



The access of GLP-1 receptor agonists to the brain

Current understanding

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Presenter disclosure

- Anna Secher reports the following:
 - Employee of, and shareholder in, Novo Nordisk A/S

The story of GLP-1 as a physiologically relevant satiety signal started in 1996

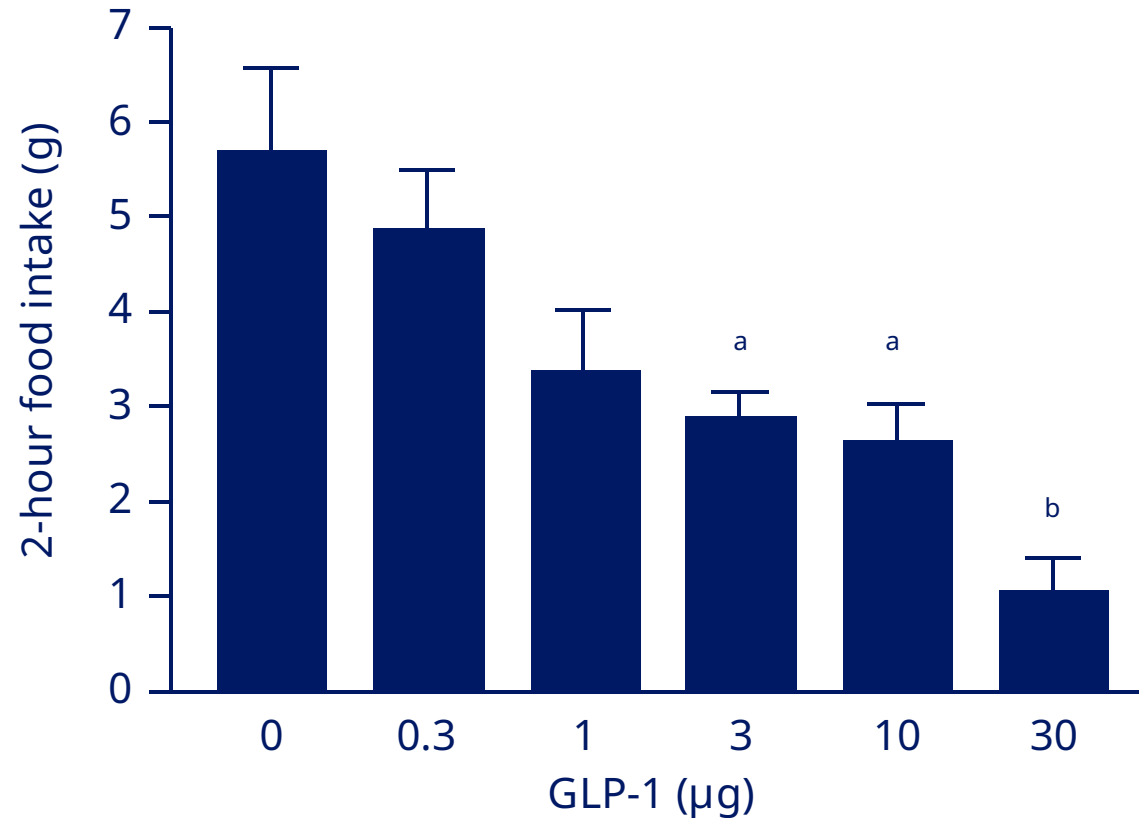
A role for glucagon-like peptide-1 in the central regulation of feeding

M. D. Turton, D. O'Shea, I. Gunn, S. A. Beak, C. M. B. Edwards, K. Meeran, S. J. Choi, G. M. Taylor, M. M. Heath, P. D. Lambert, J. P. H. Wilding, D. M. Smith, M. A. Ghatel, J. Herbert* & S. R. Bloom†

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* Department of Anatomy, University of Cambridge, Downing Street, Cambridge CB2 3DY, UK

