Central GLP1 Neurons, Axonal Projections, and Responses to Systemic GLP1R Agonists *(GLP1Rags)*

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No Conflicts to Declare

The Central GLP1 Projection System

Gcg-expressing **GLP1 neurons** located in the hindbrain *(caudal NST and IRt)*

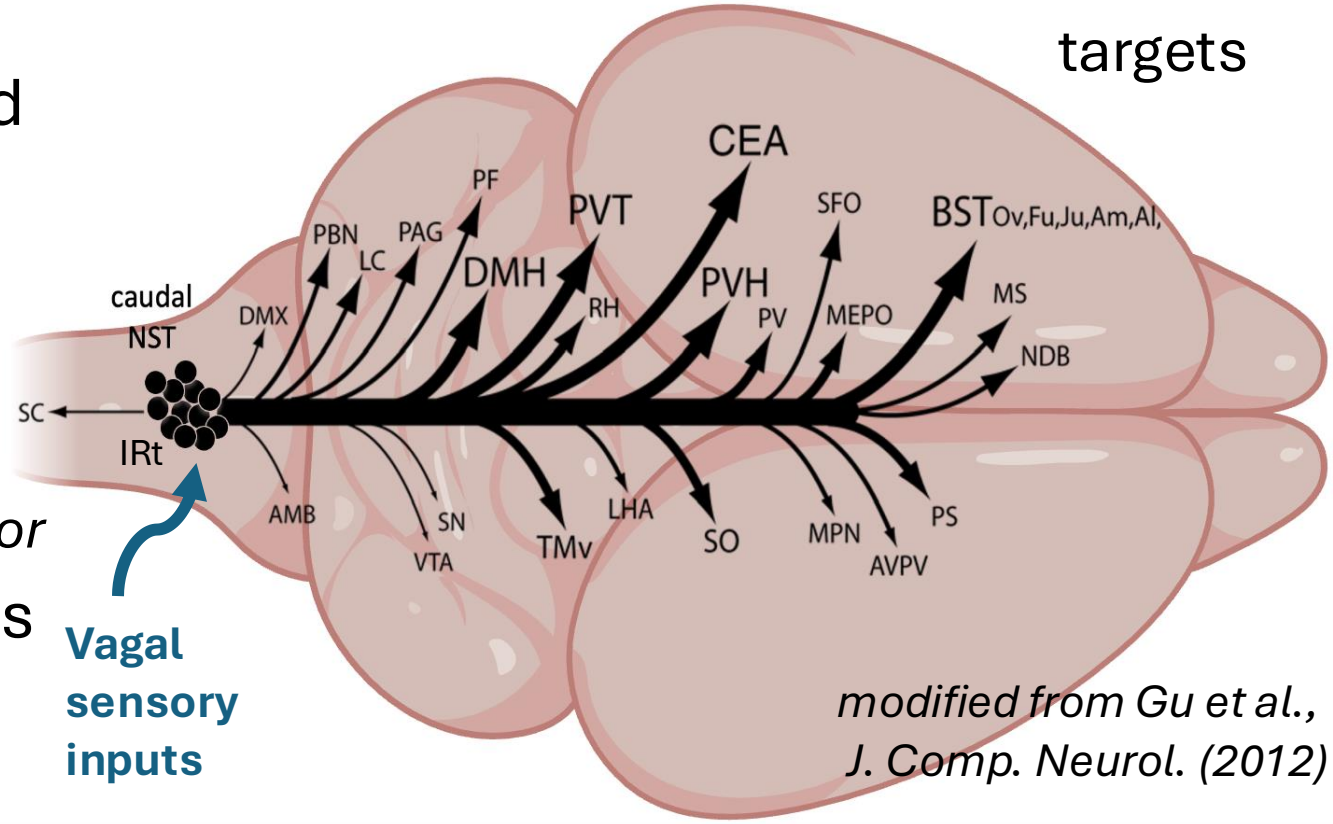
Activation of **GLP1 neurons** or central **GLP1R's** suppresses motivated behaviors

- *Food intake, drug self-administration, operant responding, exploratory behavior*

GLP1 neurons "go offline" during states of negative energy balance

- *Accompanied by increased food intake, drug self-administration, operant responding, exploratory behavior*

