

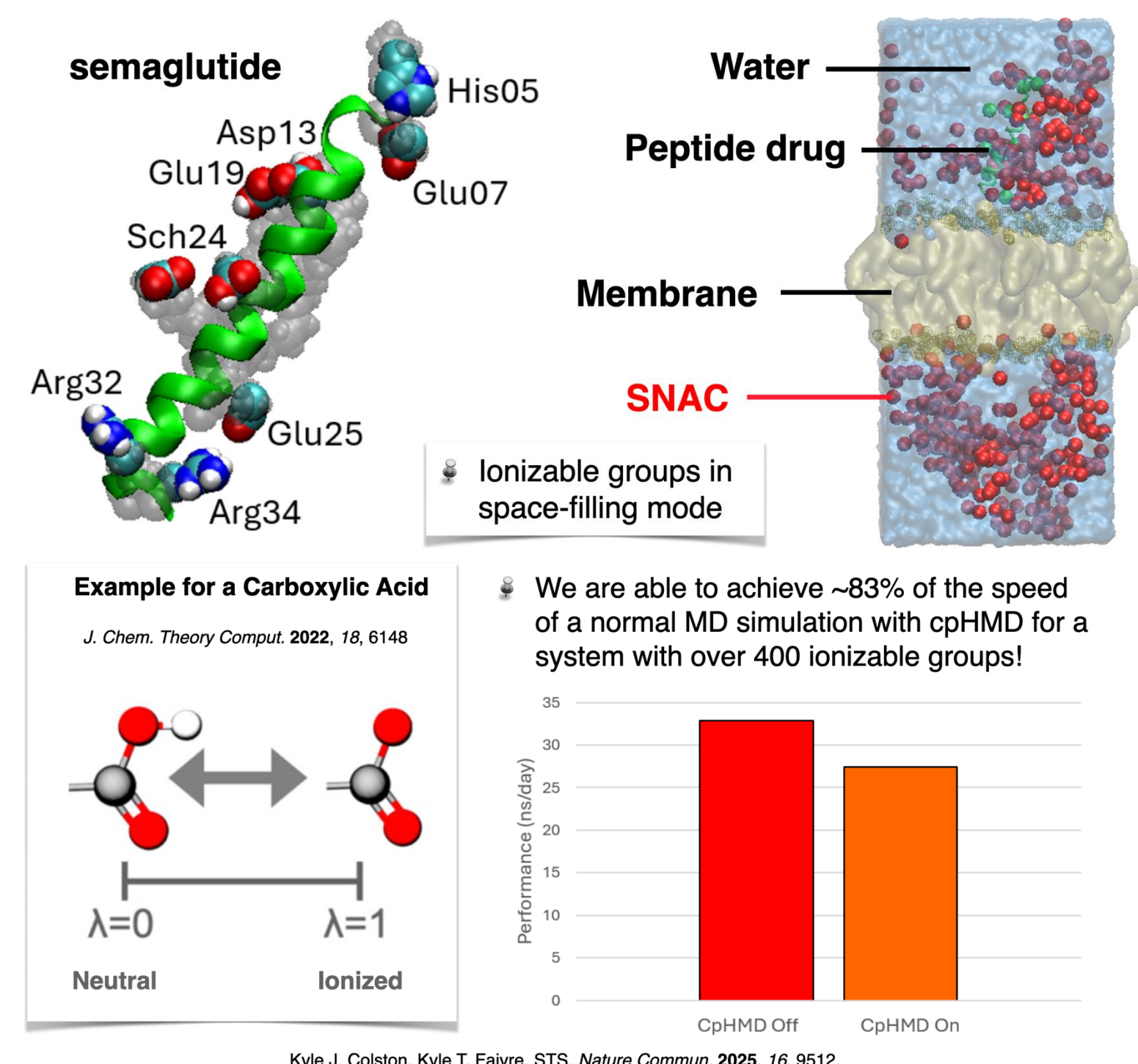
Overcoming Barriers To Oral Peptide Delivery: A Mechanistic Advance With Relevance To AD/ADRD Therapeutics

