Perinatal Western diet exposure reduces response to GLP1-R agonist in areas of the brain related to food intake

Sawyer A. Cohen, Abigail B. Randolph, and Linda Rinaman
Florida State University, Dept. of Psychology and Program in Neuroscience

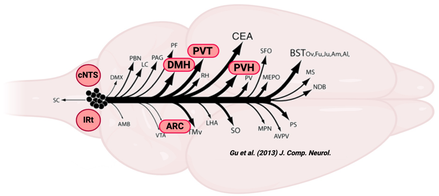
Introduction

Maternal consumption of a diet high in fat and sugar (Western diet; WD) is associated with altered metabolic and behavioral health in offspring (Gautier et al., 2018).

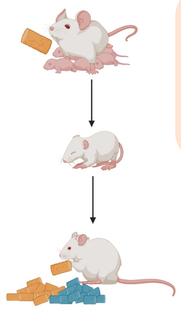
Glucagon-like peptide 1 (GLP1) is a neuropeptide produced by brainstem neurons that contribute to regulation of body energy balance and food intake.

Brainstem GLP1 neurons project to many subcortical nuclei to regulate behavior in a metabolic state-dependent manner (Decarie & Kanoski, 2021).

- GLP1 neurons are excitable and facilitate behavioral stress responses when animals are in a fed/metabolically sated state.
- GLP1 neurons are not excitable, and stress responses are reduced when animals are in a state of metabolic deficit, e.g., after food deprivation.



cNTS: caudal nucleus of the solitary tract
IrR: intermediate reticular nucleus
PVH: paraventricular hypothalamus
PVT: paraventricular thalamus
DMH: dorsomedial hypothalamus
ARC: arcuate nucleus



Question: Does early life exposure to a WD alter the development of central GLP1 signaling in pathways in offspring?

We hypothesize that perinatal WD exposure will alter the number of cFos labeled cells.

Central GLP1 circuitry appears to display diet-induced plasticity

- Long-term intake of high-fat diet by adult mice increases the ability of interoceptive stress to activate brainstem GLP1 neurons and reduces activation of GLP1R-expressing neurons in brain regions receiving GLP1 axonal input (Bales et al., 2022).
- Changes in the GLP1 system can alter ability to properly regulate stress responses and food motivation.
- Diet can induce changes in brain GLP1 circuits that control motivated behavior for adult rats

Approach

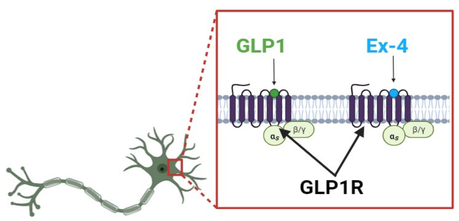
Gcg-tdTom reporter rats were used in this experiment. The glucagon gene (*Gcg)* encodes preproglucagon, which is cleaved into GLP1. Gcg-tdTom reporter rats have red reporter labeling of neurons that express *Gcg*, including brainstem GLP1 neurons.

Dams were provided either chow only or WD+chow for 48 hours prior to mating and were maintained on the same diet through the perinatal period of offspring development (i.e., gestation and lactation). Thus, offspring were divided into chow- vs. WD-reared groups.

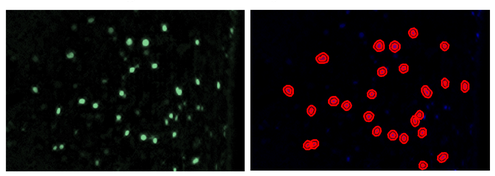
Offspring were injected with GLP1 receptor agonist Ex-4 (10µg/kg) at postnatal day (P)14 and were perfused 2 hours later
- Brains were collected for immunohistochemical labeling of cFos positive cells, indicating activation by Ex-4

cFos-positive cells were quantified in selected thalamic and hypothalamic nuclei involved in food intake

QuPath software was used to manually define regions of interest (ROI), including the PVT, PVH, DMH, and ARC
- QuPath counts c-Fos within defined ROI's using a built-in cell detection feature
- cFos cell counts indicate the number of neurons activated in each region after Ex-4 injection