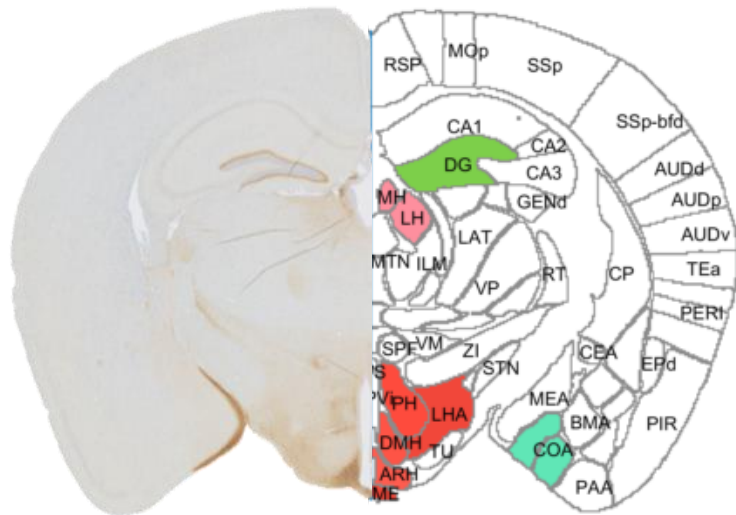
NATURE · VOL 379 · 4 JANUARY 1996

Reduction of food intake in fasting rats



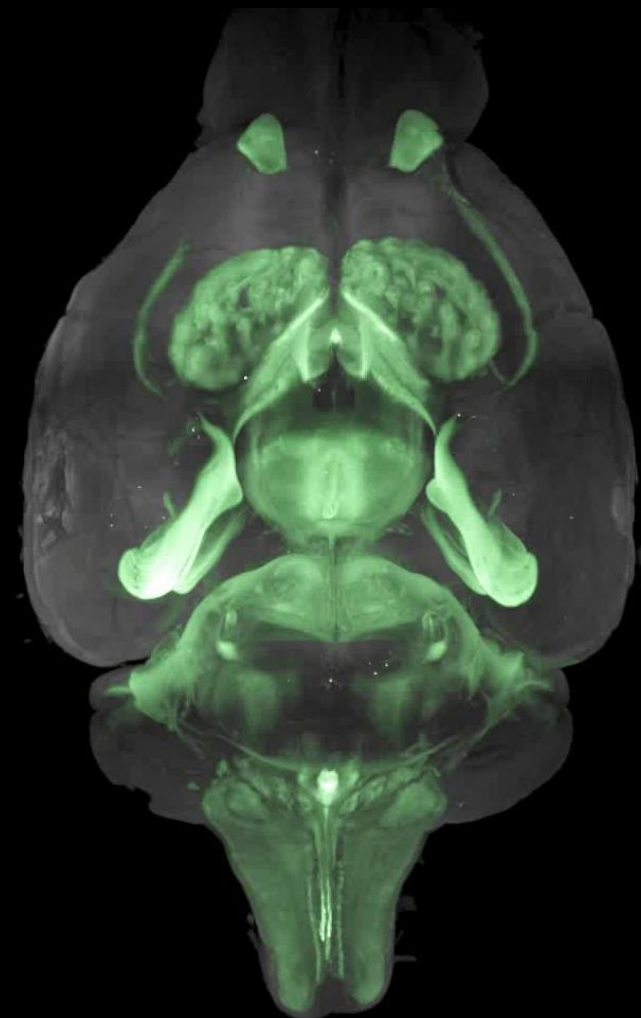
GLP-1 versus control; ^a $p < 0.05$; ^b $p < 0.01$

