



Florin Despa Laboratory

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UNMET NEED

Clinical responses to amyloid- and tau-directed therapies in AD remain highly variable, particularly among individuals with metabolic dysfunction. Brain energy failure and peripheral metabolic stress (insulin resistance, obesity, prediabetes and type-2 diabetes) are tightly correlated, substantially increase AD risk and accelerate cognitive decline, yet metabolic status is rarely incorporated into therapeutic strategies or trial design. This gap represents both a biological blind spot and a missed opportunity for patient stratification and combination therapy.

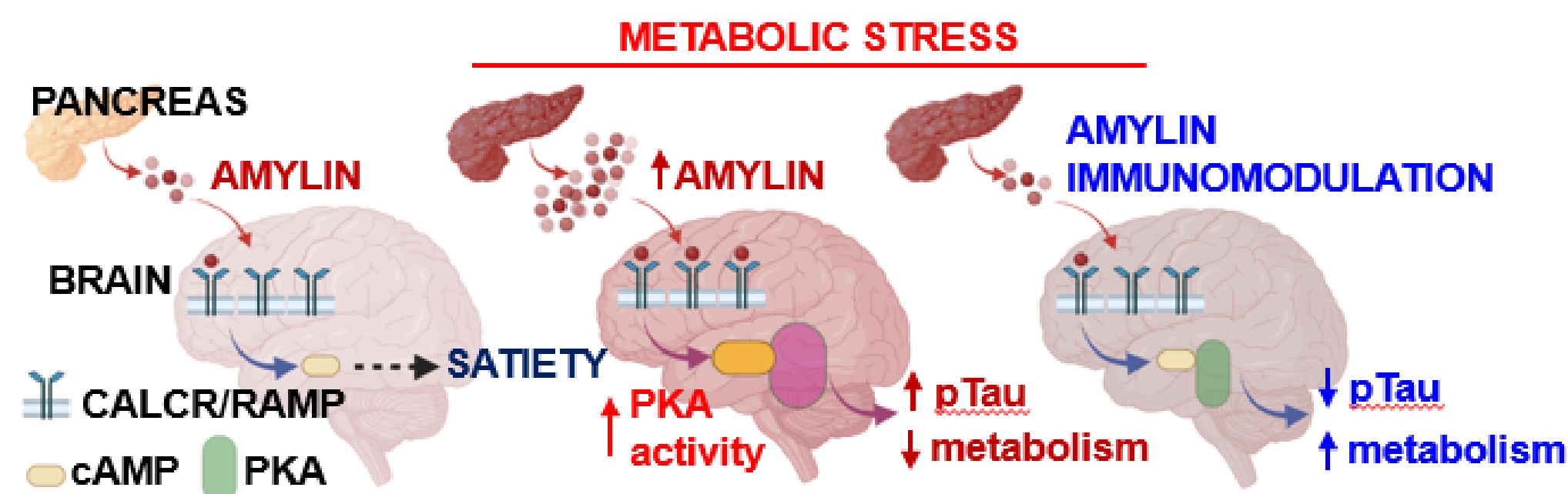
INNOVATION & DIFFERENTIATION

Circulating amylin, a pancreatic hormone dysregulated early in insulin resistance, is a **modifiable upstream driver of tau pathology and neuronal metabolic dysfunction**. Unlike CNS-penetrant agents, we target a **peripheral factor that engages CNS signaling indirectly**, offering a differentiated safety and regulatory profile.

Key differentiators:

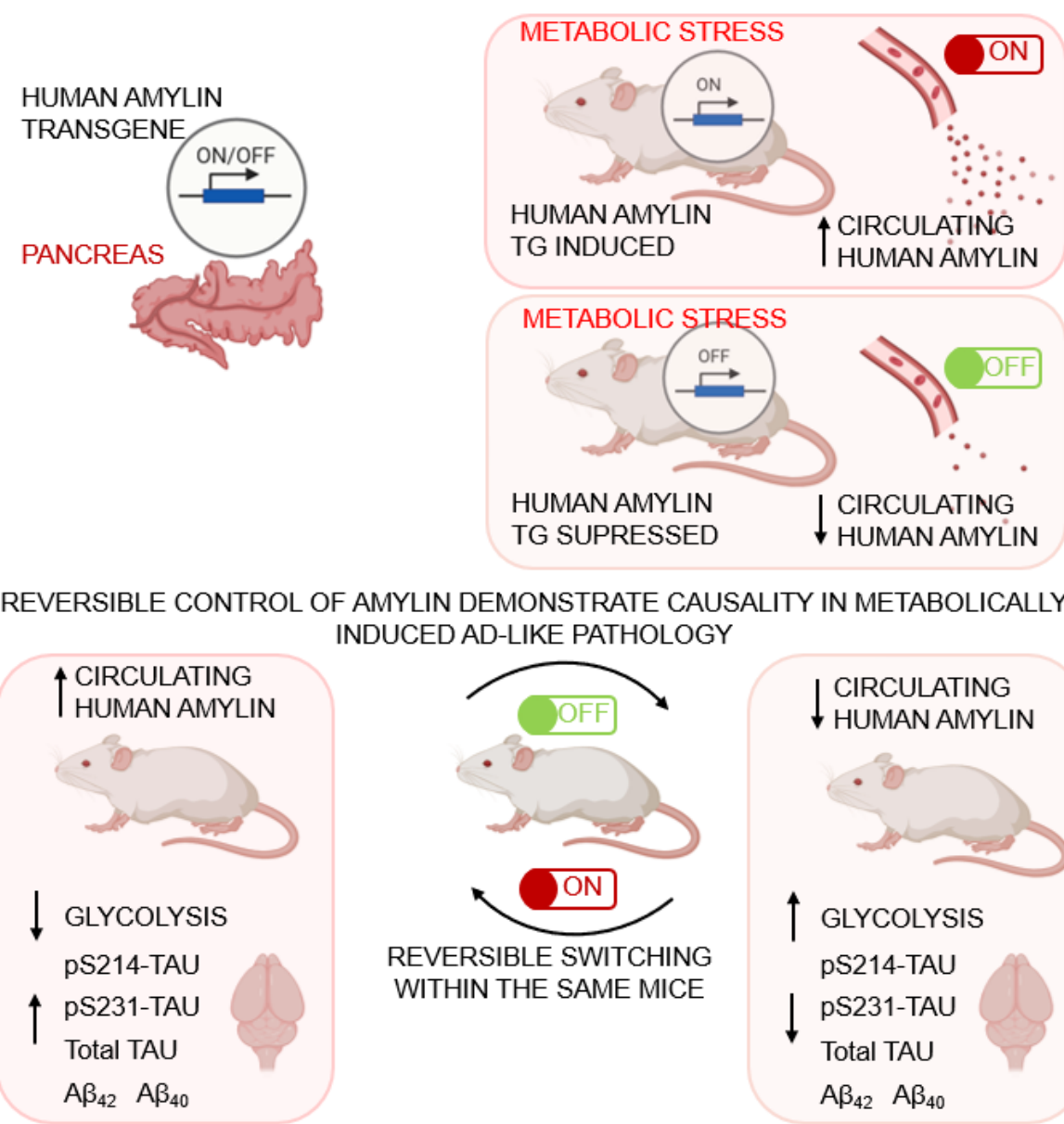
- Targets an **upstream metabolic trigger** rather than downstream tau aggregates
- Operates through **cAMP-PKA and convergent tau kinase pathways**, addressing redundancy in tau phosphorylation
- Enables **precision medicine** by identifying a metabolically defined patient subset
- Compatible with, and potentially synergistic with, existing anti-tau and anti-amyloid therapies

BIOLOGICAL RATIONALE



EXPERIMENTAL DESIGN

Genetic switching of amylin expression (ON/OFF) alters brain levels of pS214-tau, pT231-tau, total tau, and A β species measured by immunoassays.