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ABSTRACT

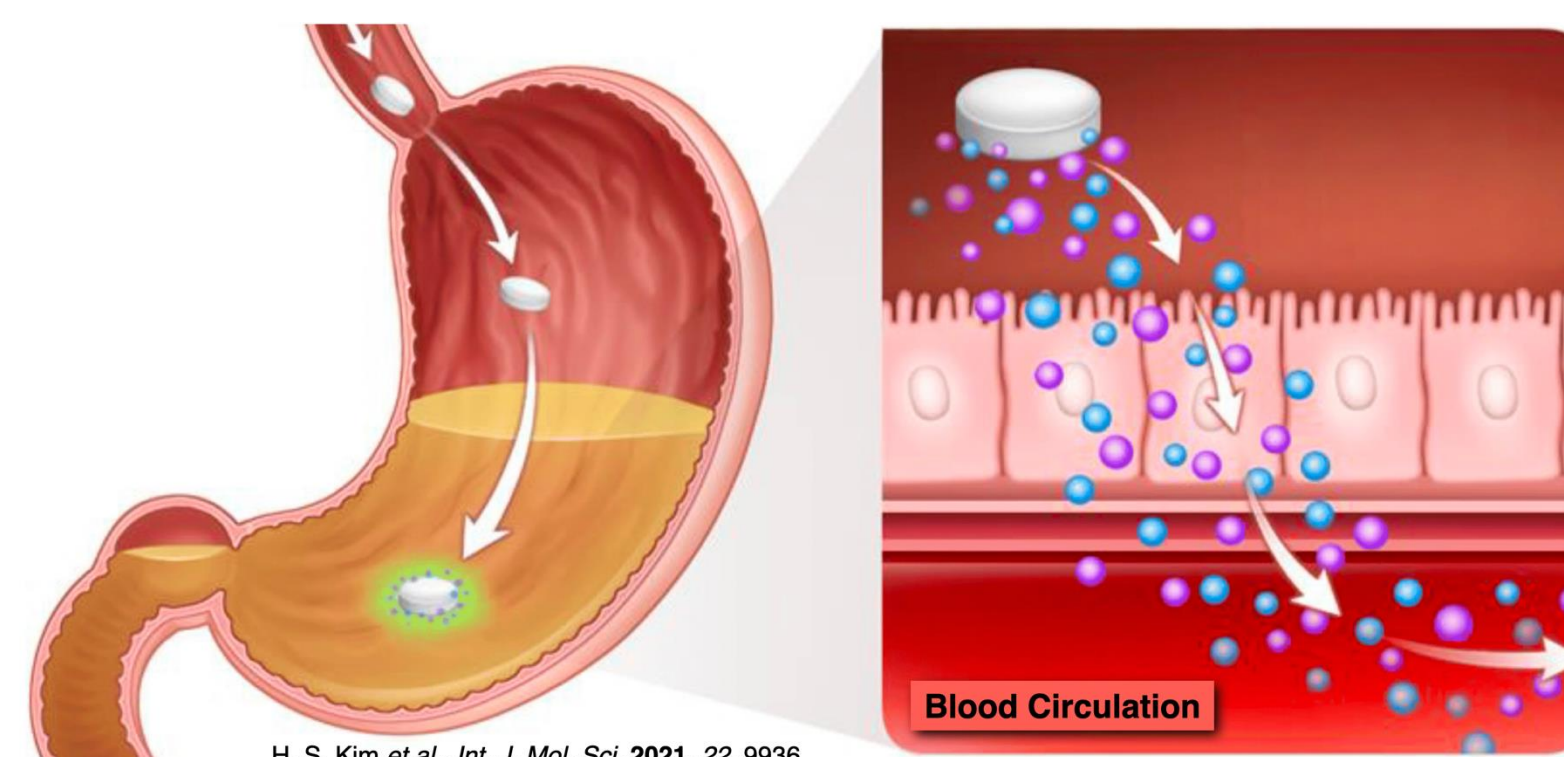
Peptide therapeutics are promising candidates for Alzheimer's disease and related dementias (AD/ADRD) due to their high specificity and ability to target amyloid processing, tau pathology, neuroinflammation, and synaptic dysfunction. However, most peptide drugs require chronic injections because long, polar peptides exhibit poor oral bioavailability. For AD/ADRD patients, who often experience cognitive impairment and heightened caregiver dependence, injectable therapies impose a substantial practical and psychological burden. Enabling oral peptide delivery is therefore a critical unmet need. To advance the general understanding and design rules for oral peptide delivery, we combined scalable all-atom constant-pH molecular dynamics (CpHMD) simulations with experimental validation to elucidate the molecular mechanism of permeation-enhancer-assisted oral peptide absorption. Uniquely, our CpHMD simulations captured environment-dependent protonation, aggregation, and membrane interactions across hundreds of ionizable groups, corroborated by NMR spectroscopy, dynamic light scattering, and membrane-mimetic experiments. Through this approach, we identified a previously unrecognized transcellular permeation mechanism in which the permeation enhancer salcaprozate sodium (SNAC) dynamically aggregates to form fluid, SNAC-filled membrane defects that preserve bilayer integrity while enabling peptide incorporation. This work establishes a mechanistically validated framework for the oral delivery of long, polar peptides, with direct relevance to AD/ADRD therapeutics. By addressing a key delivery barrier and reducing reliance on injectable dosing, our findings support the future development of orally administered peptide treatments that could improve adherence, reduce caregiver burden, and enhance quality of life for individuals living with AD/ADRD.