Broad GLP-1R expression in the brain in preclinical models



GLP-1R identified in 50+ regions

High translation to other species

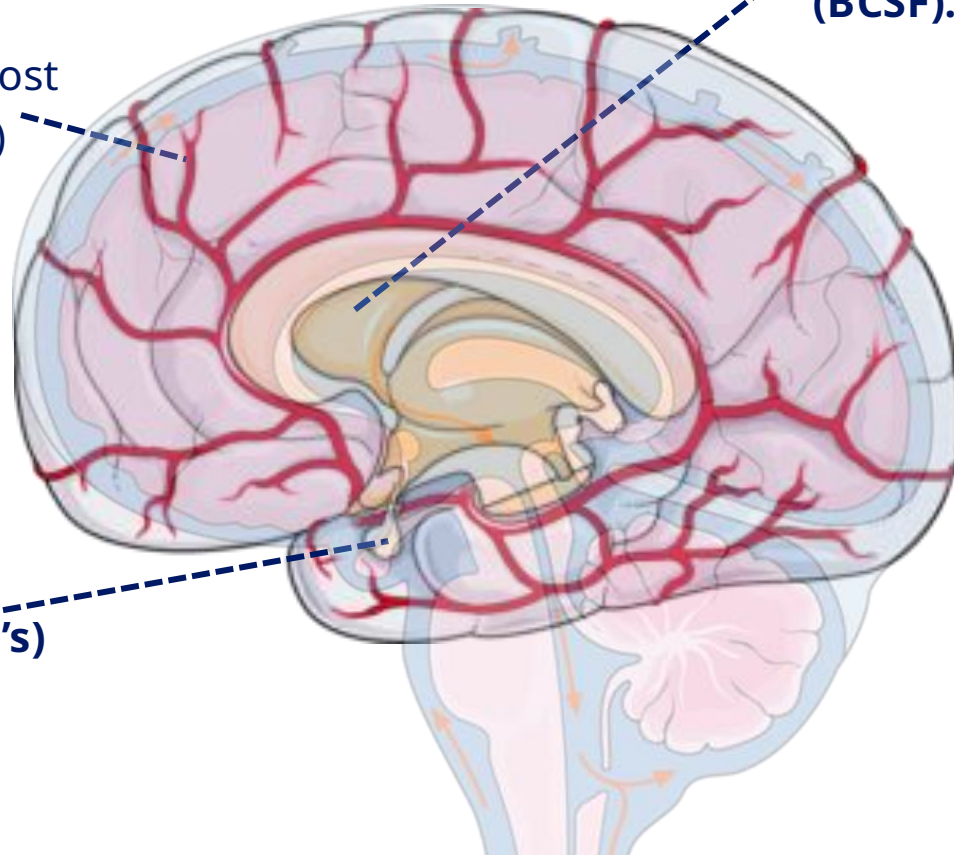


Brain access is restricted

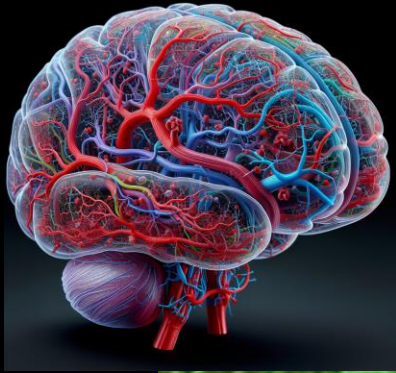
The brain is highly vascularized, but vessel walls form the **Blood-Brain-Barrier (BBB)**. Molecules that pass the BBB can access most parts of the brain (parenchyma) directly.

The **pituitary** and a few other regions of the brain (**circumventricular organs, CVO's**) have fenestrated capillaries and provide direct access from the circulation.

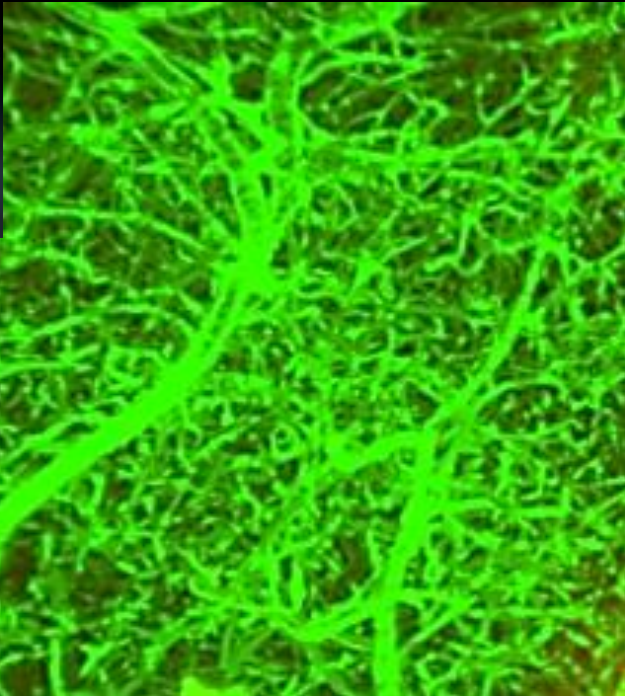
Cerebro-Spinal Fluid (CSF) is secreted into the ventricular space from Choroid Plexus (CP). The CP contains a **Blood-CSF Barrier (BCSF)**.