Subcortical targets

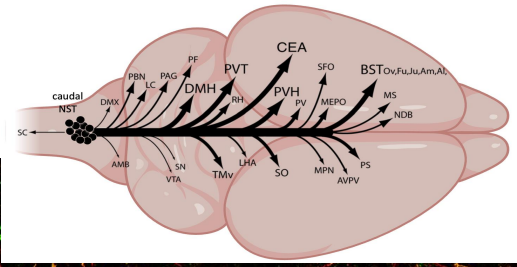


modified from Gu et al., J. Comp. Neurol. (2012)

The endogenous GLP1 system modulates motivated behavior in a metabolic state-dependent manner

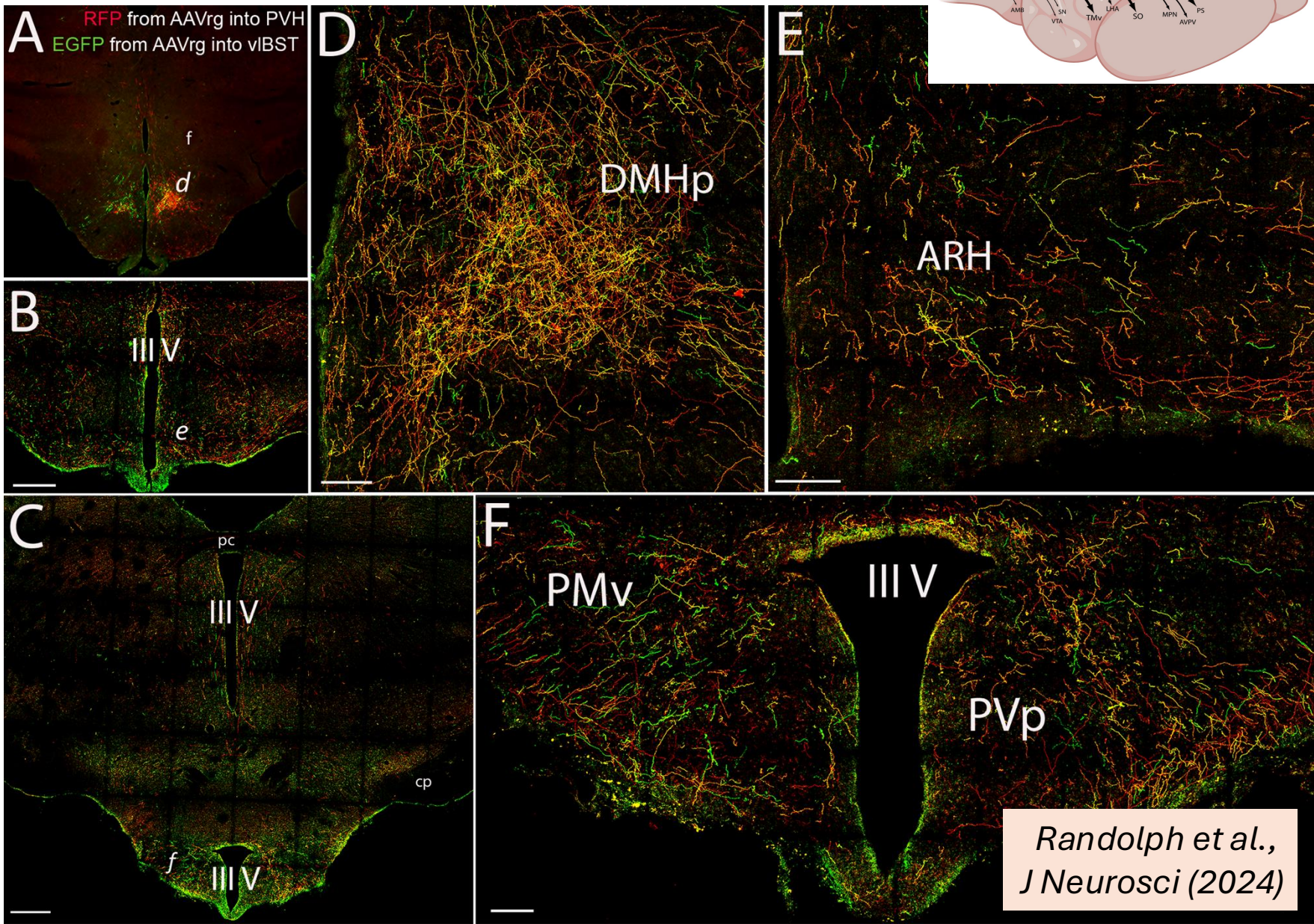
Maniscalco & Rinaman, Physiology (2018)

