The effect of daily oral administration of tonabersat on cellular pathology in a mouse model of Alzheimer's Disease

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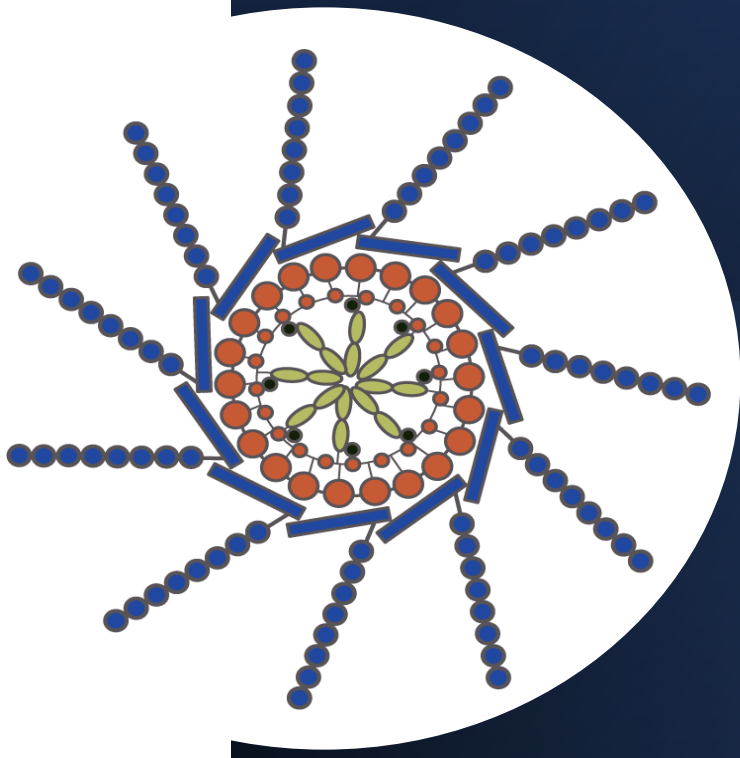

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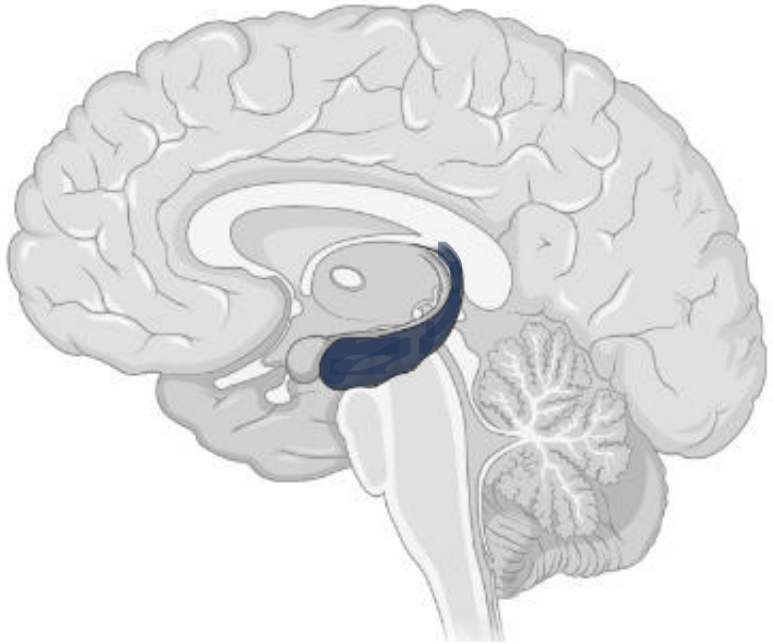
Inflammasome Biology Research Group

MEDICAL AND HEALTH SCIENCES

Alzheimer's Disease (AD)

Progressive neurodegenerative disease that involves:

- Accumulation of neurotoxic $A\beta_{1\text{-}42}$
- Increased state of inflammation
- Neuronal loss
  - Hippocampus → memory impairment → dementia