REFERENCES

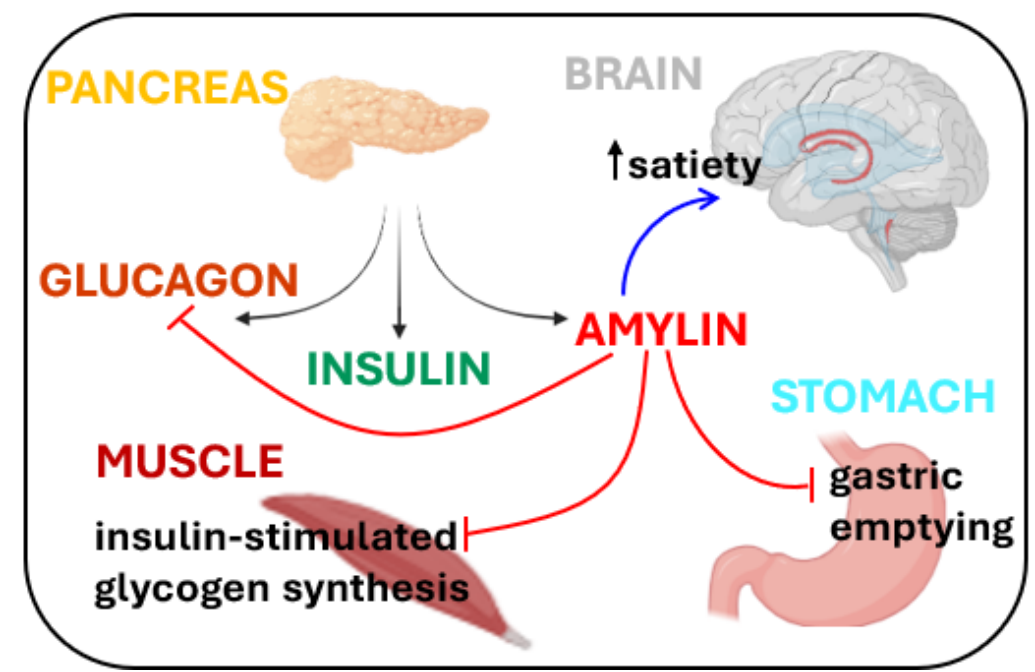
PMID: 41858884; PMID: 33521236;
PMID: 28696548; PMID: 36596993;
PMID: 37030503; PMID: 24077098;
PMID: 23794448

ACKNOWLEDGEMENTS

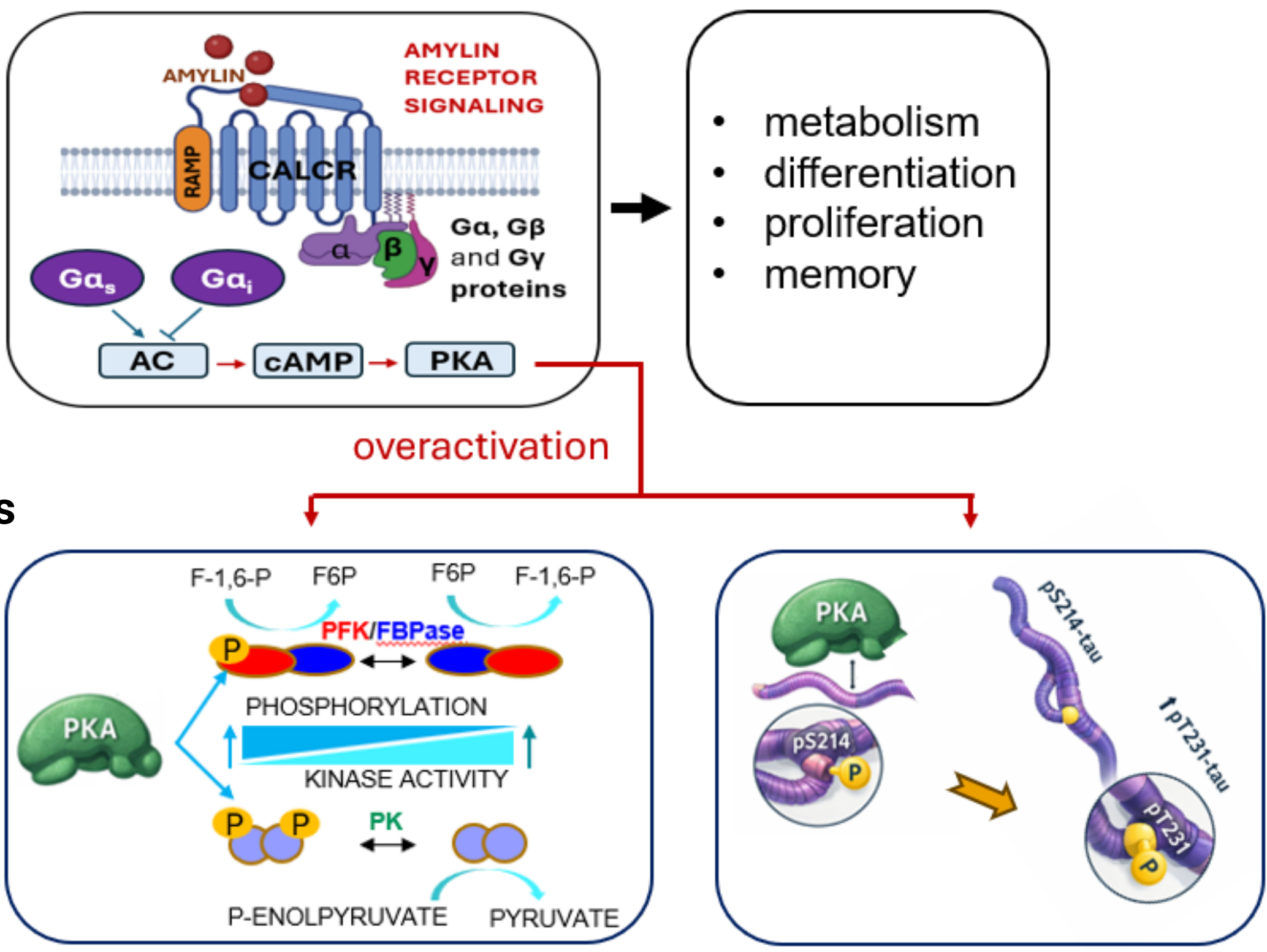
National Institutes of Health
NS116058, AG057290, & AG053999
and Alzheimer's Association
ABA-25-1376326

