

The role of phosphodiesterase-4 in the mediation of the comorbidity of memory impairment and depression in 3 × TG-AD mice and its cellular mechanisms

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Research
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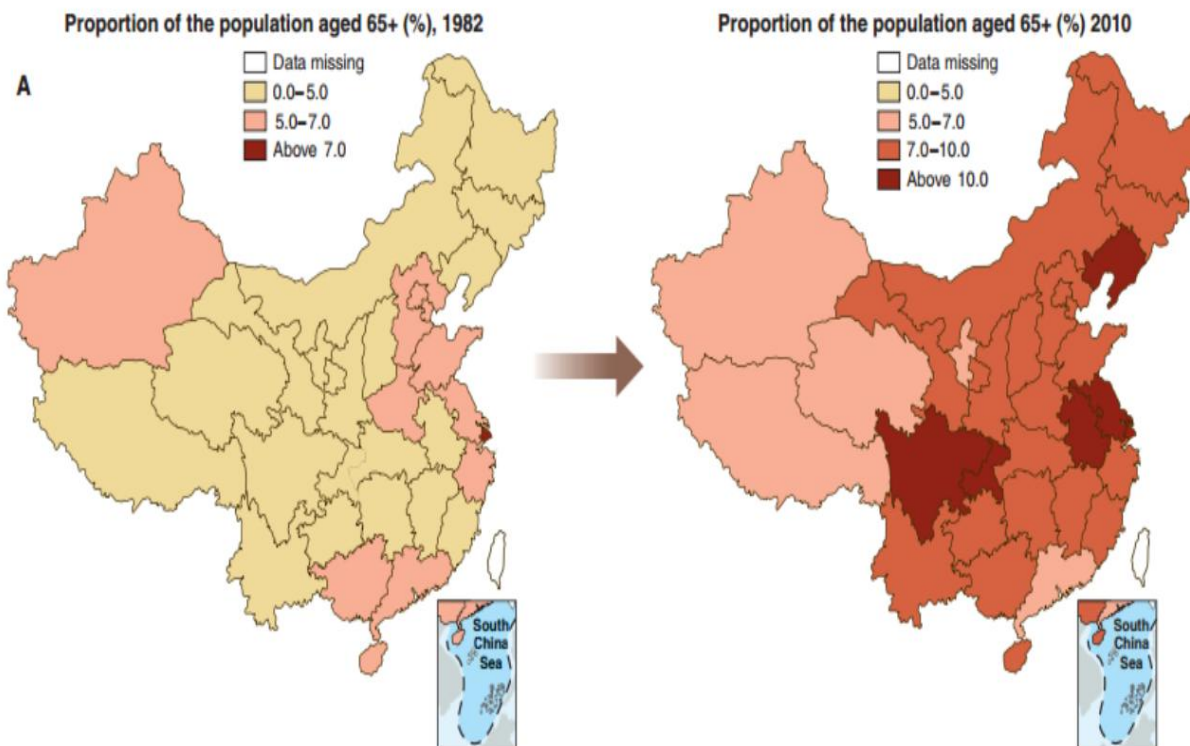
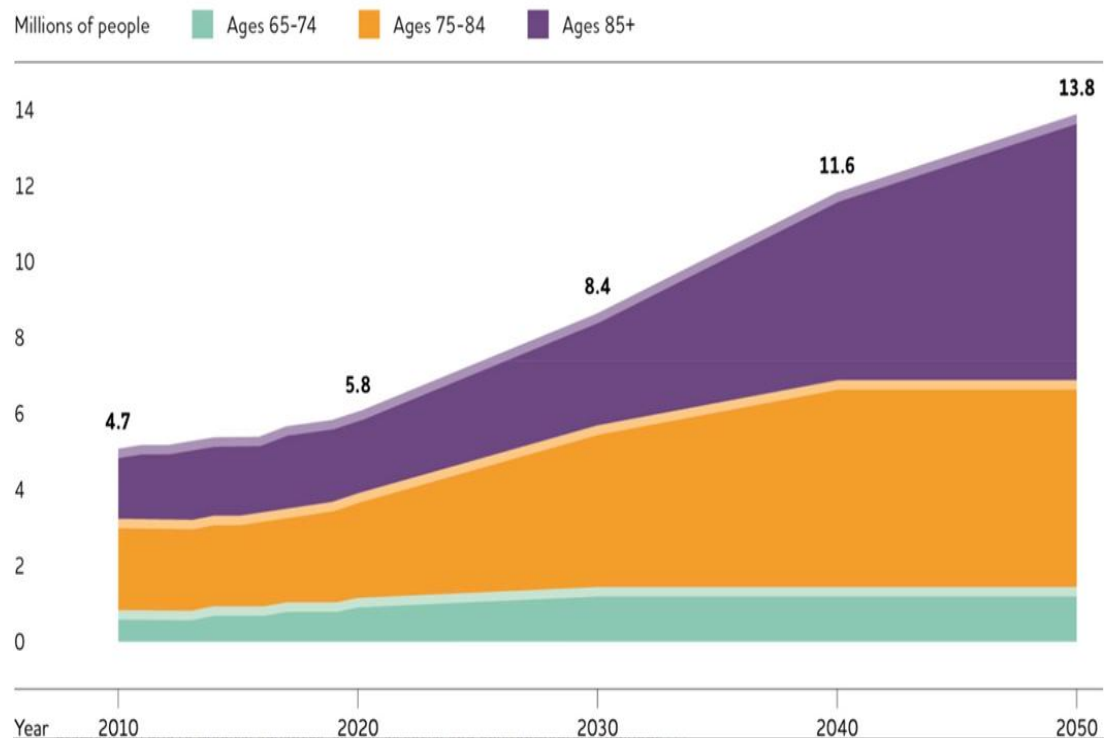
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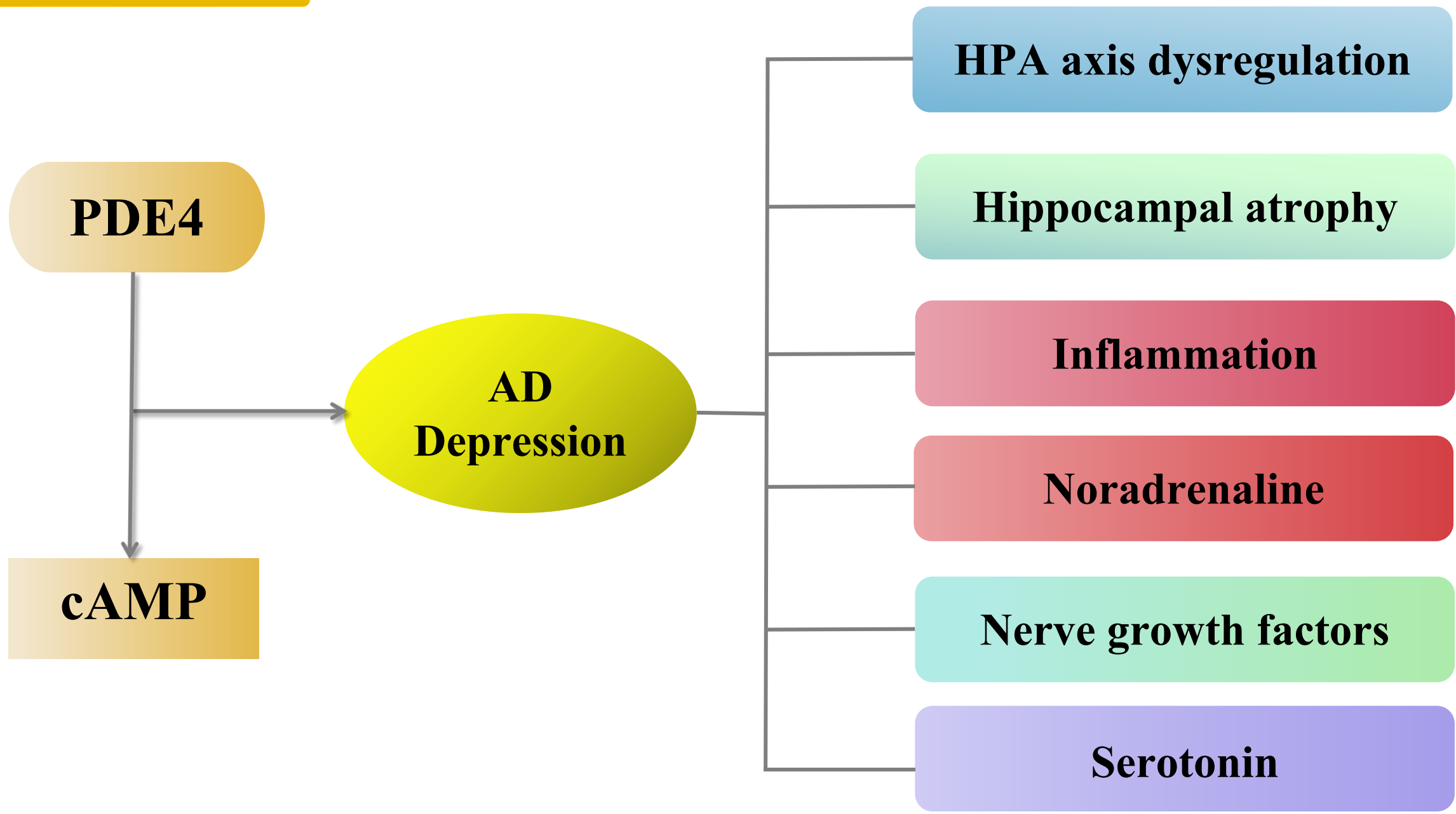
Research
Results