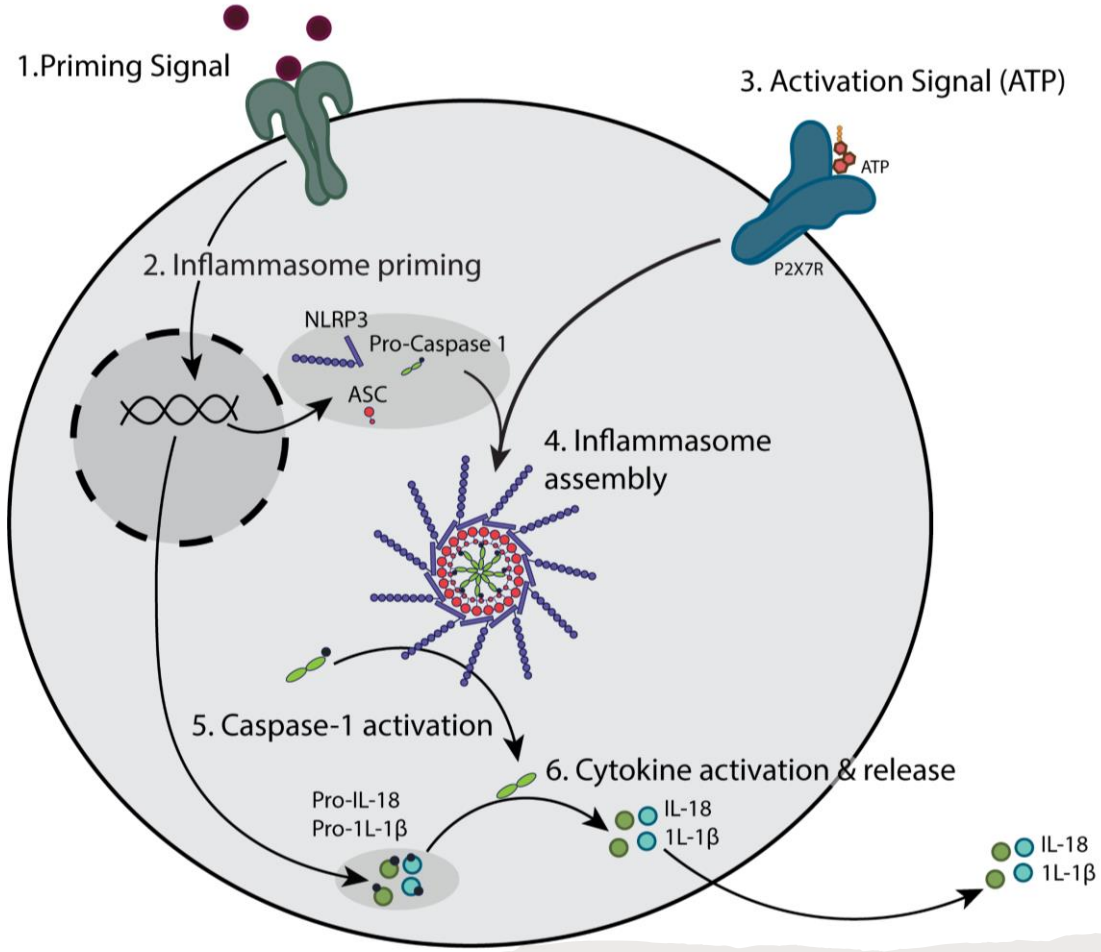


Advanced age is the most significant known risk factor for AD

Inflam-aging is the increased state of inflammation with advanced age, which may contribute to AD development and progression