Ionizable Groups Treated with CpHMD



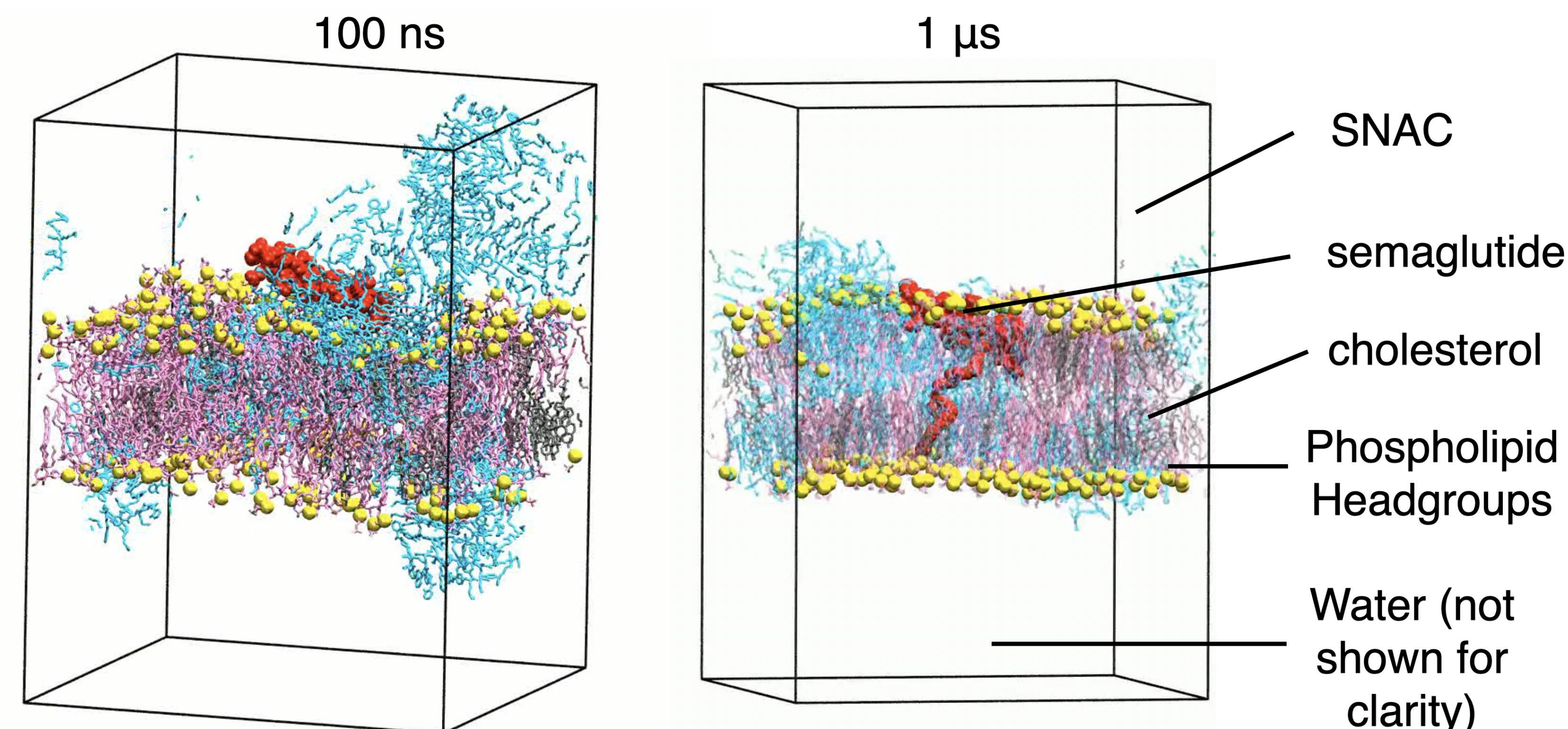
The constant-pH molecular dynamics (CpHMD) model we are using in GROMACS is nearly as fast as regular MD. However, it enables accurate treatment of the environment-dependent pKa values on the peptide drugs and the permeation enhancer (SNAC), greatly enhancing the accuracy of our models.