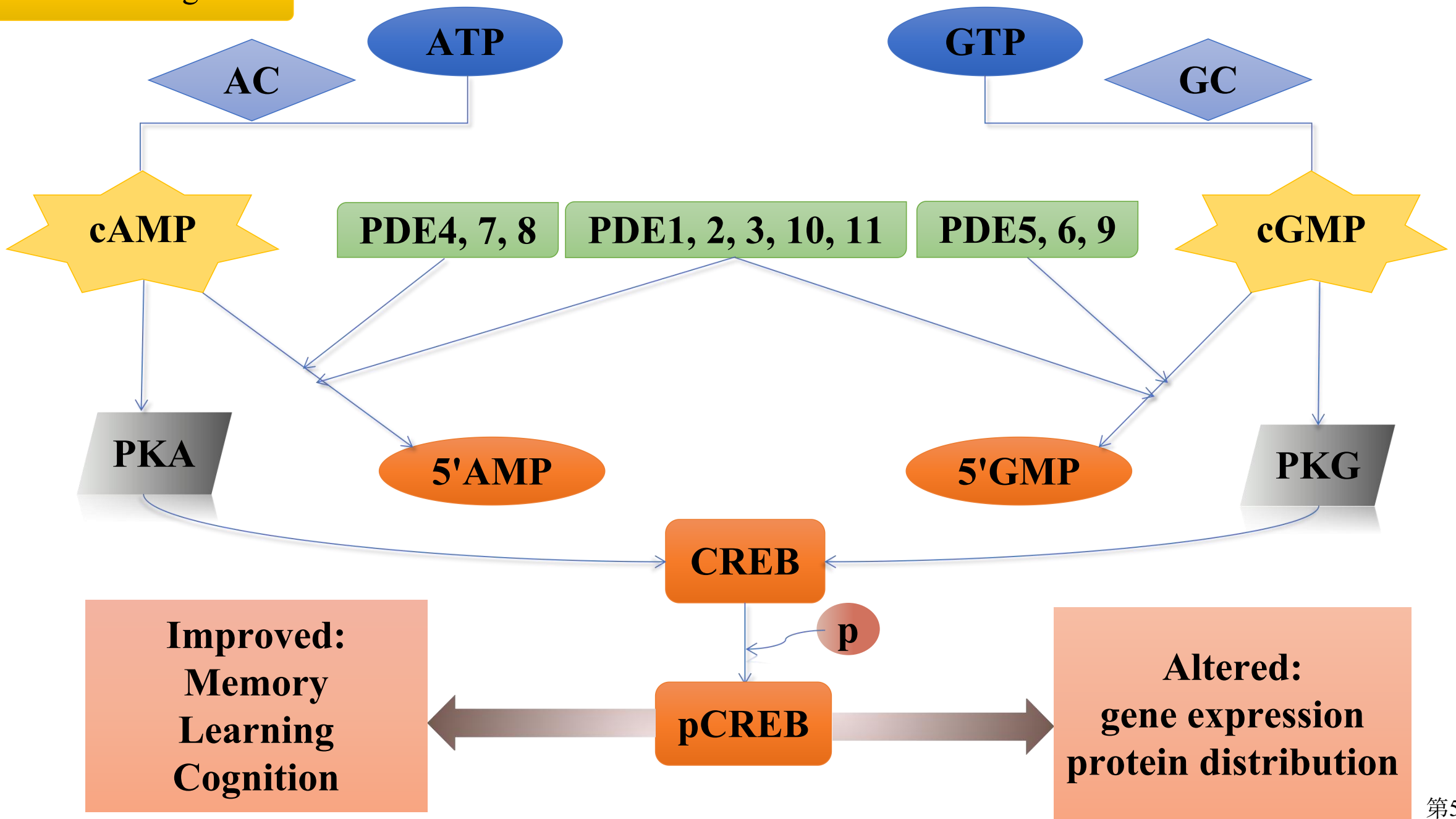
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Research
Conclusion