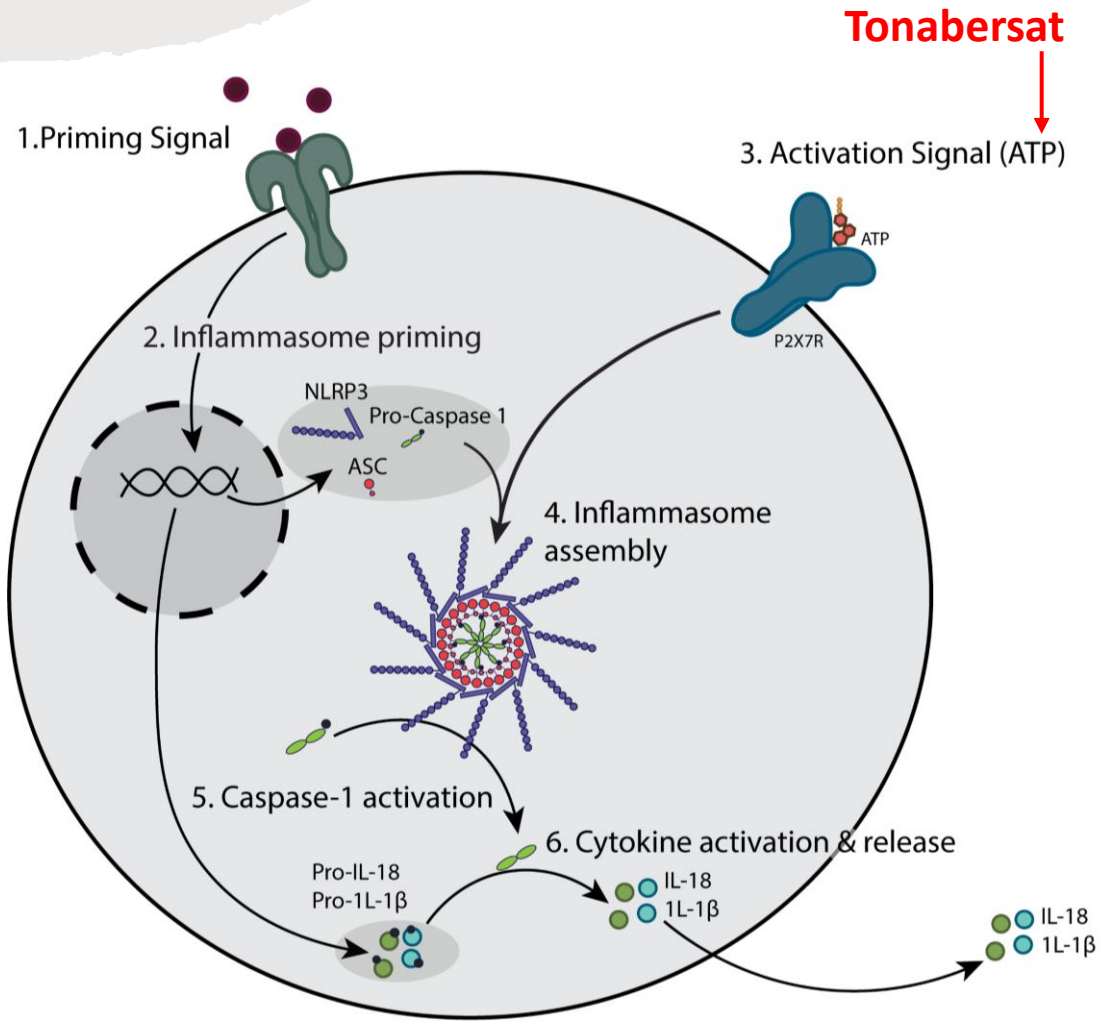
Inflammasomes in AD

- Multiprotein inflammatory signalling complexes
- <u>Two-step activation required:</u>
  1. **Inflammasome priming** leads to expression
  2. **Inflammasome activation** generates cleaved caspase-1 (CC1) → Inflammatory response
- <u>Inflammasome dysregulation:</u>
  - *Inflamm-aging* induces priming
  - Aβ1-42 increases ATP available for inflammasome activation



Tonabersat (Xiflam)

- Tonabersat
  - Orally bioavailable
  - Can cross the BBB
  - Safety & tolerability in clinical human trials
- Anti-inflammasome & neuroprotective effects in rodent models of retinal degeneration and Multiple Sclerosis.
- Reduces the amount of ATP available to activate the inflammasome



Objective and Hypothesis

Objective:

Investigate the effect of tonabersat on the **inflammasome pathway** and **neurodegeneration** in the mouse hippocampus following injection of $A\beta_{1\text{-}42}$

Hypothesis:

The anti-inflammasome activity associated with tonabersat will restore some regulation of inflammation and reduce the level of inflammation-associated neurodegeneration