Modulating Brain Entry of Circulating Amylin Controls cAMP-PKA Signaling to Balance Glycolysis, Tau-A β Coupling and ATF4-Dependent Proteostasis

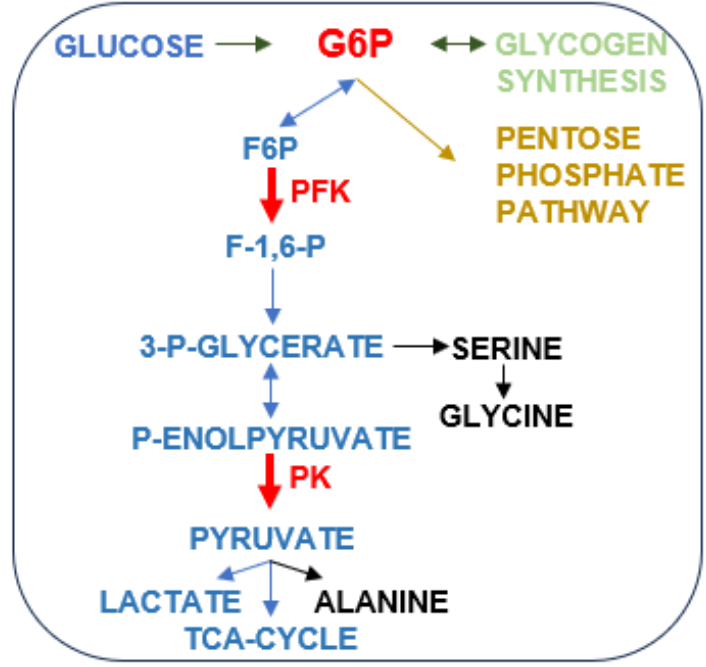
Amylin Regulation & Functions



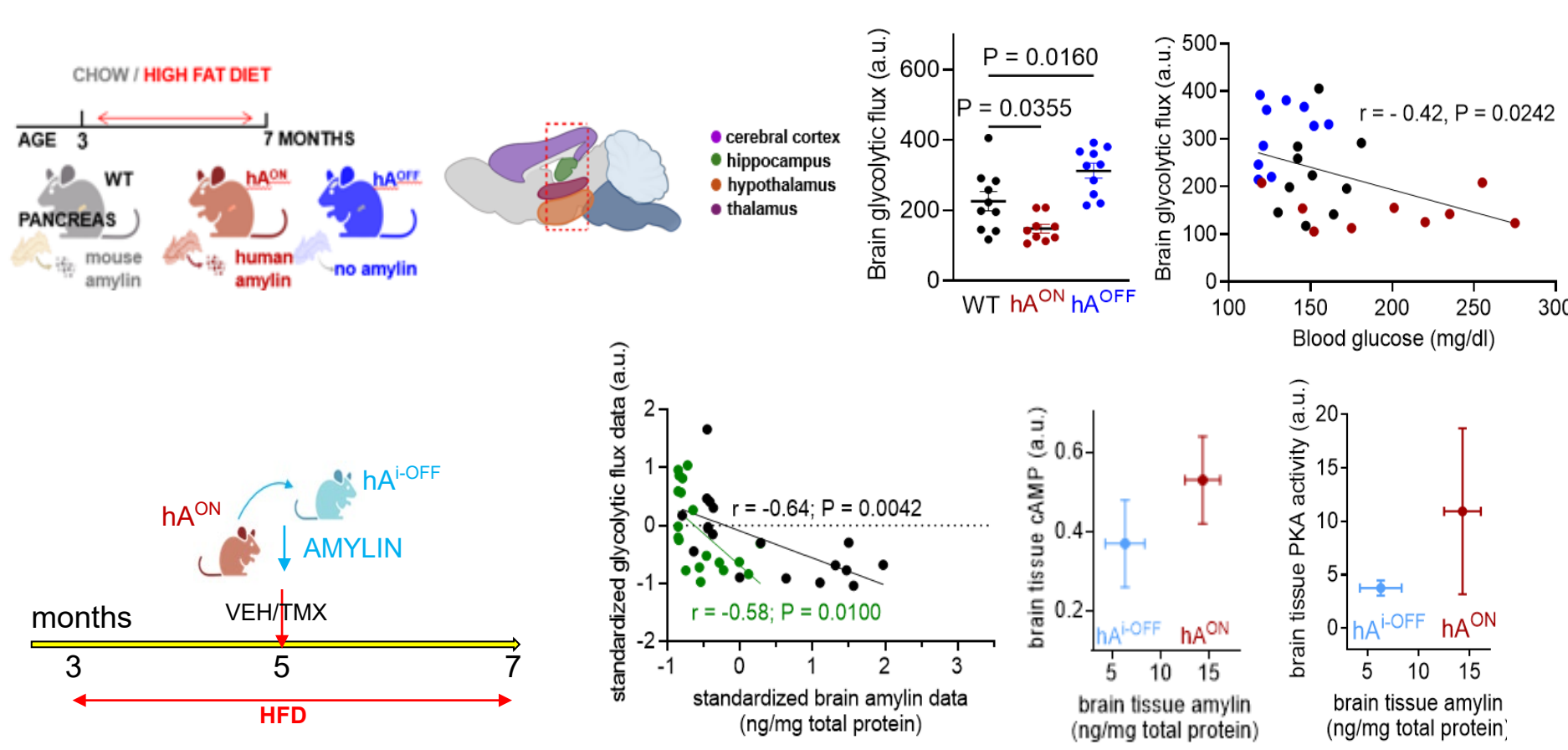
Amylin Dysregulation, Metabolic Failure & Tau Pathology



