Chronic Semaglutide Treatment Reduces GLP1R-Mediated Activation of Hindbrain Neurons

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Introduction

- GLP1 is an endogenous hormone and neurotransmitter that acts on GLP1 receptors **(GLP1R)** in the body and brain to regulate glucose balance and to induce satiety.
- Semaglutide **(SEMA)** and Exendin-4 **(Ex4)** are GLP1R agonist drugs that act in the brain to reduce food intake.
- SEMA is taken chronically by thousands of people to control diabetes, and for weight loss.
- In rats, SEMA and Ex4 activate neurons that express GLP1R in brain regions that control eating and body weight regulation.
- Neural activation can be visualized by increased expression of **cFos** protein.
- In rats, nausea correlates with activity in the hindbrain area postrema (**AP**) and nucleus of the solitary tract (**NTS**) (Miller & Leslie, 1994).
- Humans receive SEMA treatment with dose escalation and maintenance to increase their tolerance against the nausea-inducing effects of the drug (Huang et al., 2024).
- Reduced nausea after chronic SEMA treatment may be due to reduced effects on AP/NTS neurons, perhaps due to reduced sensitivity of GLP1R.

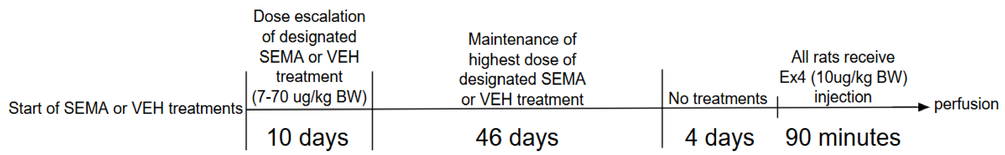
Hypothesis:

Chronic SEMA treatment in rats will reduce GLP1R sensitivity, leading to reduced ability of Ex4 to activate cFos in the AP and NTS.

Approach

Experimental Animals and Treatment

- N=8 adult male Sprague-Dawley rats received daily SEMA treatment, with a 10-day dose escalation period (7-70 ug/kg BW) followed by the maximum dose for 46 days.
- N=7 control rats received vehicle (VEH) injections instead of SEMA for 46 days.
- Four days after the final SEMA or VEH injection, all rats received a subcutaneous injection of Exendin-4 (Ex4) (10 ug/kg BW) 90 minutes before transcardial perfusion and brain harvest.



Tissue Treatment

- All 15 brains were sectioned into 6 series of 35um coronal slices.
- 1 series from each brain was processed for immunohistochemical localization of cFos.