Alzheimer disease, AD





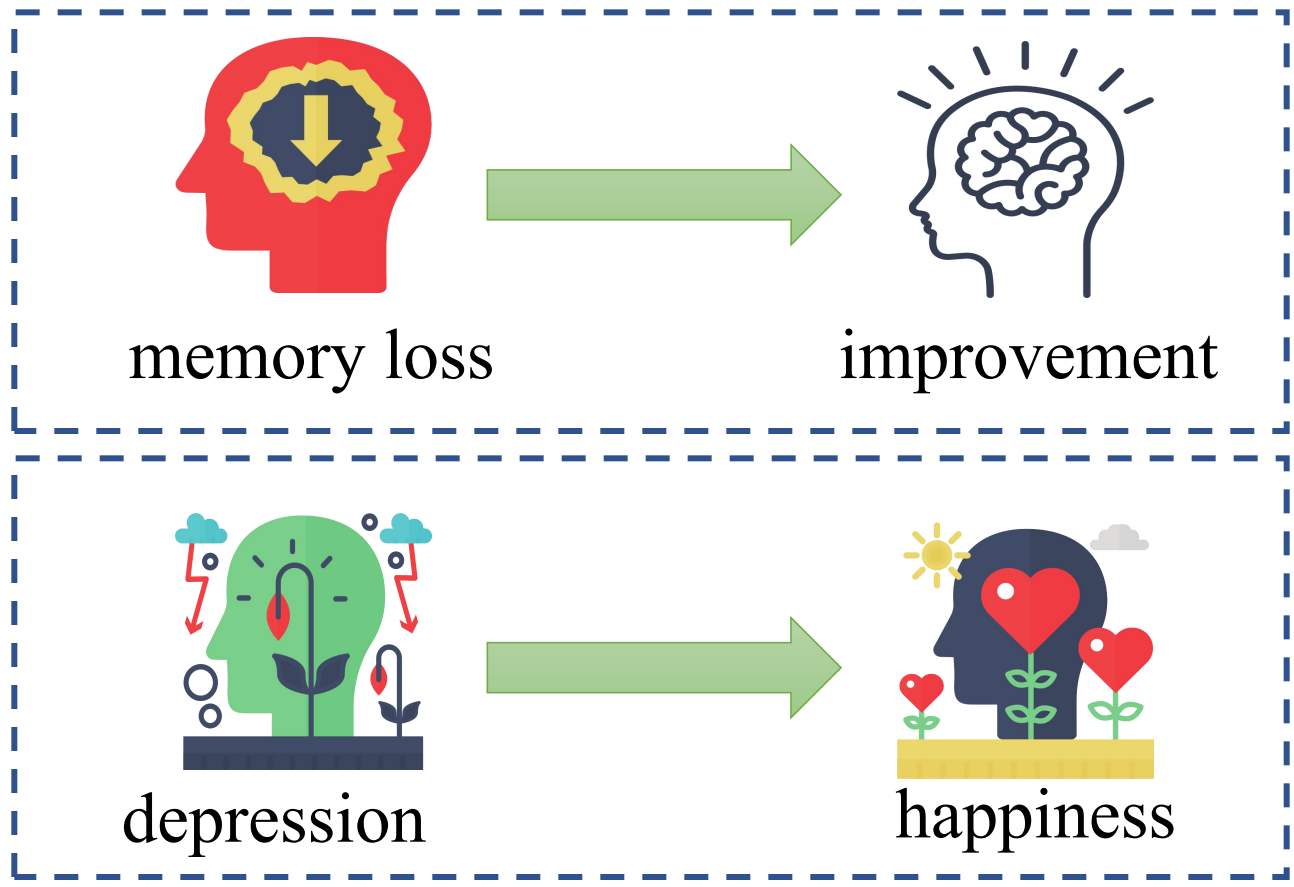


Research Background

70-80% of cAMP in nerve cells is hydrolyzed by PDE4.
PDE4 is encoded by four genes, namely PDE4A, B, C, and D.



The first generation PDE4 inhibitor can pass through the blood-brain barrier, enhance synaptic plasticity and cognitive ability of rodent AD models, and play a role in regulating emotion.



01

Disease Course Simulation

3 × Tg-AD mice at 2, 4 and 10 months of age were used to simulate the behavioral changes of AD patients at different stages

02

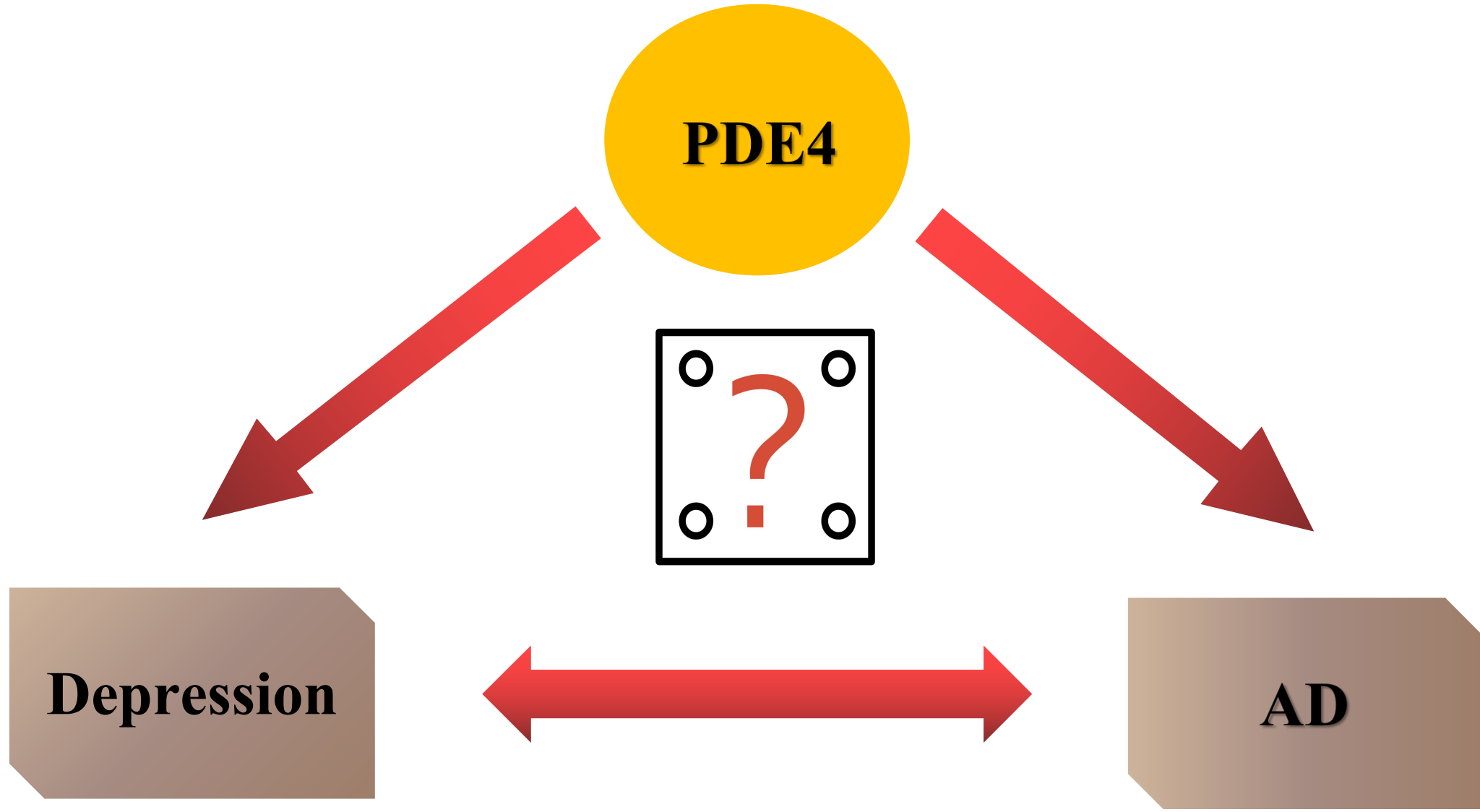
Signaling Pathways

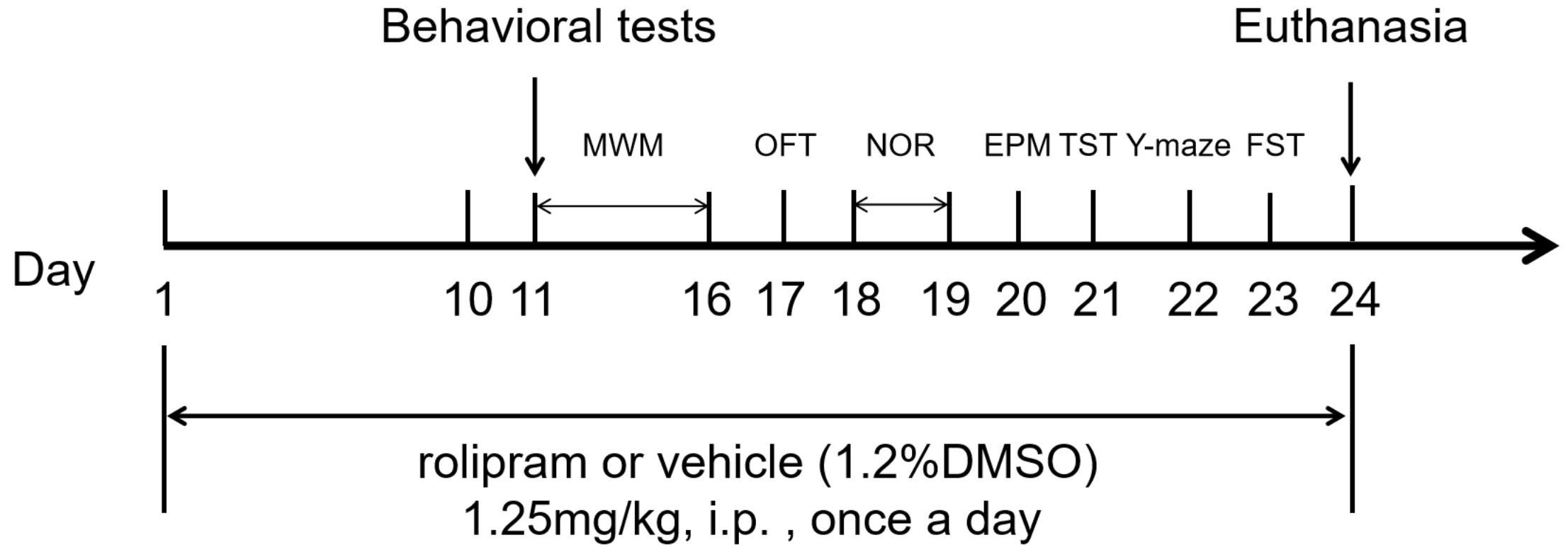
Targeted study of the regulatory roles and mechanisms of cellular signaling systems involved in PDE4