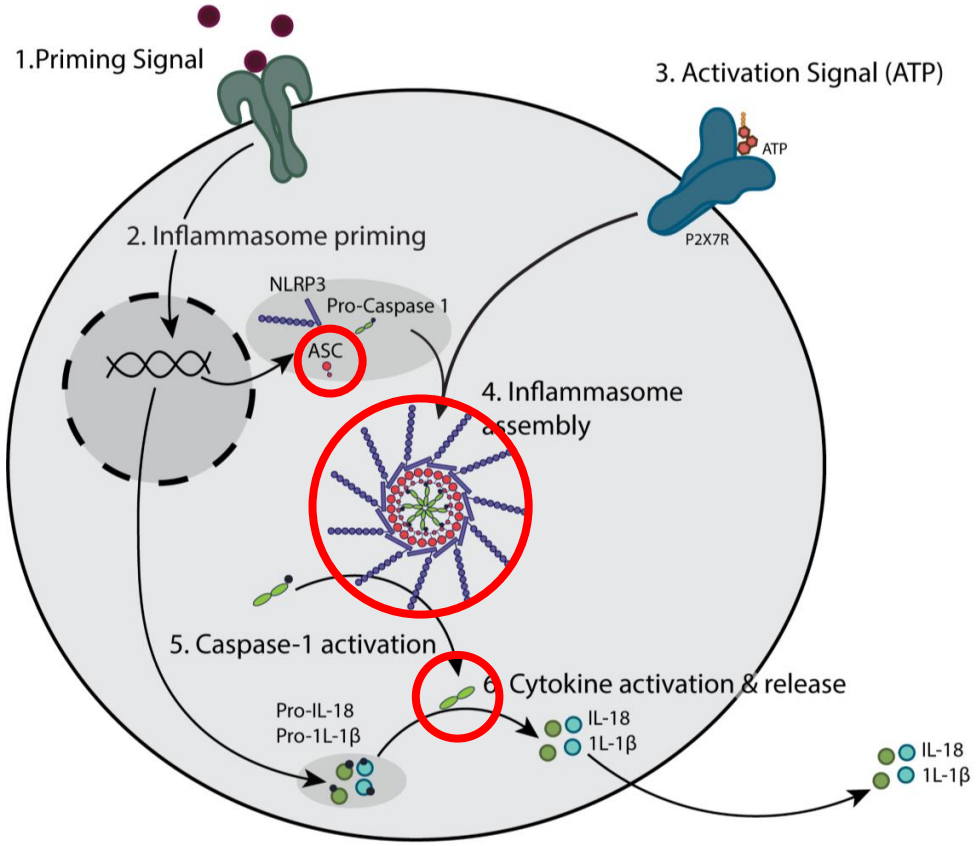
Methods

- Inject aggregated Aβ1-42 into the hippocampus
- After 1 day, mice were either fed tonabersat in peanut butter or peanut butter only daily for 16 days.
- Brain tissue collected and fluorescent-immunohistochemistry undertaken

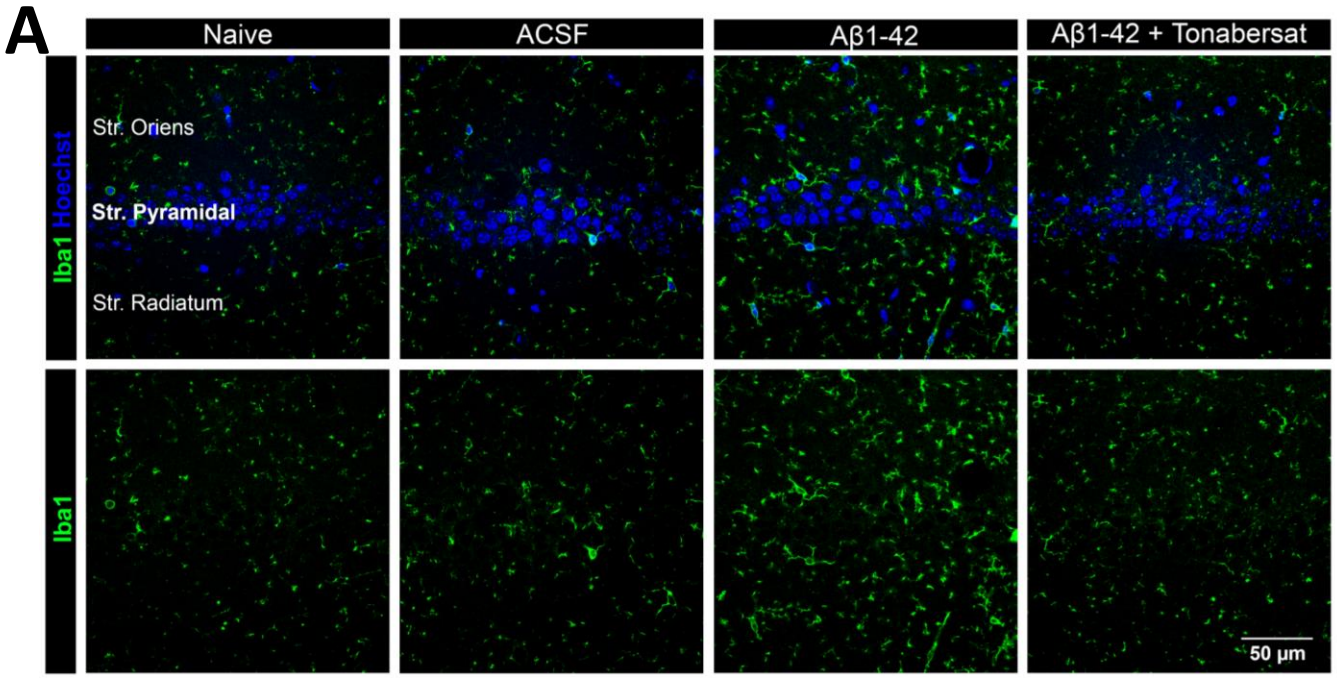
Group	n
Naïve	8
Vehicle(ACSF)-injected	8
Aβ1-42-injected	8
Aβ1-42 + Tonabersat	9
Tonabersat only	8