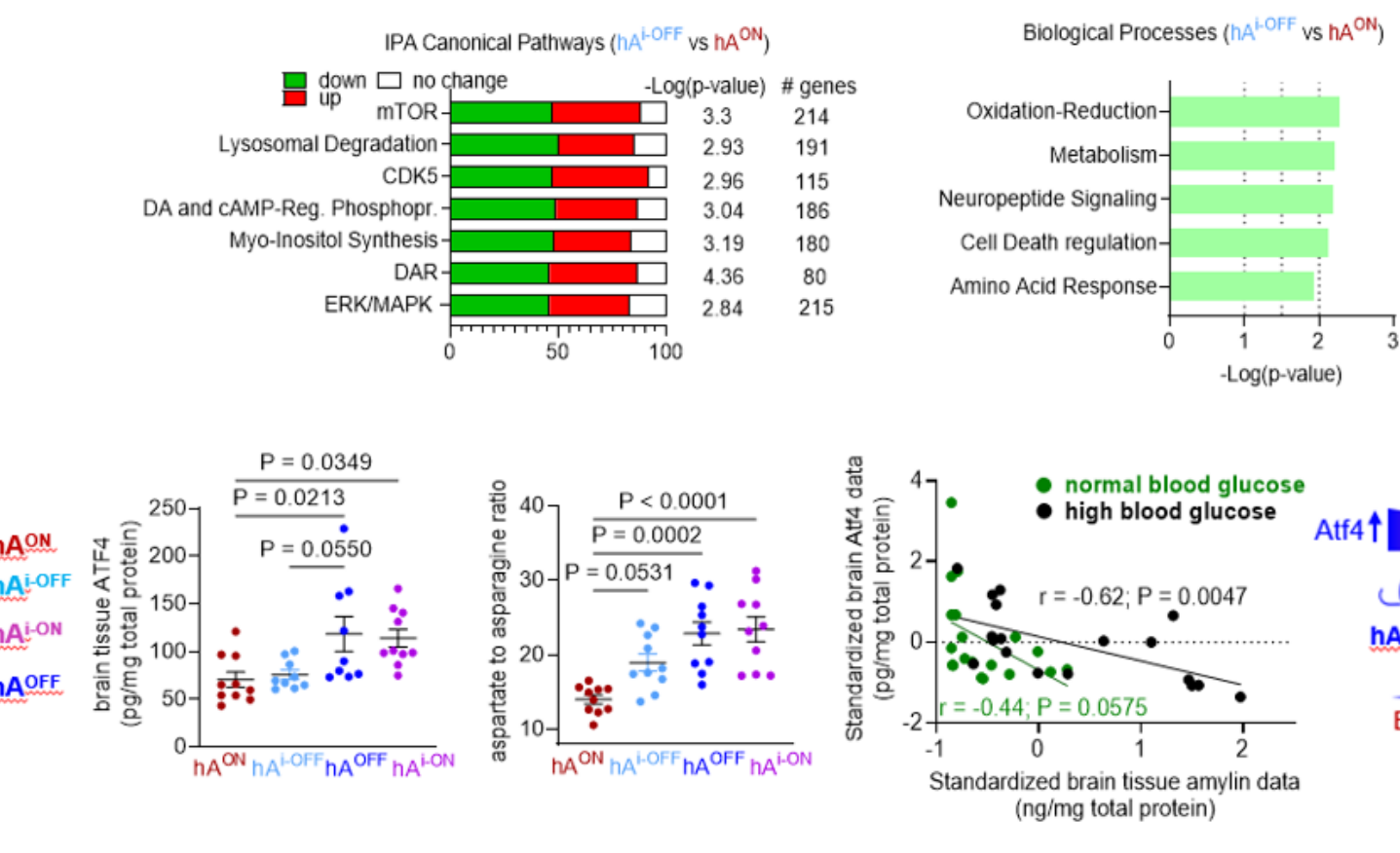
Glycolysis – metabolic pathways



Peripheral Amylin Modulation Rebalances Brain Glycolysis via cAMP-PKA Signaling

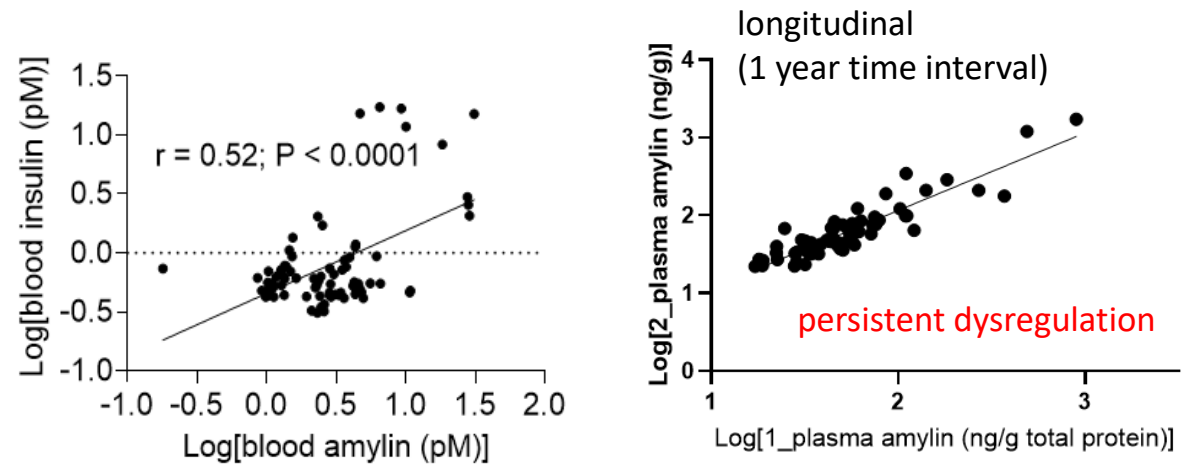


Reducing Excess Amylin Rebalances Atf4-Regulated Proteostasis



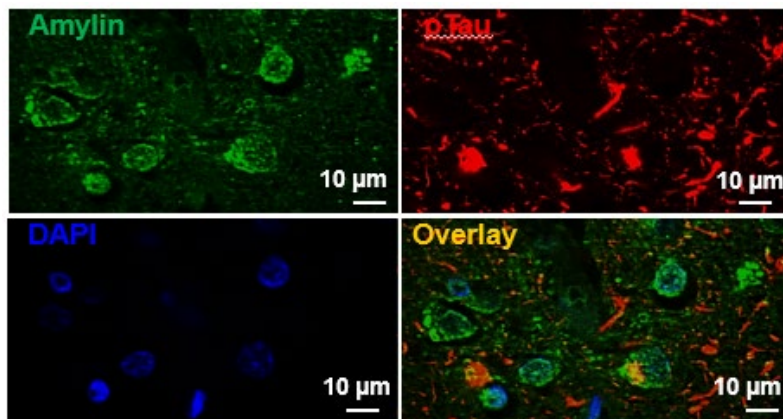