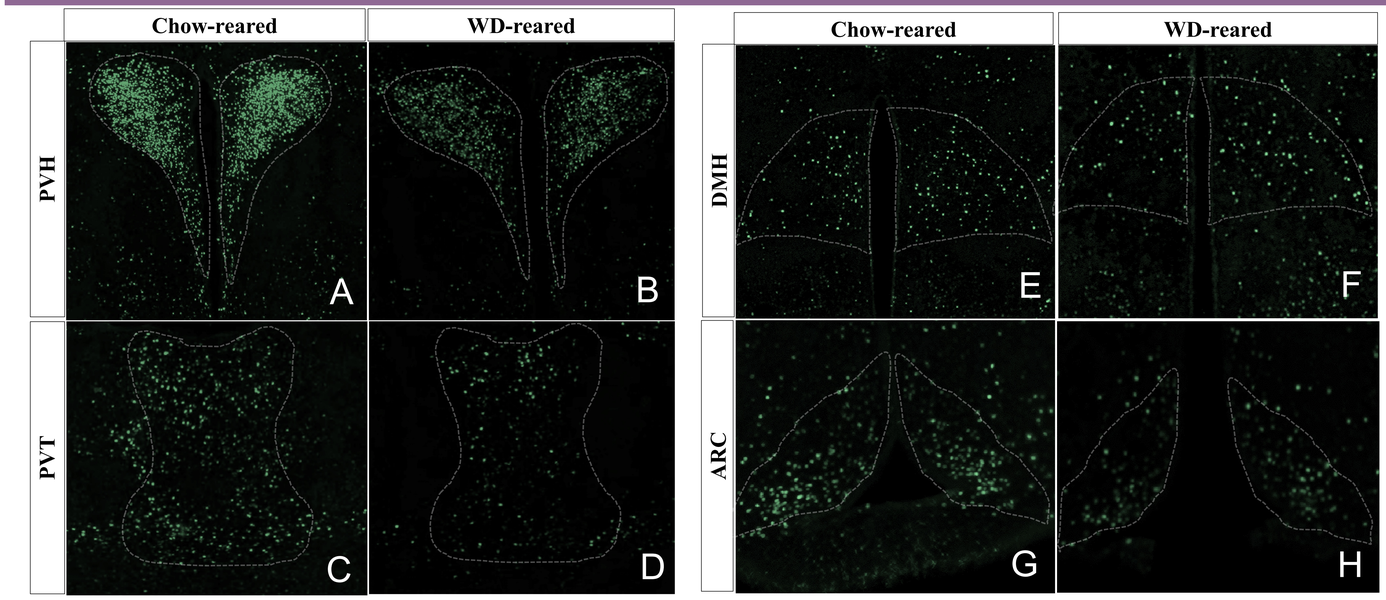


Mechanism of Ex-4 (GLP1 agonist) activating GLP1 receptors

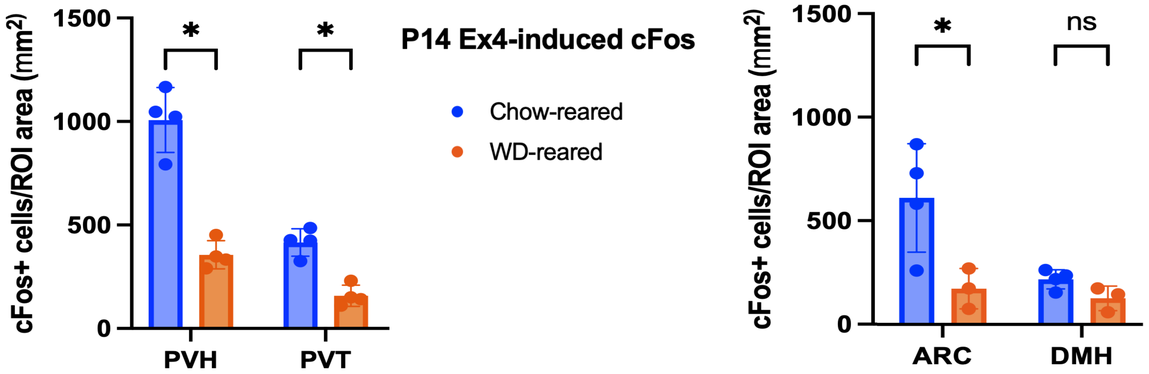


QuPath's cell detection feature reliably detects c-Fos positive labeling in cell nuclei.
Images demonstrate photographs of labeling before (left) and after (right) QuPath cell detection

Results



Fluorescent micrographs of cFos (green) labeling in the PVH (A,B), PVT (C,D), DMH (E,F), and ARC (G, H). Outlines indicate regions assigned as the respective nuclei for cell counting. Representative images from each nuclei are shown for chow and WD raised animals



Compared to chow-reared control offspring, WD-reared offspring have significantly fewer cFos positive cells/ROI area in the PVH (*p=0.000264*), PVT (*p=0.000896*), and ARC (*p=0.0425*). Rearing diet has no significant impact on Ex-4-induced cFos in the DMH (*p=0.0669*).

The reduced ability of Ex4 to activate cFos suggests that WD-reared offspring have blunted GLP1R signaling, which may lead to altered regulation of motivated behaviors.

Discussion

Studies show high fat diets alter activation of GLP1 and GLP1R neurons in adult rats. but does early life exposure to WD also alter the developing GLP1 system in immature rats? Our data suggest developing rats with perinatal WD exposure have significantly less Ex-4 induced cFos labeling in some parts of the brain (PVH, PVT and ARC, but not DMH). We conclude that WD decreases responsiveness of GLP1 circuitry during development in many parts of the brain.

The GLP1 system plays a role in regulation of food, drug, and stress response behaviors (Eren-Yazicioglu et al., 2021). Therefore, reduced firing of GLP1 related neurons during development could significantly affect these motivated behaviors. Early life exposure to high fat and sugar diets appears to impact regulation of motivated behaviors by altering GLP1 system responsiveness.

One possible implication is that diet-related impairment of GLP1 signaling can cause a vicious cycle leading to reduced regulation of motivated behaviors (e.g., over-eating) and further exposure to high fat and sugar diet. While further research is needed to connect the decline in GLP1 signaling to food choices, evidence supports WD is connected to changes in the GLP1 system, which could induce less regulated motivated behaviors.

References

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