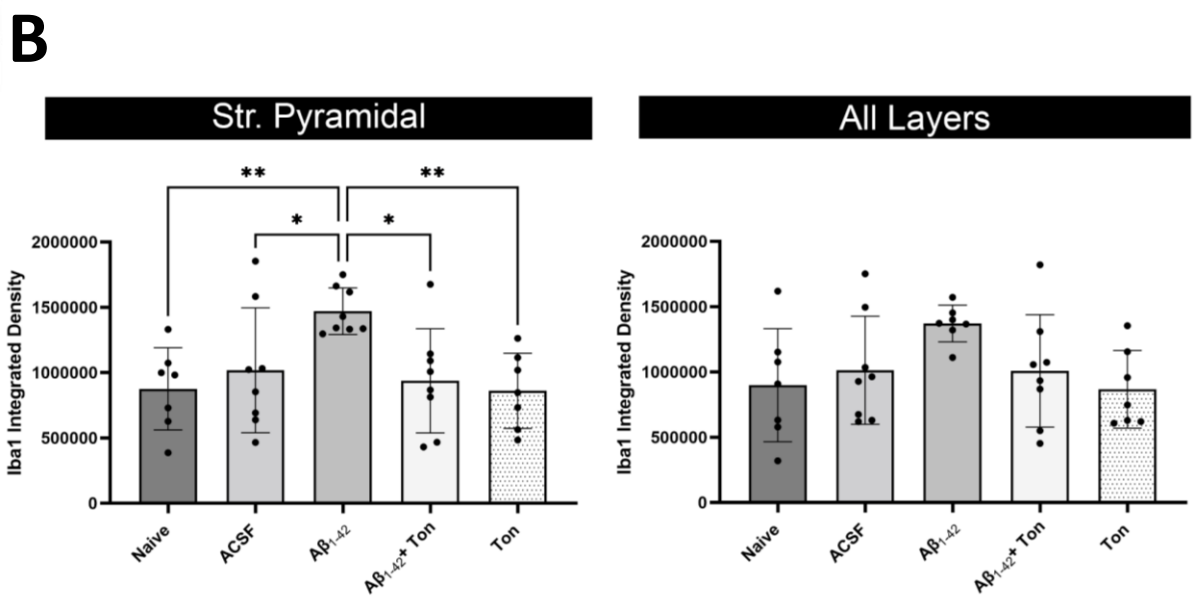
Markers:

- Microglia (Iba1); Neurons (NeuN); Apoptosis-associated speck–caspase recruit domain (ASC), and Cleaved-Caspase 1 (CC1)