HUMAN DATA SUPPORTING THE PROJECT

Metabolic Stress Drives Amylin Hypersecretion



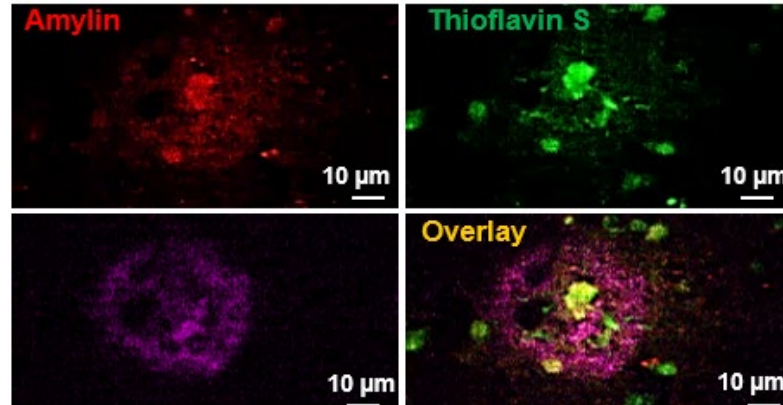
Amylin Accumulates in Human AD Brain

Confocal microscopic images of a section through a human AD brain double-stained with anti-amylin antibody (green) and anti-p-tau antibody (red). Nuclei are stained blue.

