Dose-Dependent Effects of Acute Intranasal Insulin on Neurodegenerative Markers in the Rat Brain

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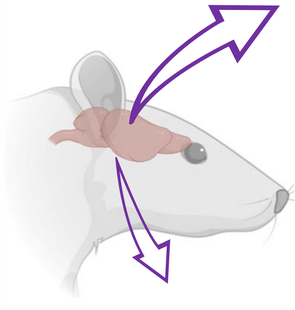
- A single dose triggers immediate but short-lived signaling in the brain, peaking at just 3 minutes.
- Acute dosing did not change levels of key Alzheimer's markers (Aβ1−42 or p-Tau) in any tissue or time point.
- Because single doses are too transient to alter neurodegeneration, long-term or repeated schedules are required for therapeutic impact.

INTRODUCTION

Brain insulin resistance in Alzheimer's disease disrupts neuronal metabolism, insulin signaling, synaptic plasticity, and cognition, contributing to amyloid-β accumulation and tau hyperphosphorylation **(1)**. Intranasal insulin offers a potential therapeutic strategy by bypassing the blood–brain barrier and directly targeting central insulin pathways **(2)**. However, its optimal dosing and molecular effects remain unclear. In this study, we aimed to determine the acute dose- and time-dependent effects of intranasal insulin on brain phosphorylation signaling and on tau and amyloid-β levels as markers of neurodegeneration.

METHODS

Animals (Wistar rats, 4 months old) were used in three independent acute intranasal insulin experiments. Animals received a single bilateral intranasal dose (0.5 IU, 2 IU **(3)**, or 6 IU) of human regular fast-acting insulin. Six untreated animals served as intact controls. Rats were sacrificed at 3, 7.5, 15-, 30-, 60-, or 120-minutes following administration. Levels of phosphorylated tau (p-Tau Ser396) and amyloid-β (Aβ 1–42) were quantified using ELISA in plasma, cerebrospinal fluid (CSF), and selected brain regions: temporal cortex (TC), hippocampus (HPC), and hypothalamus (HPT). Additionally, protein phosphorylation profiling in the TC was performed following the 2 IU dose using a Neuroscience Phospho Antibody Array optimized for Alzheimer's and Parkinson's disease–related signaling pathways. Principal component analysis (PCA) was applied to identify time-dependent phosphorylation patterns.



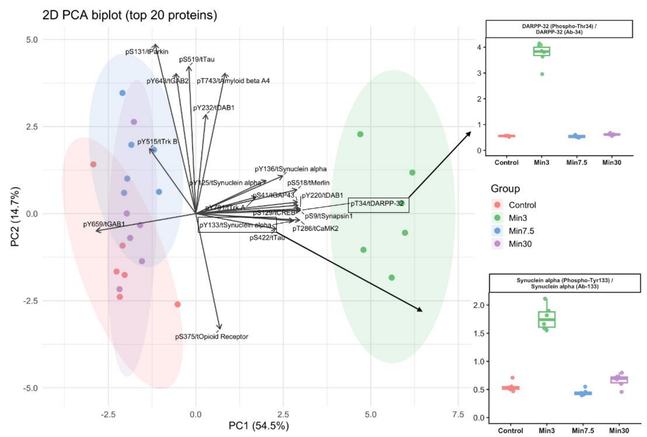
RESULTS

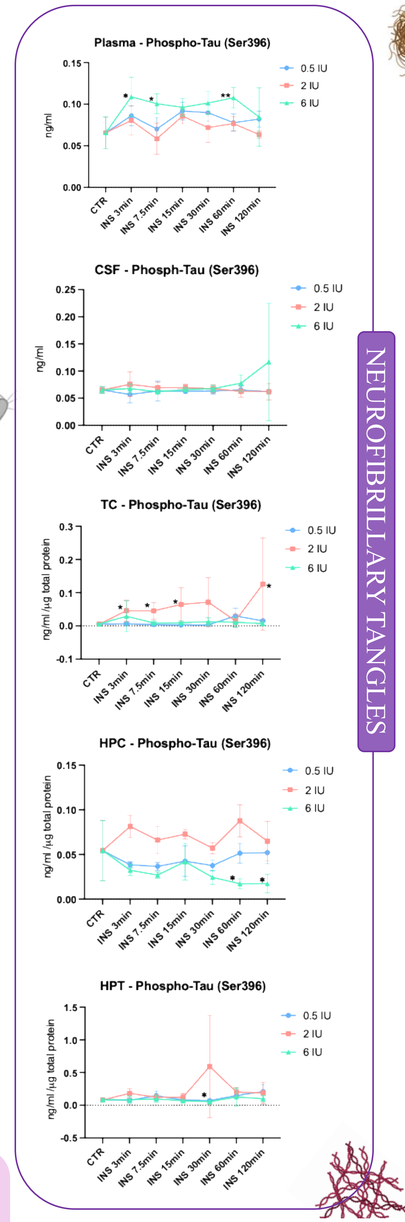
Across all doses and time points, acute intranasal insulin administration did not produce significant changes in p-Tau (Ser396) or Aβ (1–42) levels in plasma, CSF, or the examined brain regions compared with controls. In contrast, phosphorylation profiling revealed rapid insulin-induced signaling effects. PCA demonstrated a clear separation of the 3-minute post-administration group from control, 7.5-minute, and 30-minute groups, indicating that insulin-triggered phosphorylation events occur rapidly and transiently.

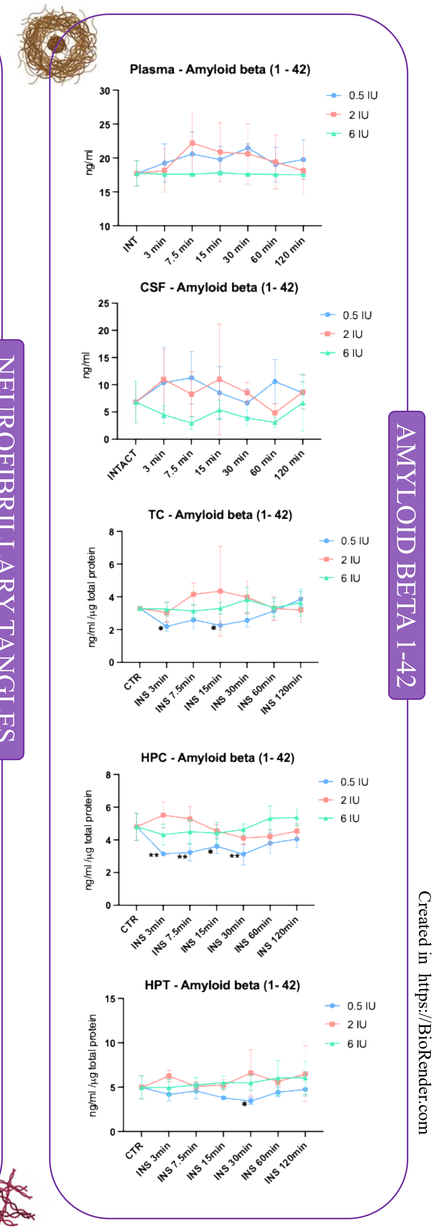
CONCLUSIONS

Acute intranasal insulin, even across a wide dose range, did not alter neurodegeneration markers, suggesting that short-lived insulin signaling is insufficient to affect tau or amyloid pathology. Nevertheless, the rapid and transient phosphorylation response observed in the temporal cortex highlights immediate insulin-mediated signaling effects, supporting the need for longer-term or repeated dosing paradigms to influence neurodegenerative processes.

NEUROSCIENCE PHOSPHO ANTIBODY ARRAY







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