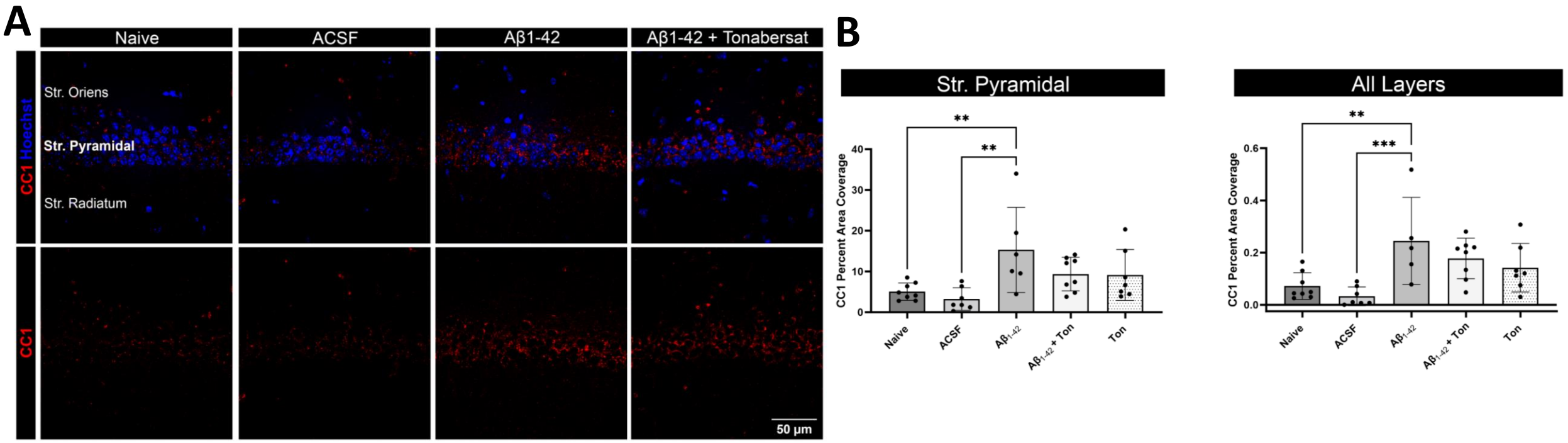


Results – Microglia (Iba1)