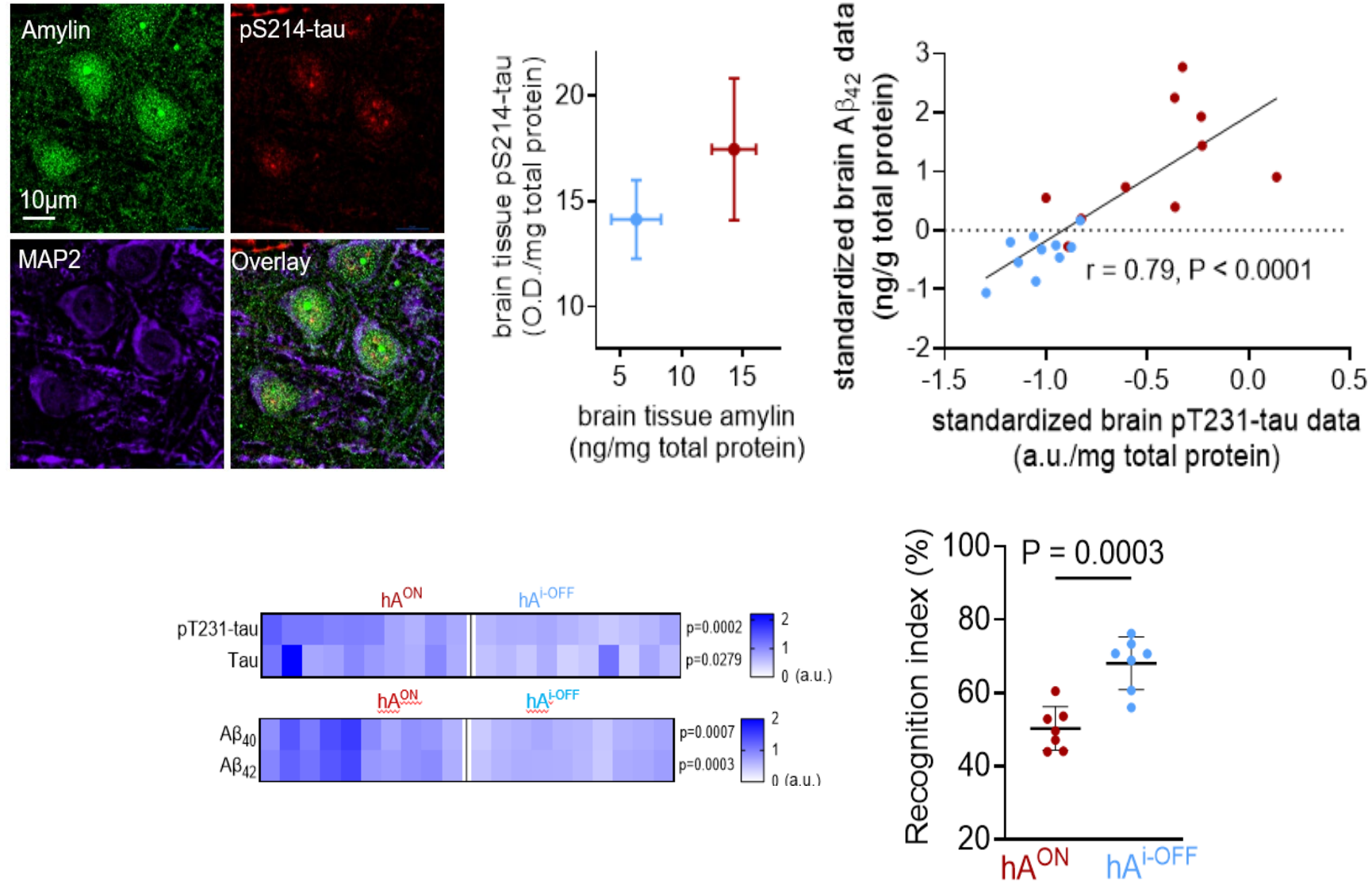


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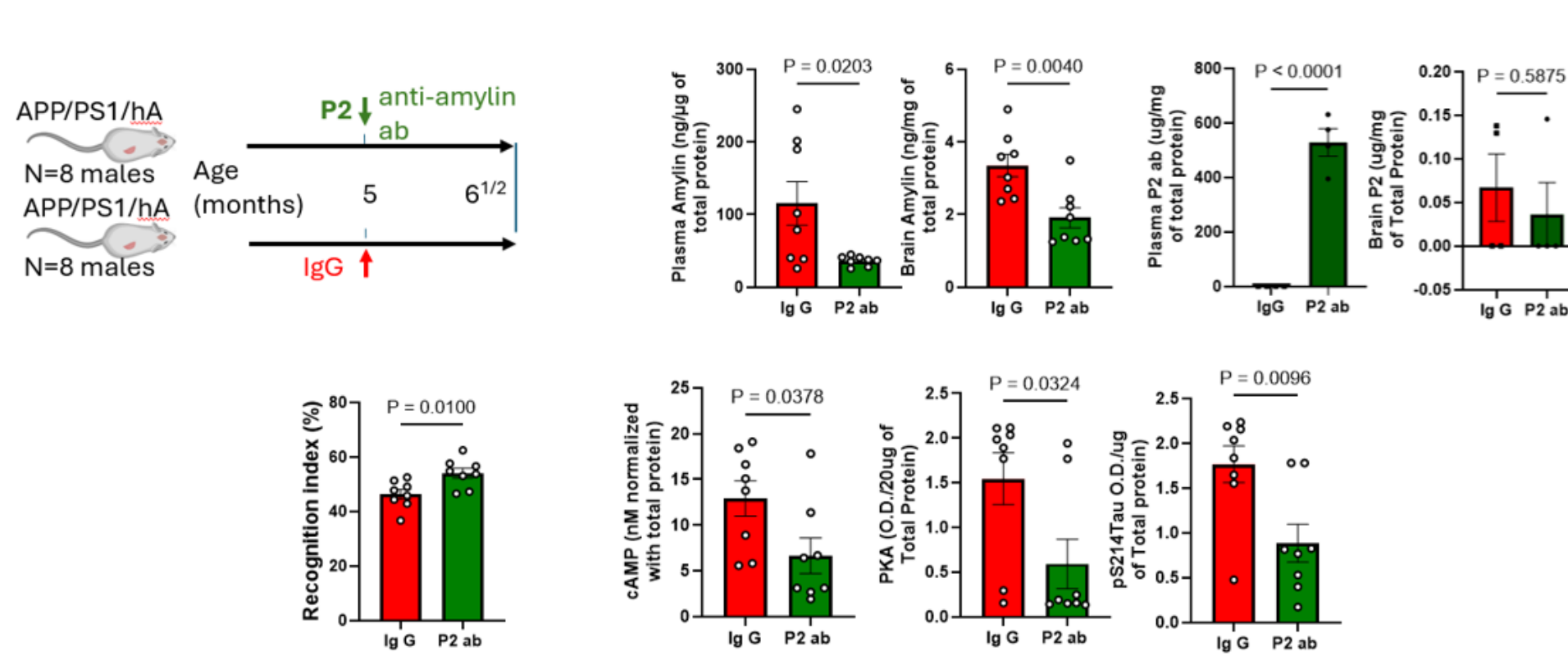
Confocal microscopic images of a section through a human AD brain triple-stained with Thioflavin S (ThioS; green), anti-amylin antibody (red), and anti-A β antibody (magenta)



Reducing Excess Amylin Slows AD Biomarker Dynamics and Improves Memory



Neutralization of Excess Circulating Amylin Interrupts Progression to Neurodegeneration in AD-Model Mice



CONCLUSIONS

- Amylin signaling connects peripheral metabolic stress to brain dysfunction.
- Sustained AmyR activation disrupts cerebral energy metabolism
- Amylin promotes tau pathology through cAMP-PKA-dependent mechanisms.
- Experimental reduction of amylin mitigates AD-like pathological changes.