to issues such as obesity, diabetes, cardiovascular disease, all of which are associated with increased risk for mortality.

References

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