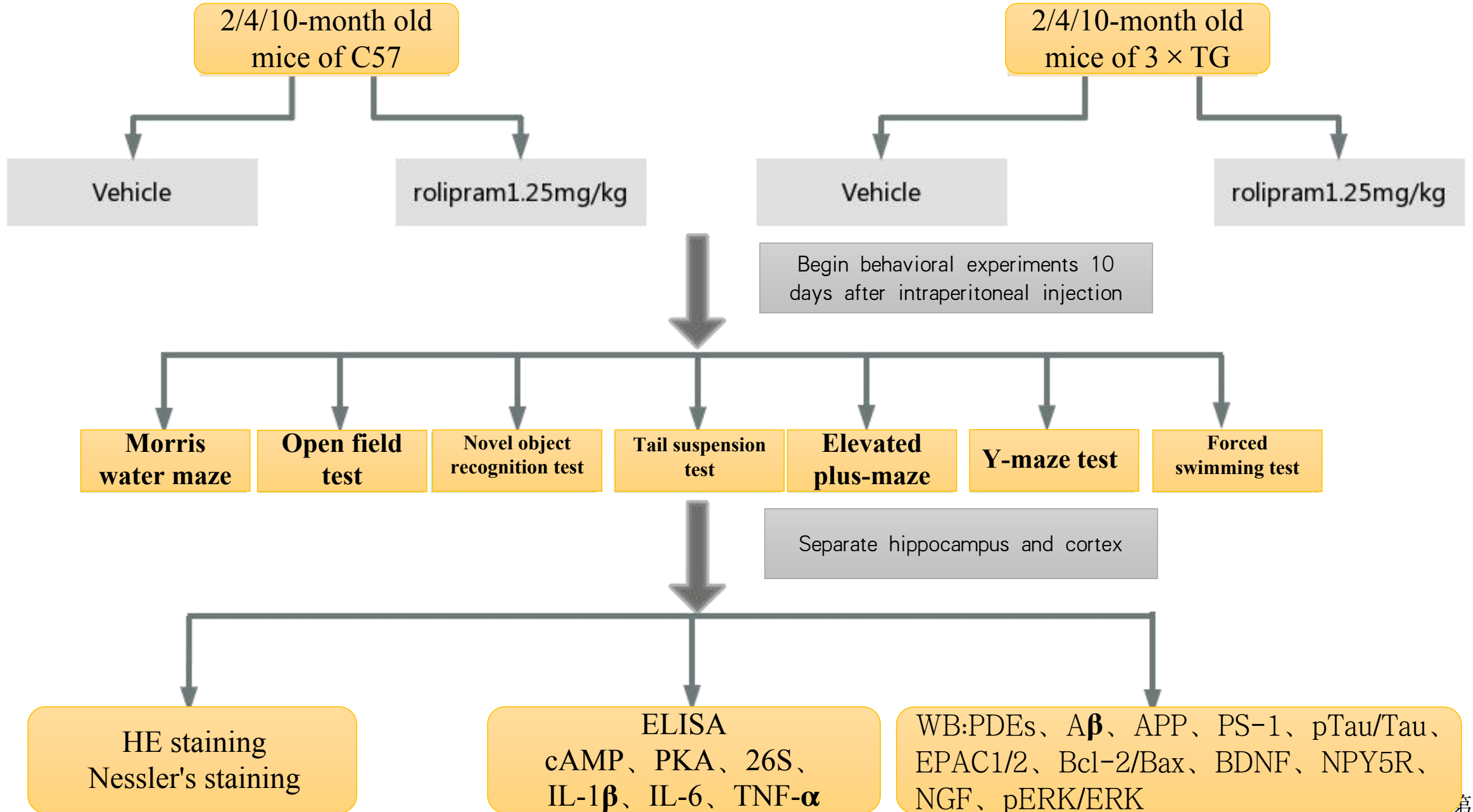
03

Pathogenesis

To elucidate the pathogenesis of AD depression co-morbidity and identify the molecular targets of AD depression co-morbidity