The Central GLP1 Projection System



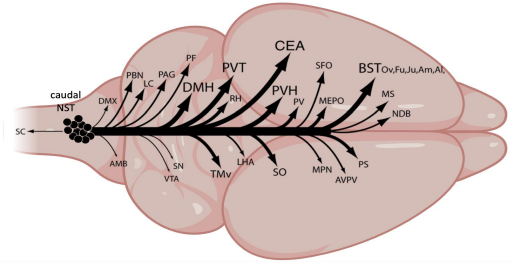
GLP1 axons innervate many subcortical brain regions

- GLP1 neurons that target one brain region *(e.g., PVH, PVT, BST)* have axon collaterals that reach <u>all</u> central GLP1 axonal targets
- ***Glp1r*** is expressed in all these subcortical target regions, **and** in cortical/hippocampal regions that lack GLP1 axonal input.
  - *Is GLP1R trafficked to terminals in regions that <u>do</u> receive GLP1 input?*



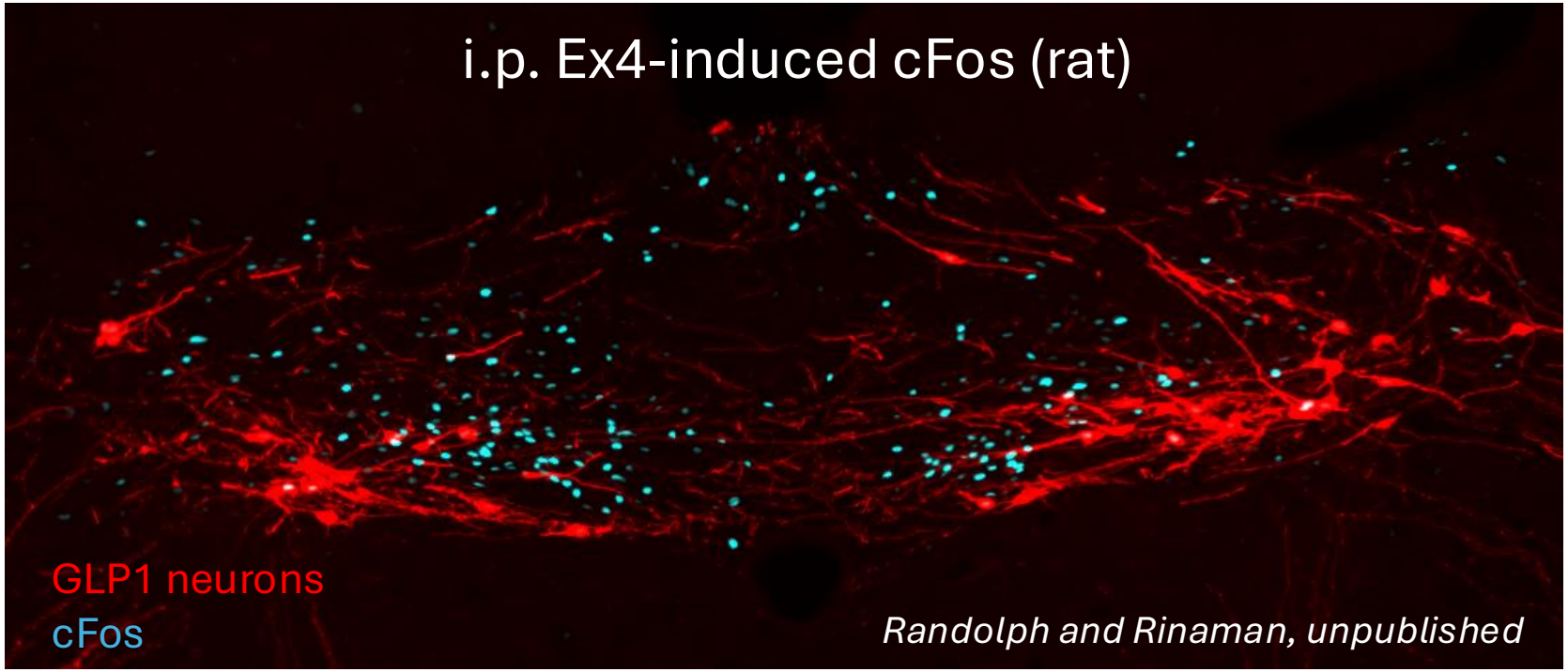
Randolph et al., J Neurosci (2024)

Systemically Administered GLP1RAgs Do Not Recruit the Central GLP1 Neural Projection System



Hindbrain GLP1 neurons. . .