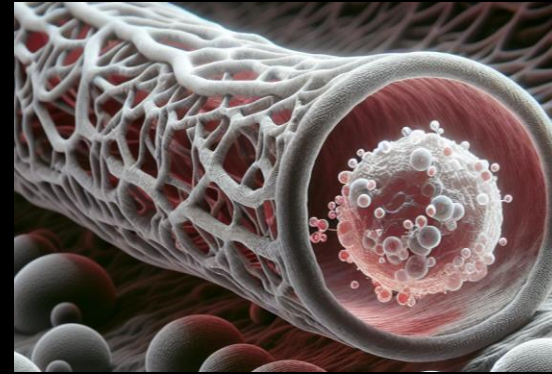
How can we measure access into the brain?



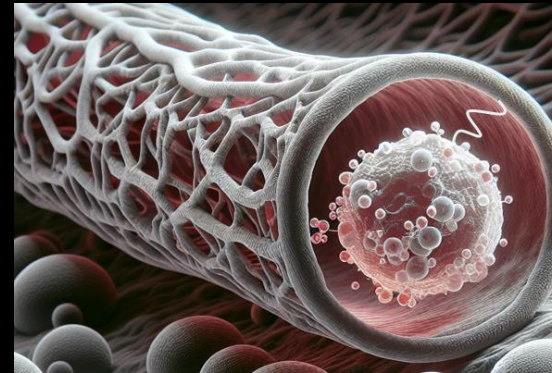
**The brain is highly
vascularized**



Green **vessels** in the brain stained by lectin



Non lipidized
molecule



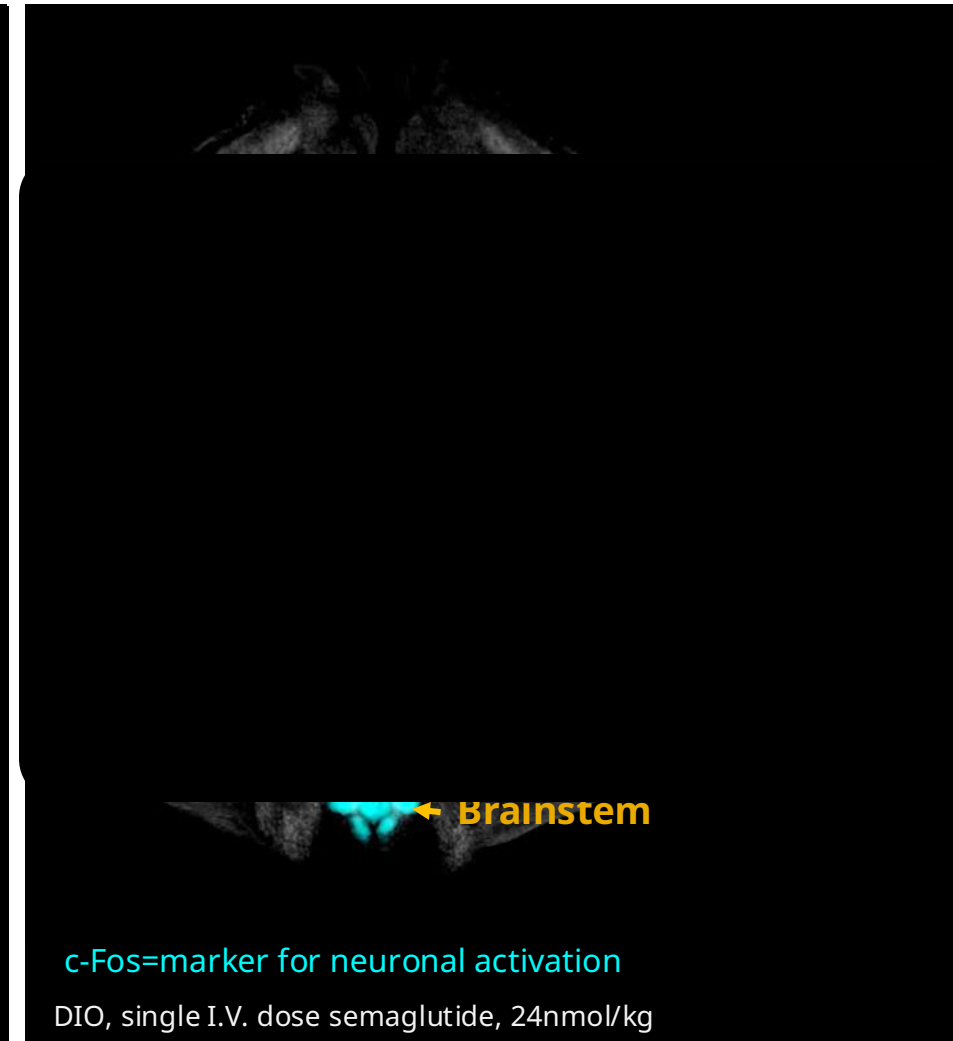
Lipidized molecule
sticks to the
membrane