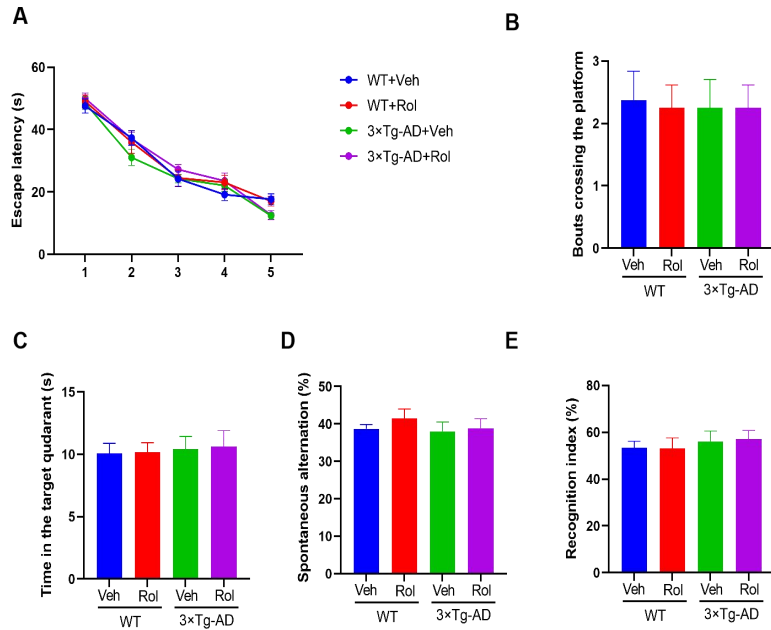




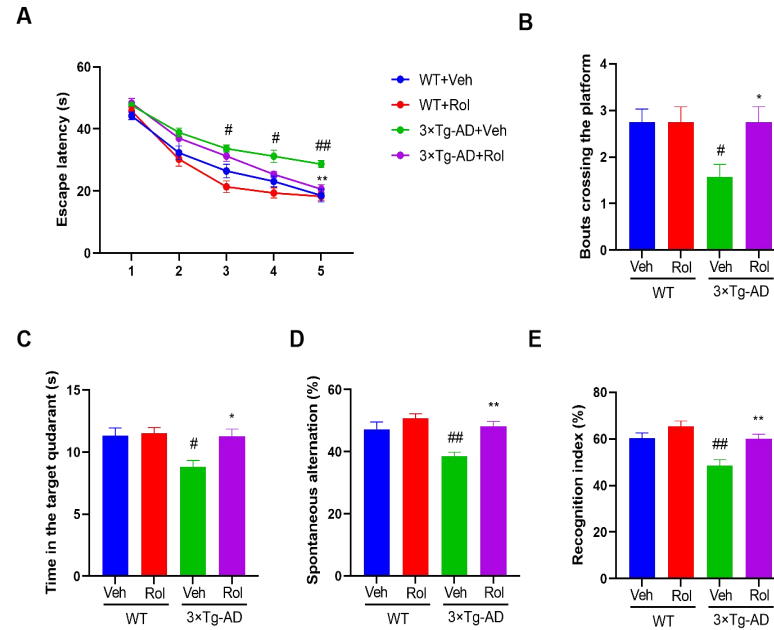


Effect of Rol on the learning memory ability of 2/4/10-month-old AD mice

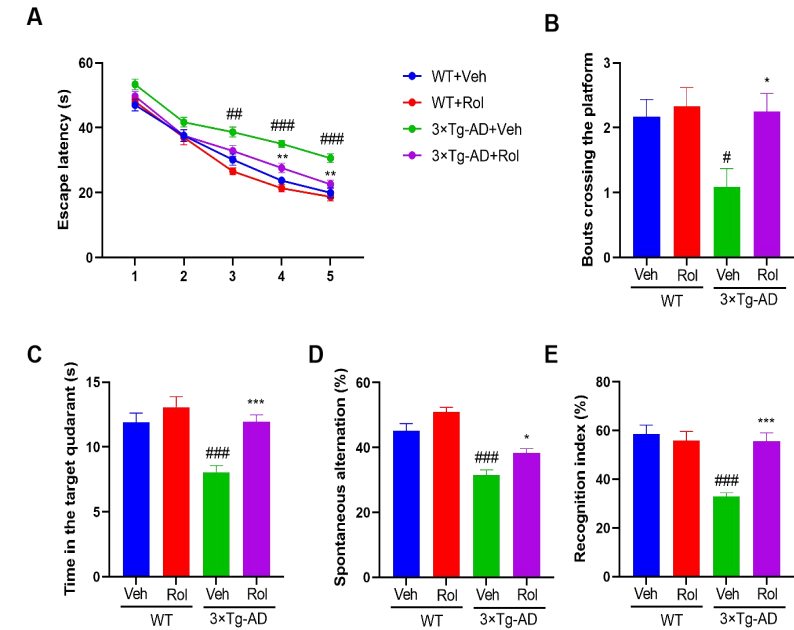
2-month-old mice



4-month-old mice



10-month-old mice

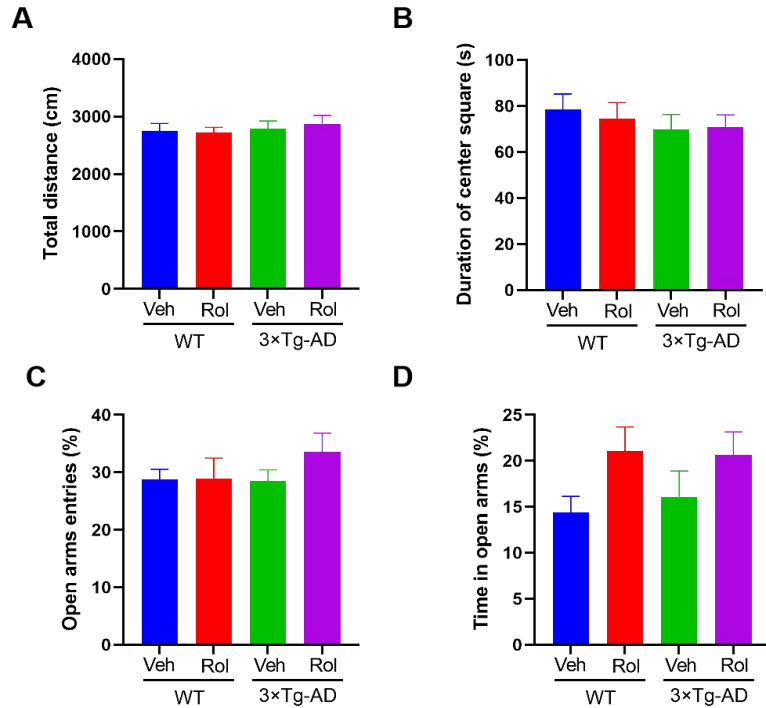


$p < 0.05$, ## $p < 0.01$ vs. WT + Veh;
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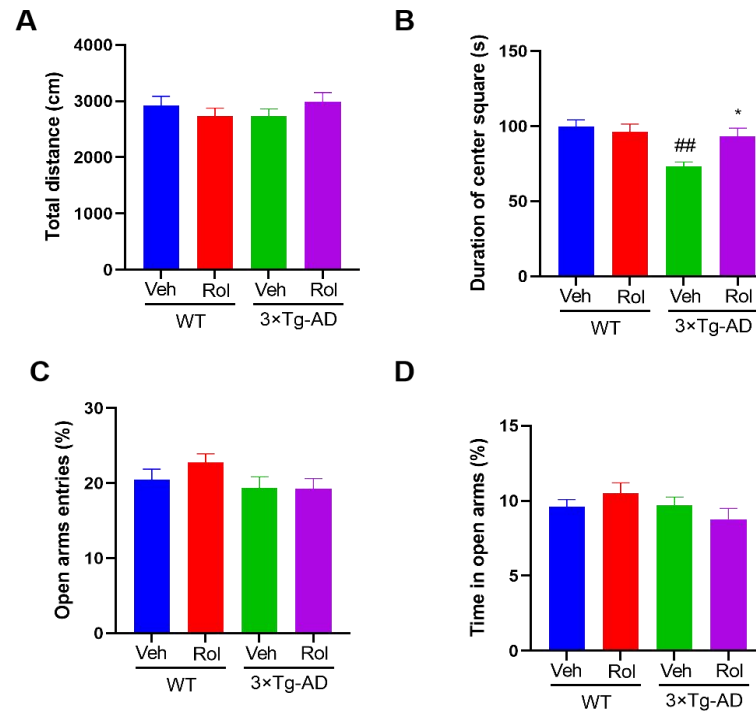
$p < 0.05$, ### $p < 0.001$ vs. WT + Veh;
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Effects of Rol on anxiety-like behavior in 2/4/10-month-old AD mice

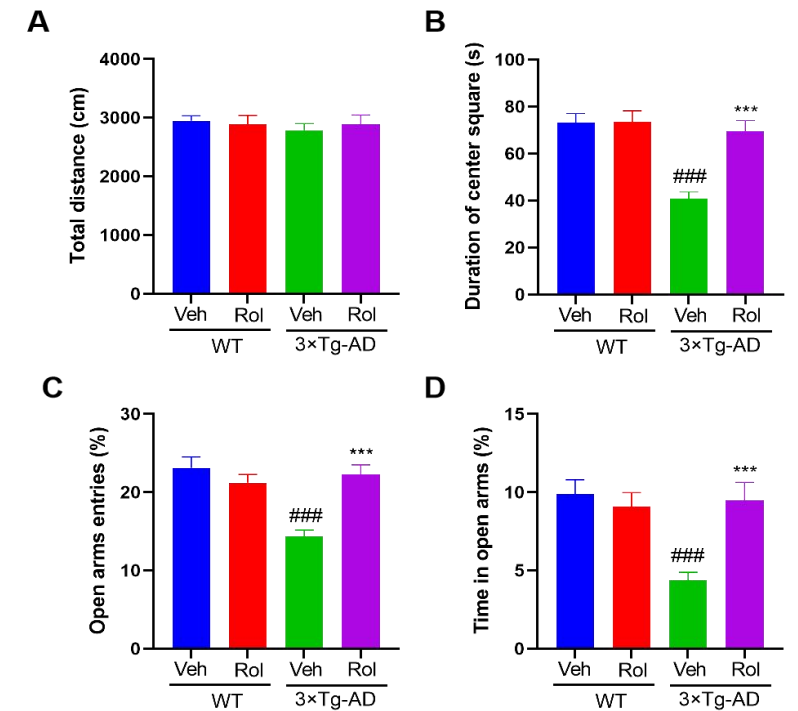
2-month-old mice



4-month-old mice



10-month-old mice



^{##} $p < 0.01$ vs. WT + Veh;
^{*} $p < 0.05$ vs. 3 × Tg-AD + Veh.

^{###} $p < 0.001$ vs. WT + Veh;
^{***} $p < 0.001$ vs. 3 × Tg-AD + Veh.