1) do not express *Glp1r*
2) receive little or no synaptic input from *Glp1r*-expressing neurons in the nodose ganglion or area postrema
3) are unnecessary for eating suppression after systemic dosing with GLP1RAgs *(liraglutide, semaglutide)*
4) are not activated to express cFos after systemic GLP1RAgs *(semaglutide, exenatide/Ex-4)*



However, ablation of *Glp1r*-expressing neurons in the hindbrain dorsal vagal complex blocks the ability of systemic GLP1RAgs to suppress intake

Secher et al., J Clin Invest (2014); Card et al., J. Comp. Neurol (2018); Brierly et al., Nature Metab (2021); Huang et al., Nature (2024)

Do Systemic GLP1RAgs Directly Access Central GLP1R's?

Circumventricular organs *(CVOs = no blood-brain barrier)*

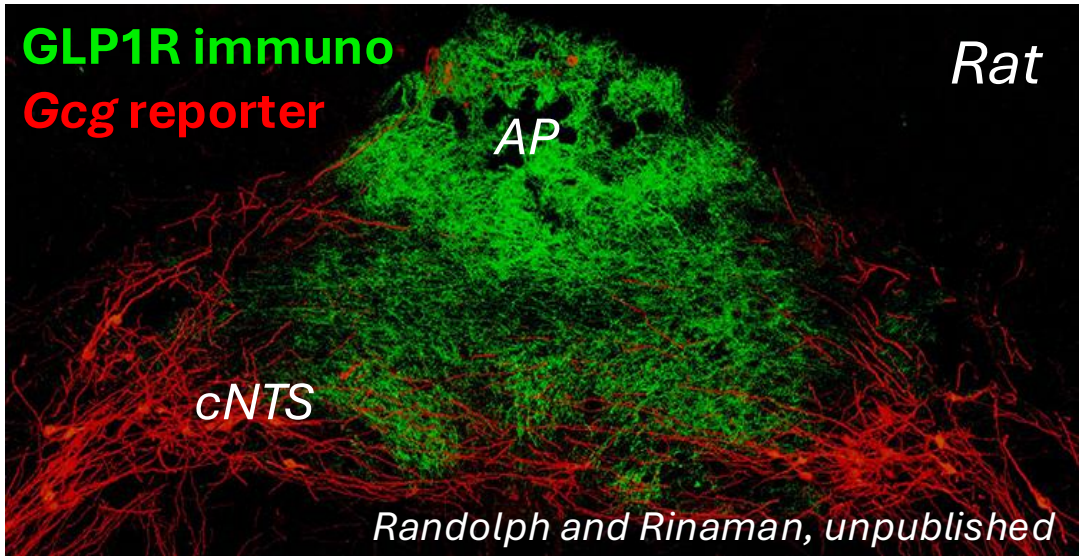
- Area postrema, median eminence, AV3V

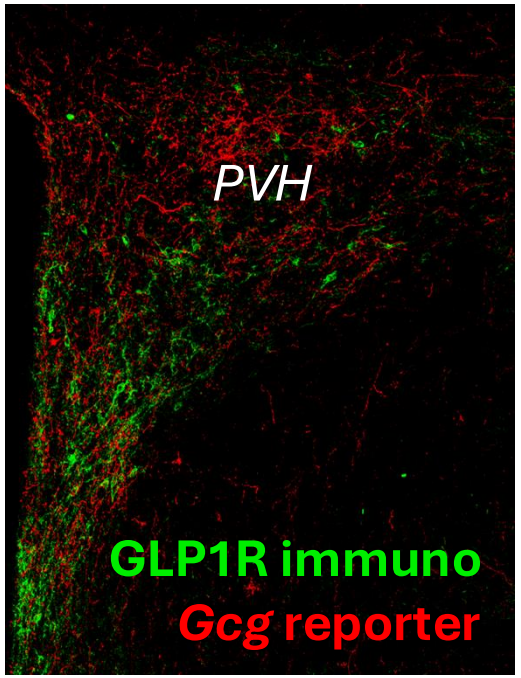
Peri-ventricular and peri-CVO regions

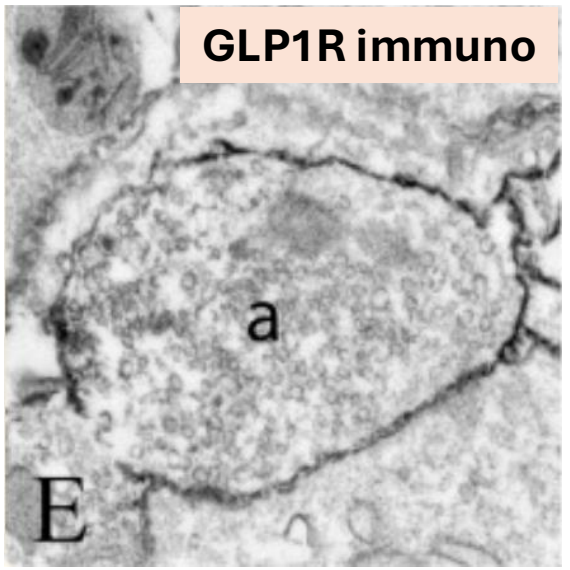
- Medial hypothalamic nuclei, NST

Ability to detect binding of FL-tagged GLP1RAgs may underestimate drug access to CNS targets

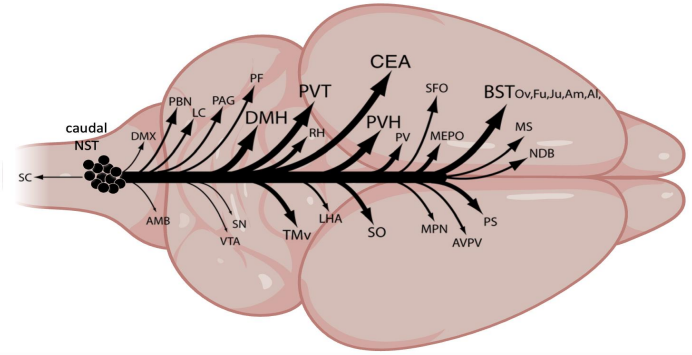
- GLP1RAg binding promotes receptor internalization; *competition with endogenous GLP1 in non-fasted state?*
- Central GLP1R's are trafficked and inserted into axon terminal membranes; *difficult to visualize binding?*