GLP-1R agonists target and activate both overlapping and non-overlapping brain structures in rodents

Several GLP-1Rs
in the brain

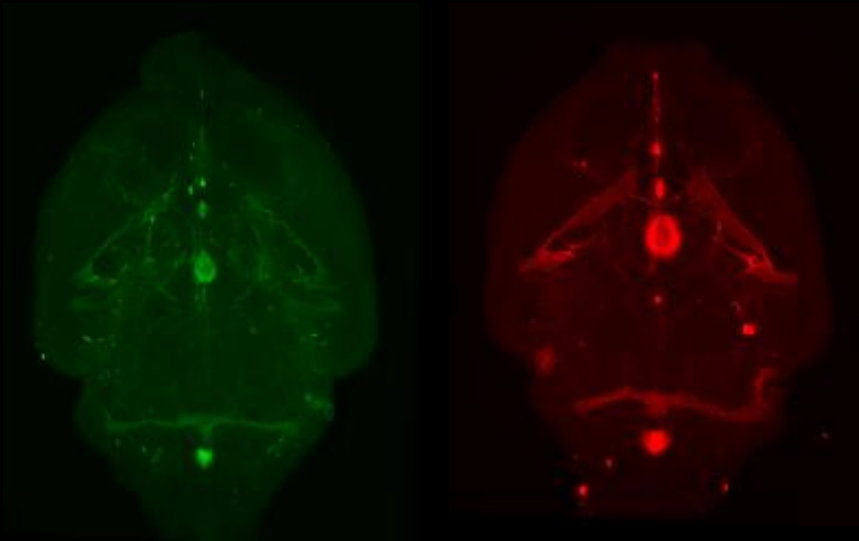
GLP-1R targeting in
septum, hypothalamus,
and hindbrain

Secondary activation in
regions associated with
control of food intake
and reward