Effect of Rol on depression-like behavior in 2/4/10-month-old AD mice

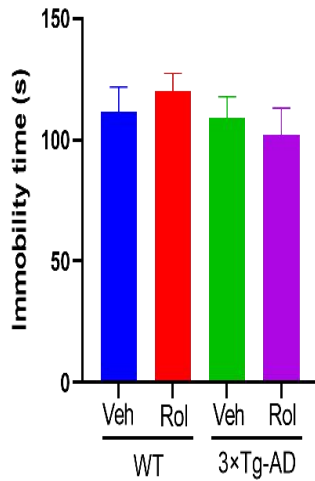
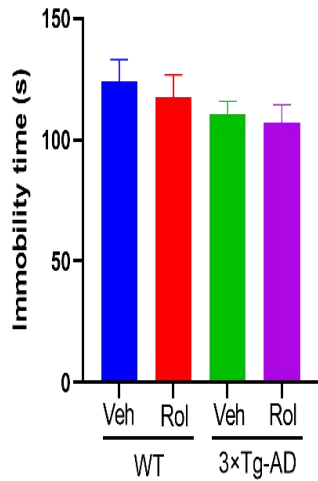
2-month-old mice

4-month-old mice

10-month-old mice

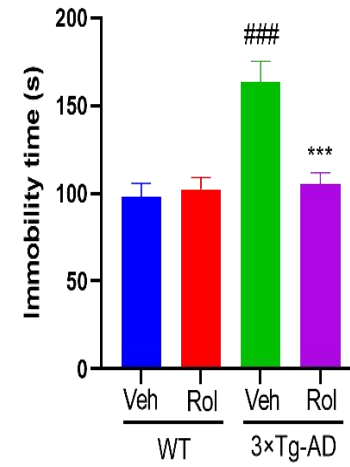
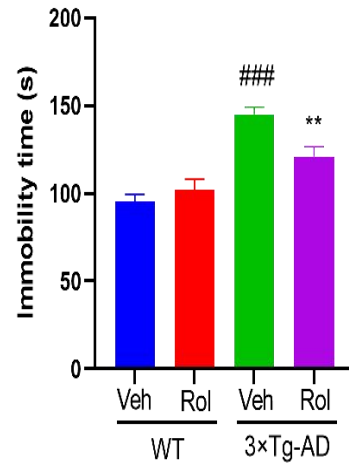
A

B



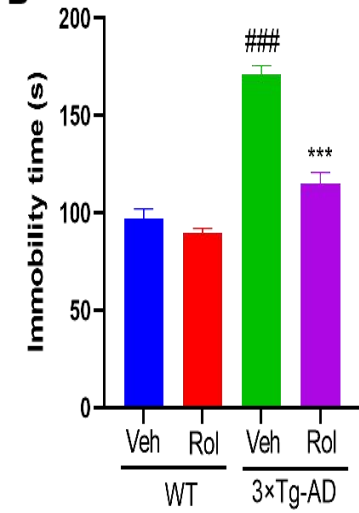
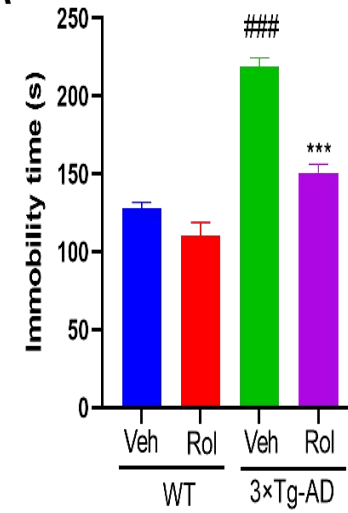
A