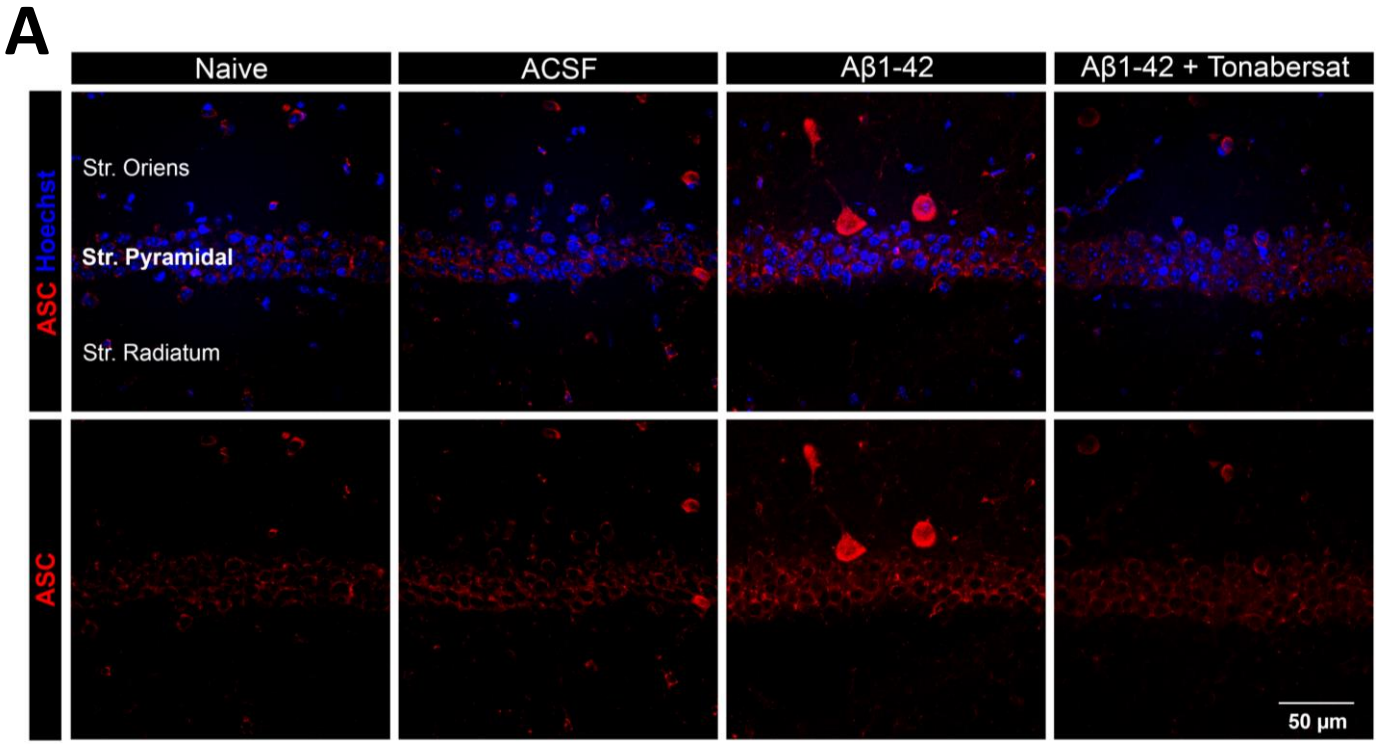


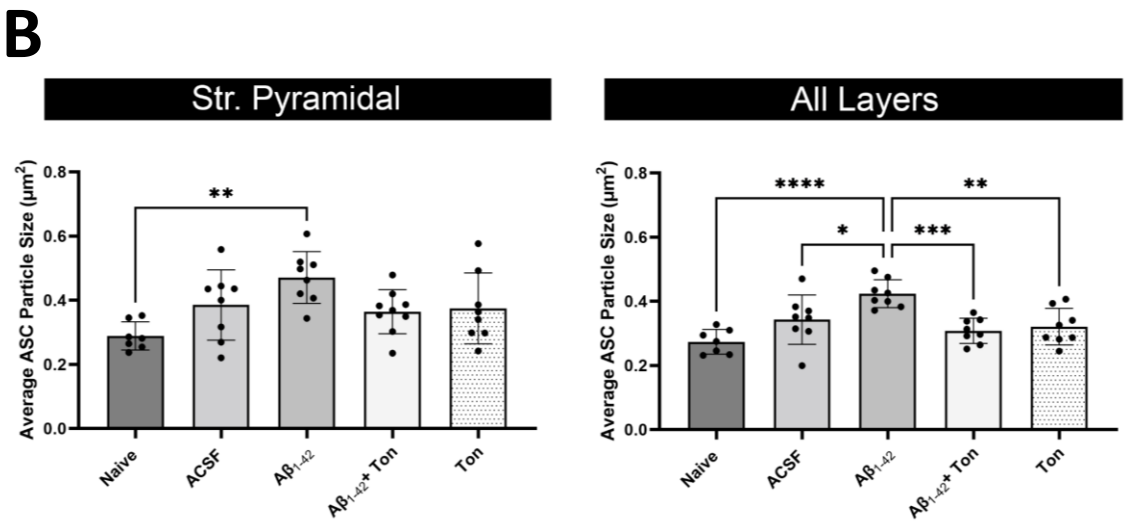


Results – Cleaved Caspase-1 (Inflammasome activation)