Current State of the Art in Oral Peptide Delivery: SNAC-Enhanced Absorption



- SNAC (sodium N-[8-(2-hydroxybenzoyl)amino]caprylate) is co-formulated with semaglutide to locally raise gastric pH and protect the peptide from enzymatic degradation.
- SNAC transiently increases epithelial membrane permeability, allowing the peptide to cross the gastric lining and enter systemic circulation.
- This absorption-enhancer strategy is the current state of the art for oral peptide delivery, yet it still yields only <1% oral bioavailability, underscoring the need for improved approaches.

Summary of Results Showing How the Peptides Interact with the Membrane



Spontaneous insertion of semaglutide into lipid bilayer membrane models (Figure reproduced with permission from: *Nature Comm.* 2025, 16, 9512);

Proposed Oral Mechanism of Semaglutide Absorption

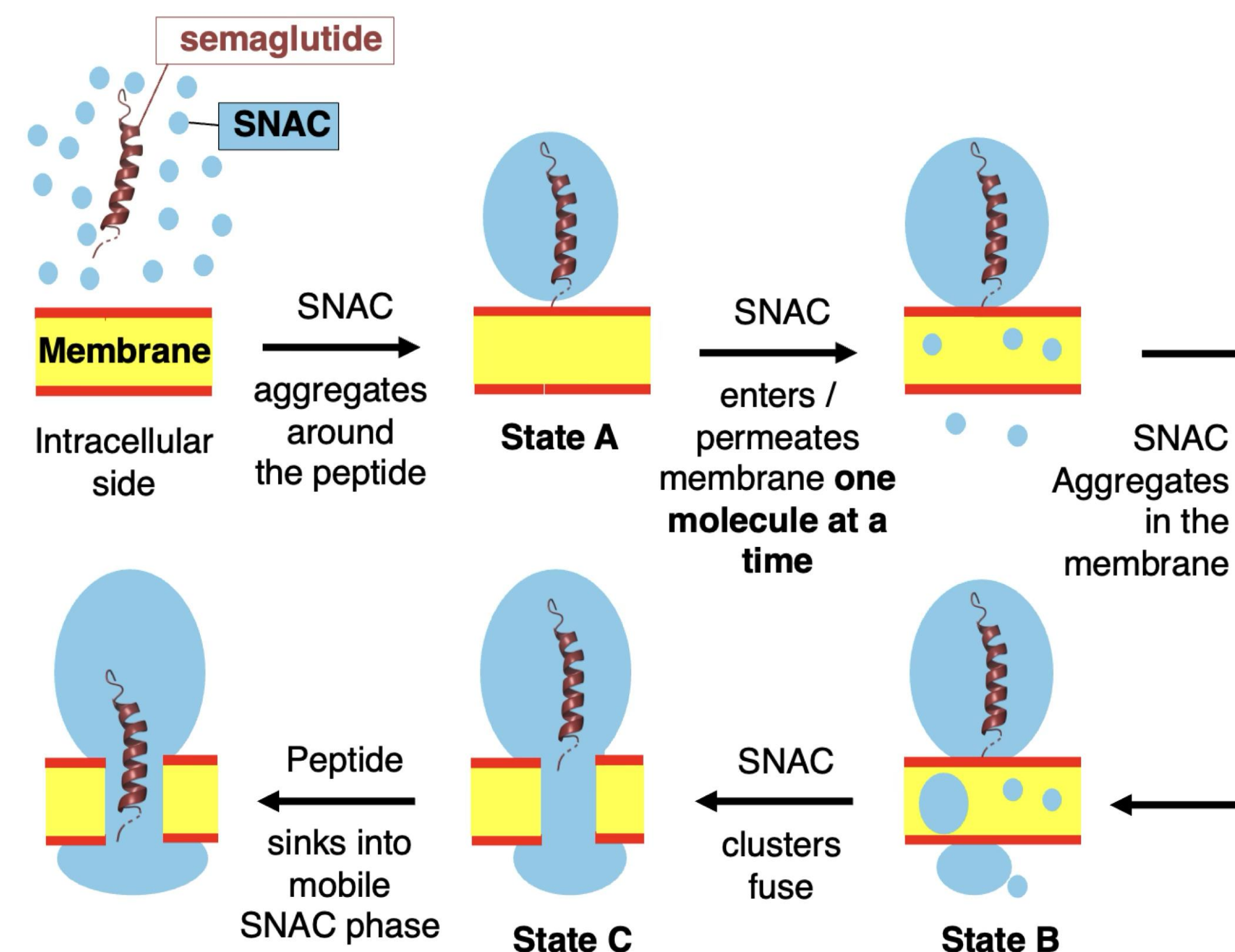


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GLP-1 Agonists Remain Promising Targets for AD/ADRD

Key premise: Isolated negative trials reflect the difficulty of trial design, not a refutation of the underlying biology. Mechanistic, epidemiologic, and biomarker evidence continue to converge.

- Mechanistic rationale.** GLP-1R signaling reduces neuroinflammation, restores neuronal insulin signaling, limits oxidative stress, and lowers amyloid/tau burden in preclinical AD models.
- Epidemiologic support.** Large real-world T2D cohorts show lower dementia incidence among GLP-1 RA users vs. other glucose-lowering agents.
- Null trials are interpretable.** Recent negative results (e.g., semaglutide, EVOKE) likely reflect limited CNS penetration, late-stage populations, short duration, or insensitive endpoints — not a failed hypothesis.
- Untested, better-designed strategies.** Brain-penetrant analogs, dual/triple incretin agonists (GLP-1/GIP/glucagon), earlier intervention, and biomarker-enriched cohorts remain largely unexplored.

- The GLP-1 pathway is a scientifically grounded, multi-mechanism target; disappointing injectable trials likely reflect insufficient or inconsistent brain exposure, not a failed hypothesis.
- Improved delivery, especially bioavailable oral formulations for sustained dosing, is the rational path to a fair test in AD/ADRD.