Farkas et al. (2022) Brain Struct. Funct.

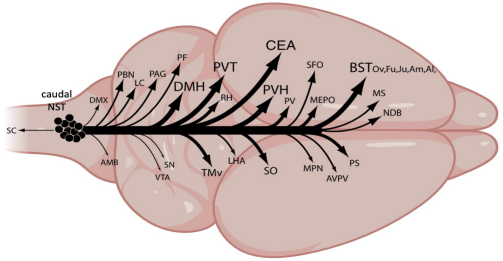


Take-Aways

1. The endogenous central GLP1 system contributes to metabolic state-dependent modulation of motivated behavior.
2. Hindbrain GLP1 neurons are neither directly nor indirectly engaged by systemically administered GLP1Rag's.
3. Systemic GLP1Rags may access only a subset of central GLP1R's, including those in CVO's and adjacent brain regions.
   - *Current fluorescent imaging techniques may underestimate brain penetrance*
4. GLP1R protein is more prevalent in axon terminals vs. neuronal cell bodies
   - *Endogenous GLP1 and GLP1Rag's may bind GLP1R in regions beyond those in which Glp1r mRNA is expressed.*

Research Gaps and Opportunities

1. Perinatal development of GLP1/GLP1R system
   - *Accounting for individual differences in responsiveness to GLP1RAg's?*
2. Sex differences in endogenous GLP1/GLP1R system
   - *Why are systemic GLP1RAg's more effective for weight loss in women?*
3. Does chronic exposure to GLP1RAg's impact central GLP1R?
   - *If so, where, and is the effect reversible?*
   - *Is the potential impact on GLP1R more robust or long-lasting after adolescent-onset GLP1Rag treatment?*



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