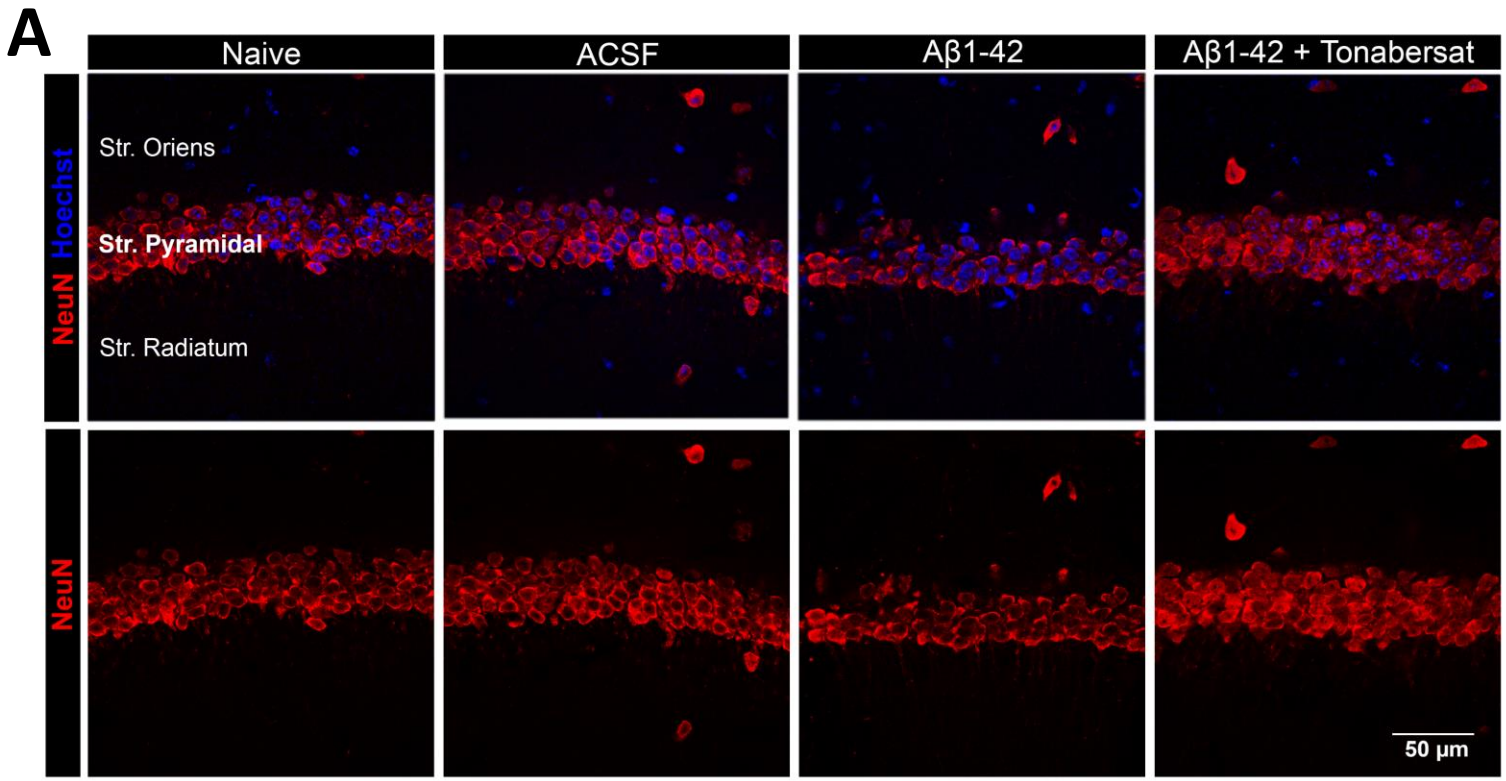
Results – ASC (Inflammasome marker)

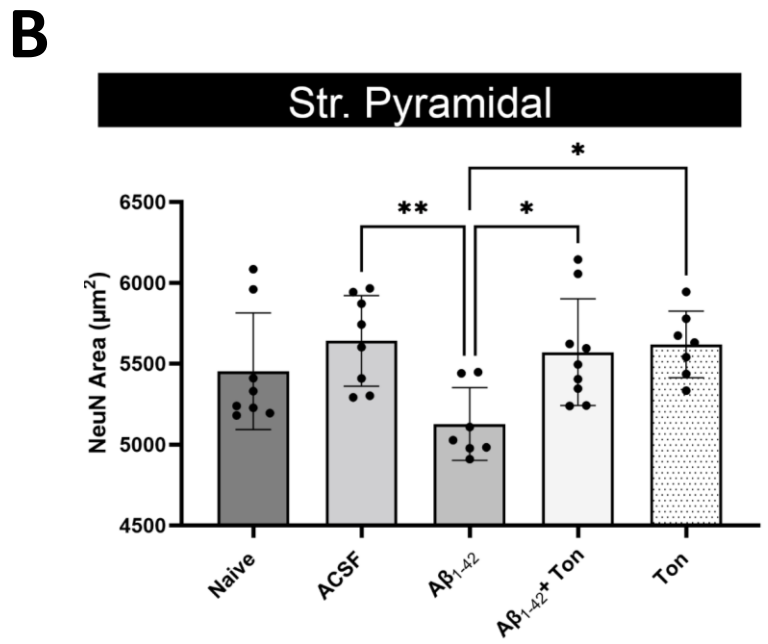




- ASC specks can also be released by cells after inflammasome activation and have inflammasome-independent functions

Results – NeuN (Neurons)





Summary

- Tonabersat treatment:
  - Reduced the Iba1 response of microglia surrounding neurons
  - Prevented the loss of pyramidal neuron area
  - Reduced the size of ASC particles in the hippocampus
  - Did not prevent the increase in Inflammasome activation (CC1)

Future Directions

- Determine functional significance
  - Does the reduced loss of neuron area with tonabersat treatment result in improved memory and cognitive scores
- Understand the predominant type(s) of inflammasome active in the human AD brain
  - To find most relevant therapeutic targets

Thank you

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