B



A

B

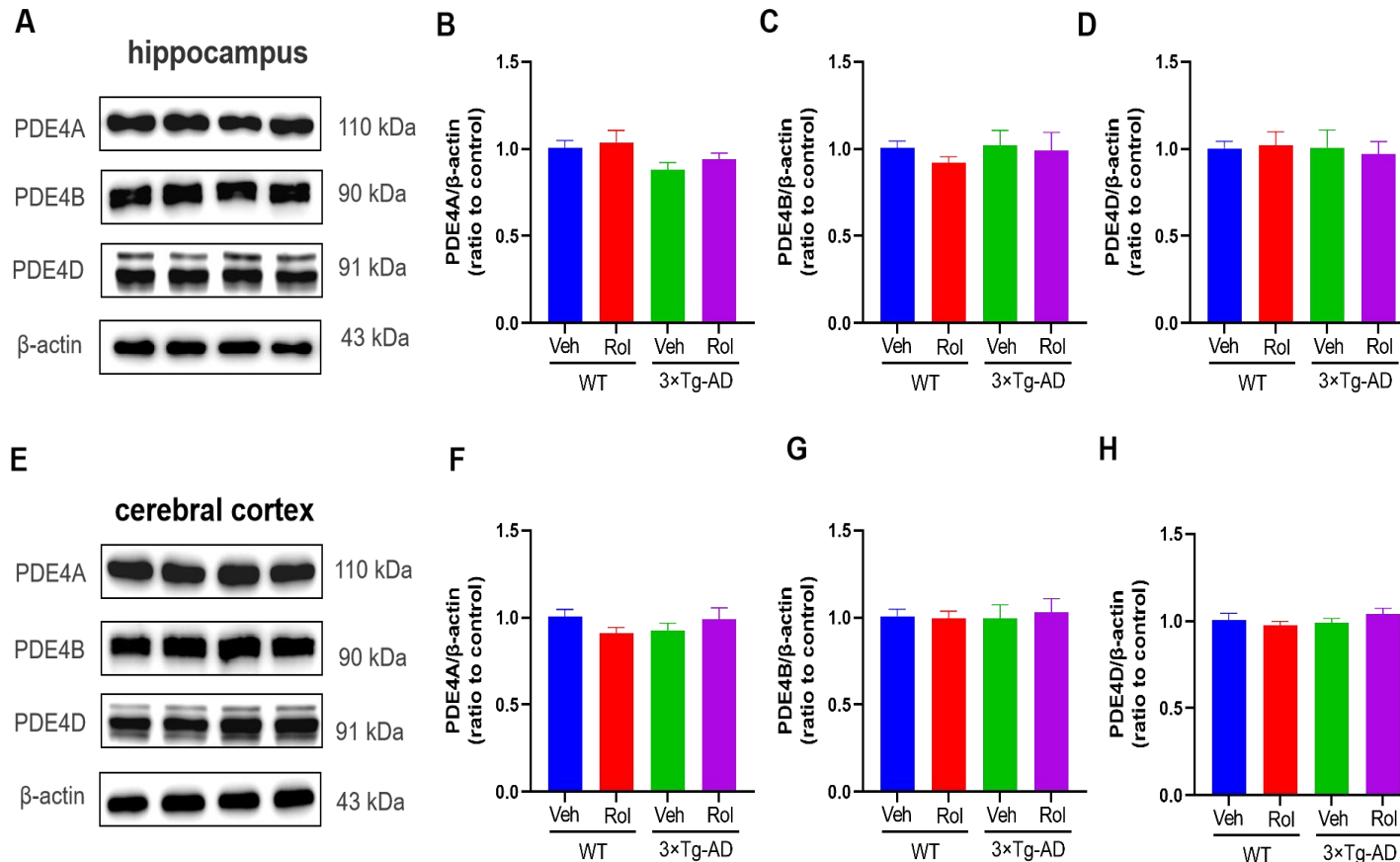


^{###} $p < 0.001$ vs. WT + Veh;
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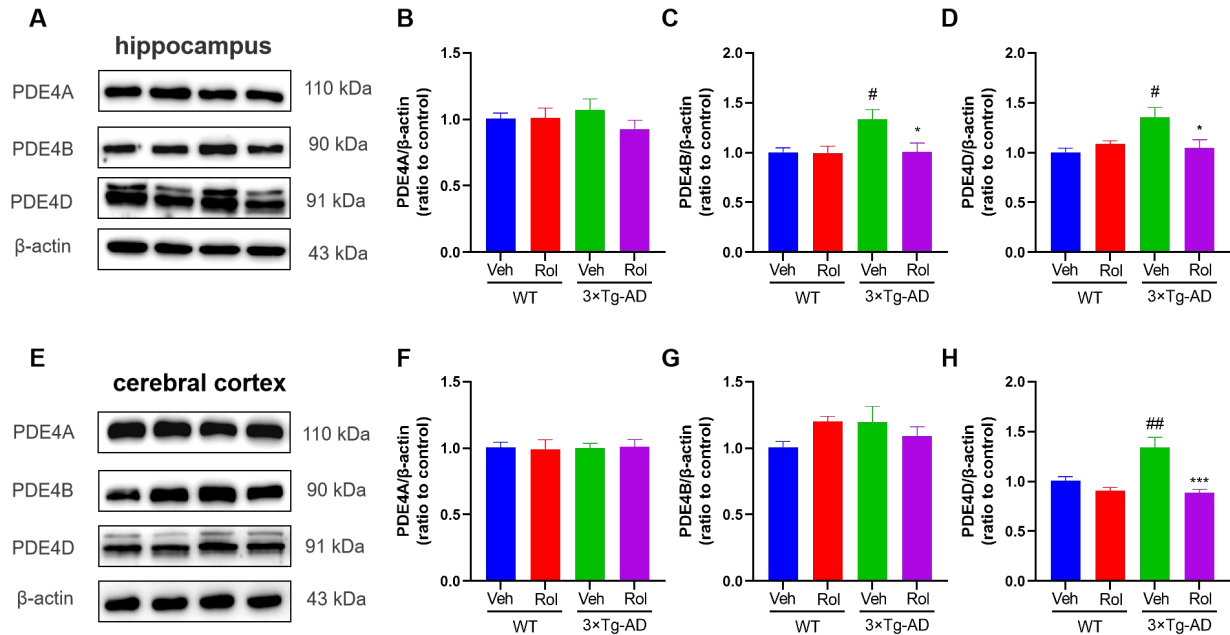
Effect of Rol on PDE4 subtypes in 2/4/10-month-old AD mice

2-month-old mice



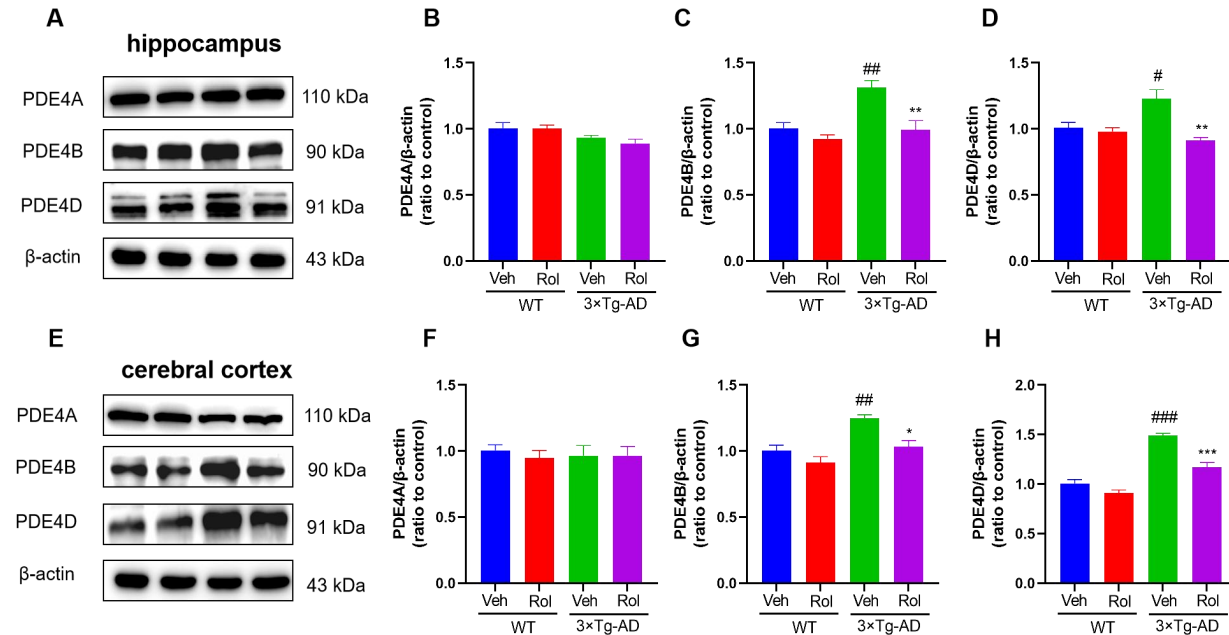
Effect of Rol on PDE4 subtypes in 2/4/10-month-old AD mice

4-month-old mice



$p < 0.05$, ## $p < 0.01$ vs. WT + Veh;
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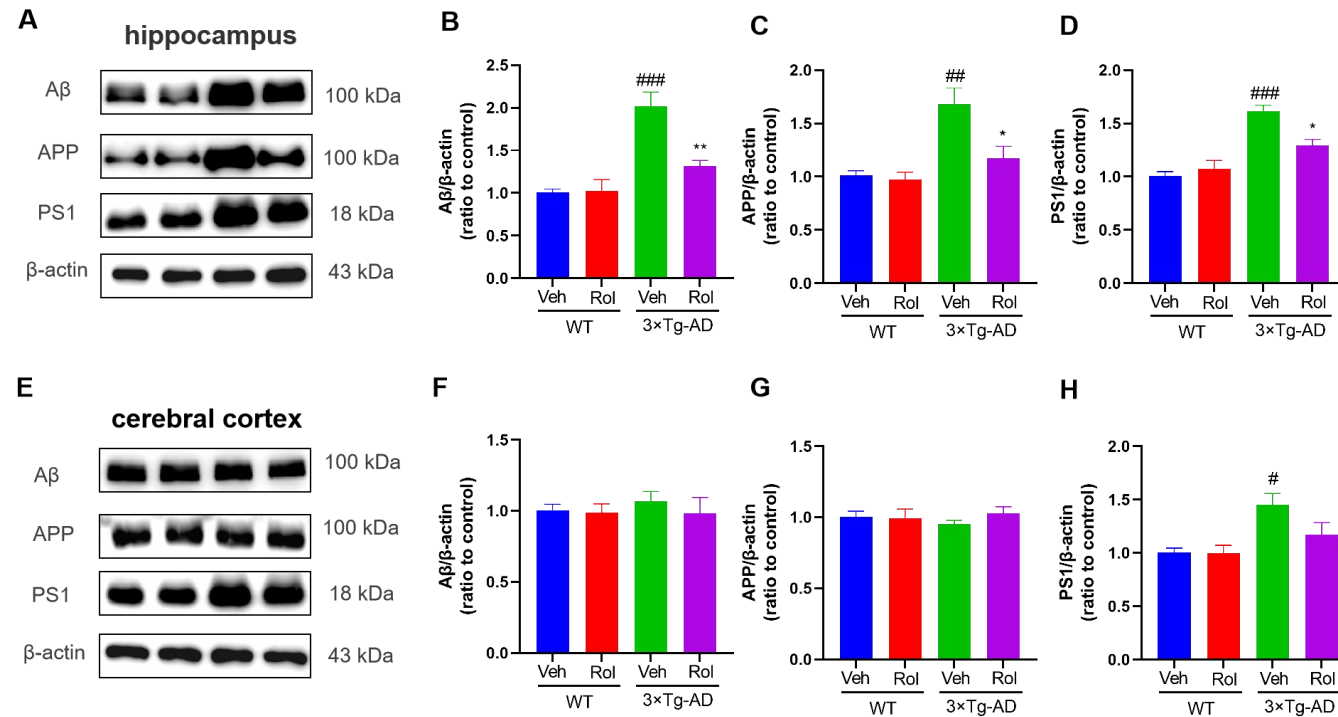
10-month-old mice



$p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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Effect of Rol on A β and related proteins in 2/4/10-month-old AD mice