GLP-1 seems to target the same brain areas as the GLP-1 analogues

10 min



Liraglutide⁷⁵⁰

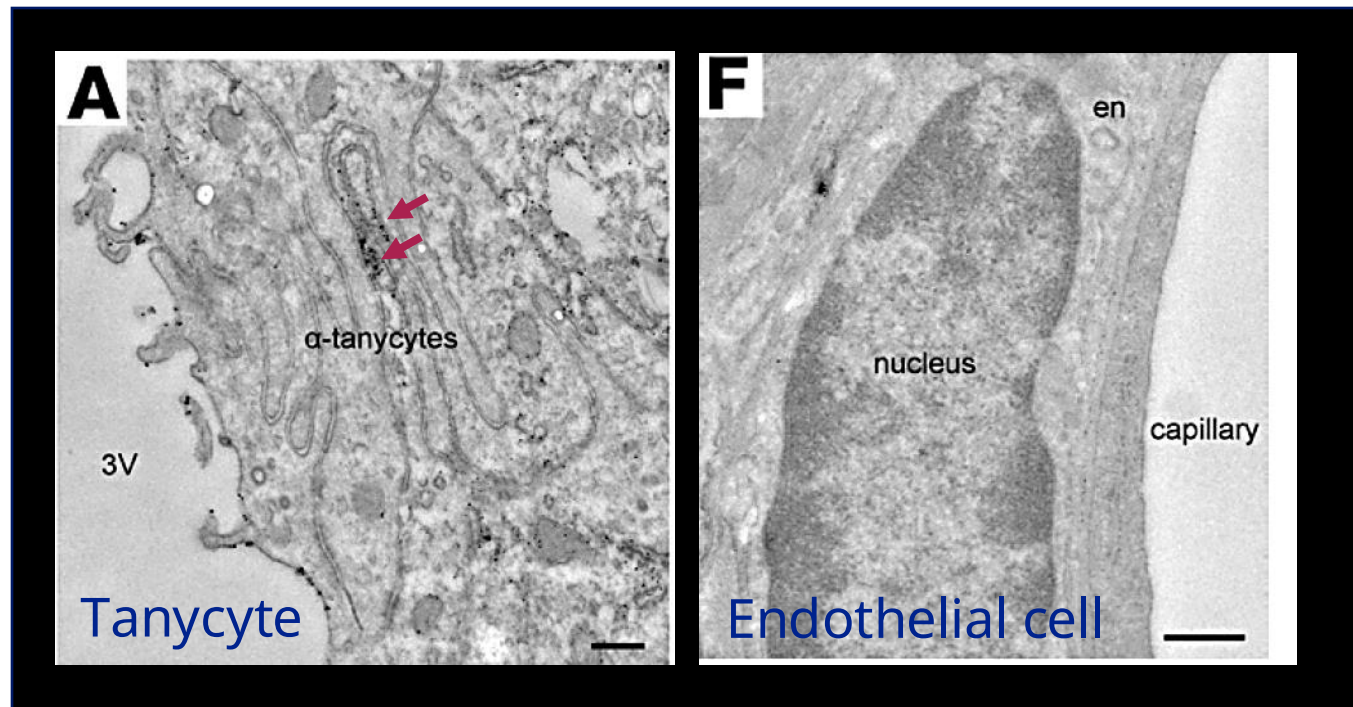
GLP-1⁷⁵⁰



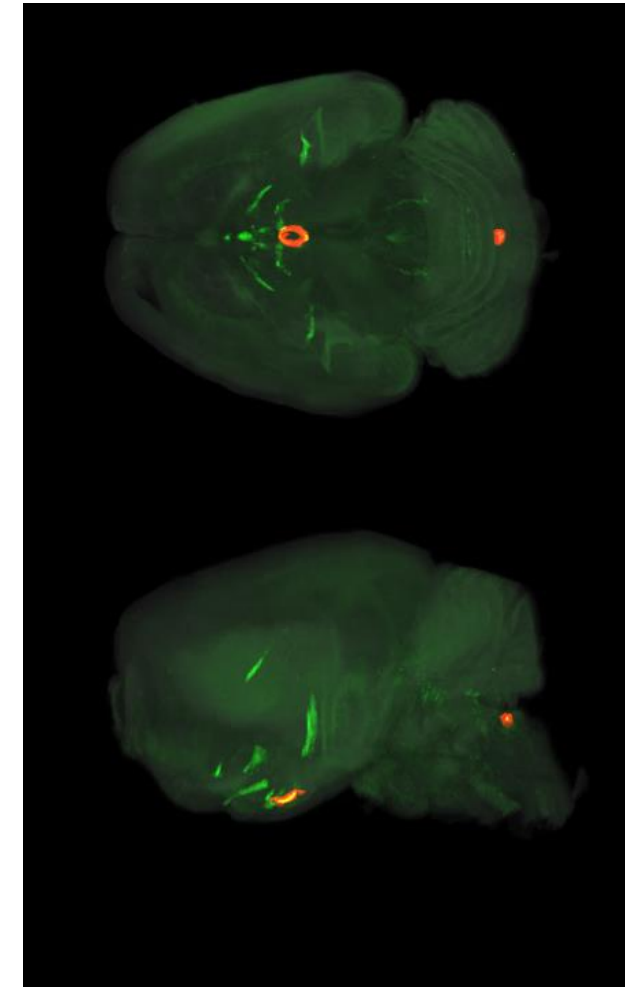
Liraglutide⁷⁵⁰

GLP-1⁷⁵⁰

How do GLP-1R agonists gain access into the brain?



Tanycytes are specialized cells lining the brain ventricular systems



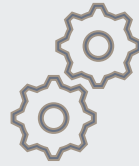
Csaba Fekete

Institute of Experimental Medicine
Hungarian Academy of Sciences

Key takeaways from brain access of GLP-1 R binding peptides



Both GLP-1 and acylated GLP-1 analogues have access to discrete brain regions



The access does not seem to be through the BBB but rather through a specialised uptake around the CVOs



The mechanism behind this transport remains to be explained

THANK YOU FOR YOUR ATTENTION

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