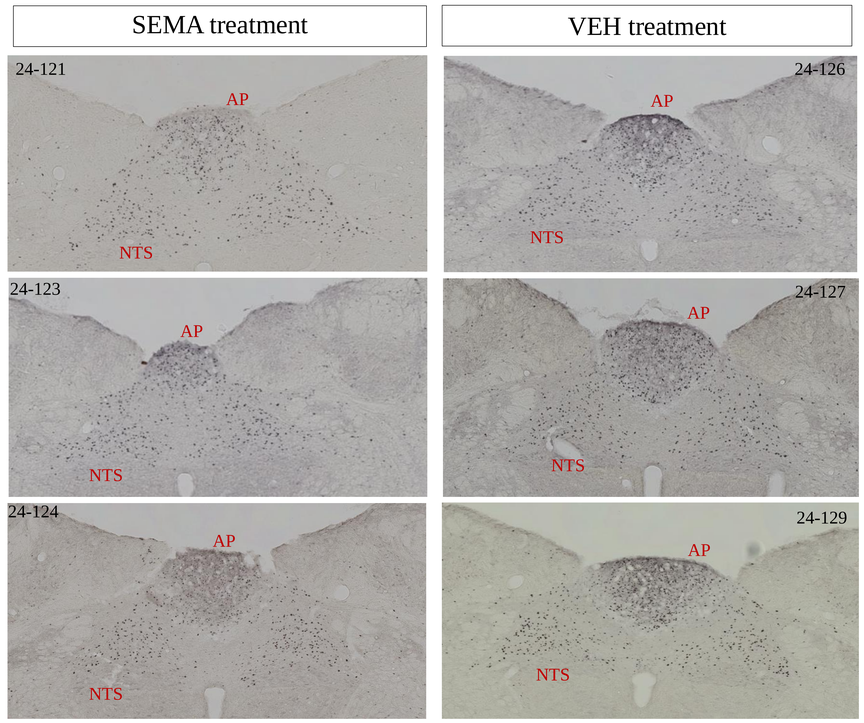
Data collection

- Labeled tissue was imaged on a Keyence Microscope.
- Using QuPath software, cFos labeling was quantified in the AP and NTS, two brain regions that contribute to appetite regulation and nausea and contain GLP1R.

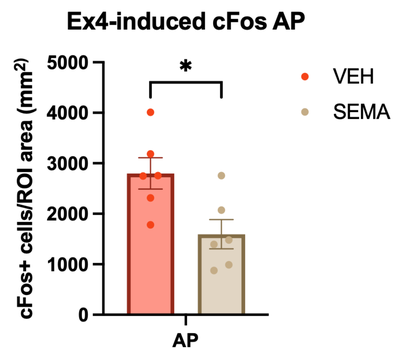
Data Analysis

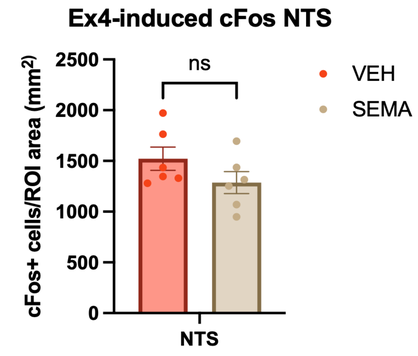
- Tissue samples from 6 SEMA-treated rats and 6 VEH-treated rats were used for data analysis. *(One rat in each treatment group was removed due to missed injection of Ex4, and an additional SEMA rat was removed due to lack of sections containing the AP).*
- A standardized cell detection test was used to count how many cFos-positive cells were present within a designated tissue area, then that count was divided by the area to obtain cFos counts/mm^2 for each region in each animal.
- Data were compared between SEMA and VEH groups using a 2-tailed t-test .

Results



Images depicting cFos activation in brain tissue containing the AP and NTS regions that were analyzed in this experiment. SEMA-treated rats have less cFos labeling in the AP compared to VEH-treated rats.





Average cfos count/area (mm^2) compared between SEMA treated and VEH treated rats.

- Chronic SEMA administration significantly reduces the ability of Ex4 to activate cFos in the AP *(P = 0.01766)*, but does not significantly alter cFos within the NTS *(p-value = 0.16708)*

Discussion

Chronic SEMA appears to reduce GLP1R sensitivity within the AP.

Results from this study suggest that chronic SEMA treatment alters brain responses to a different GLP1R agonist, Ex4. These results also suggest that chronic SEMA may reduce GLP1R-mediated responses to natural, endogenously released GLP1 in thousands of humans currently taking SEMA to treat diabetes and obesity.

Future experiments

- Analyzing GLP1R protein (expression) in the same rats to determine if reduced cFos activation correlates with reduced GLP1R.
- Examining cFos and GLP1R in additional brain regions (including the parabrachial nucleus, hypothalamus, and central amygdala).
- Examining the ability of Ex4 to produce nausea (measured using a conditioned taste aversion assay) in rats that were previously maintained on SEMA vs VEH.

Funding

Research supported by NIH award DK059911 to Linda Rinaman

& NIH award DK106112 to Alan Spector

We gratefully acknowledge the chronic SEMA and VEH treatments conducted by Dr. Carolina Cawthon on these experimental rats during her postdoctoral work in Dr. Alan Spector's laboratory.

References