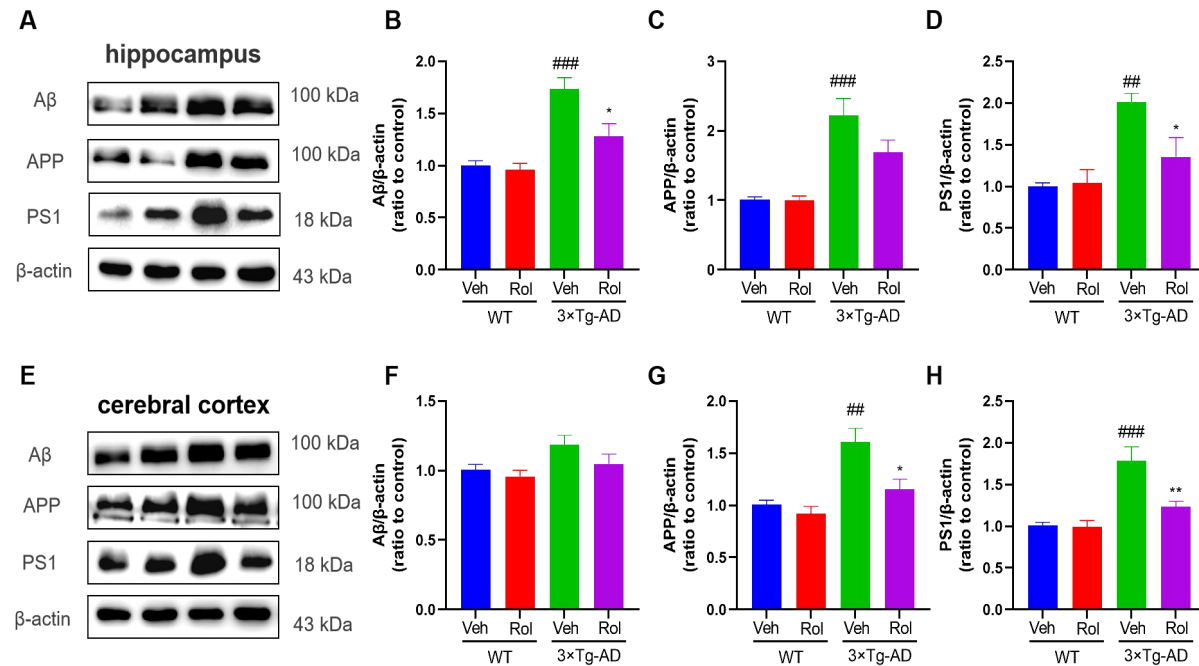
2-month-old mice



$p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. WT + Veh; * $p < 0.05$, ** $p < 0.01$ vs. 3 \times Tg-AD + Veh.

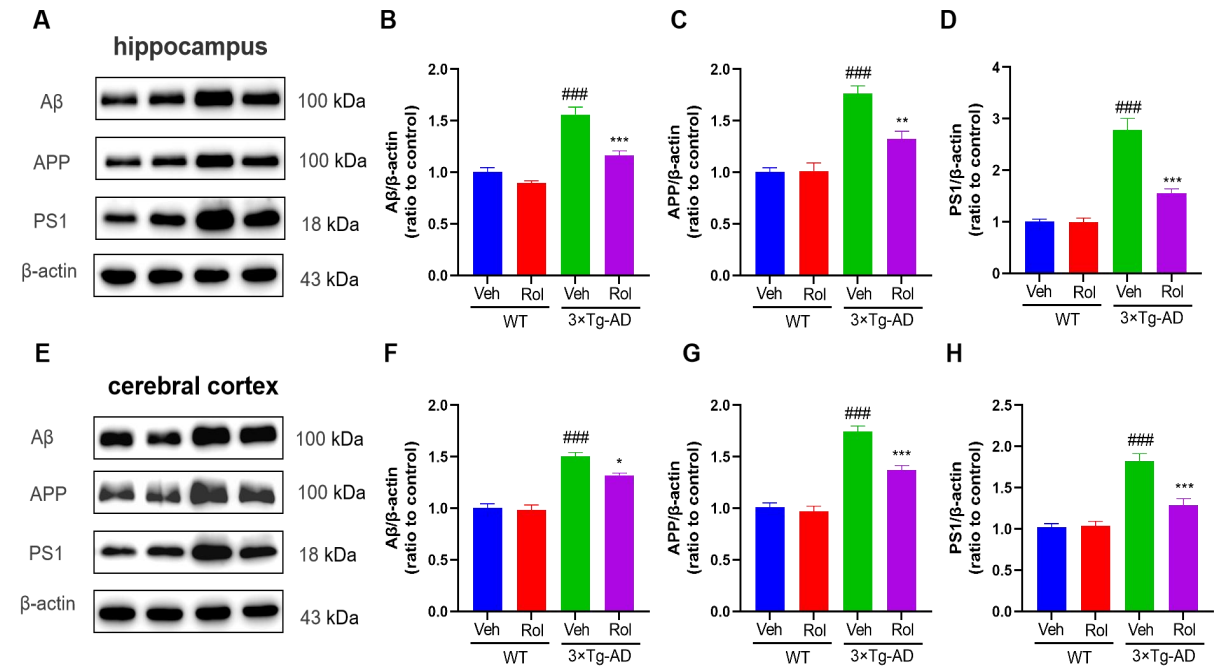
Effect of Rol on A β and related proteins in 2/4/10-month-old AD mice

4-month-old mice



$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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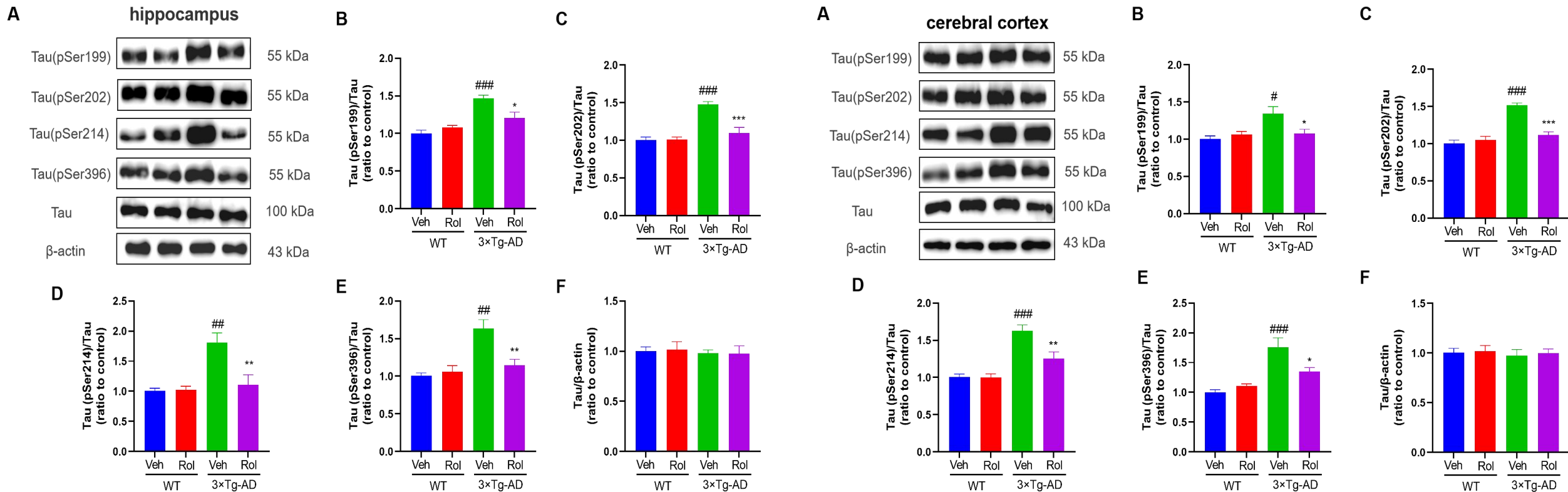
10-month-old mice



$p < 0.001$ vs. WT + Veh;
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. 3 \times Tg-AD + Veh.

Effect of Rol on phosphorylated Tau protein in 2/4/10-month-old AD mice

2-month-old mice

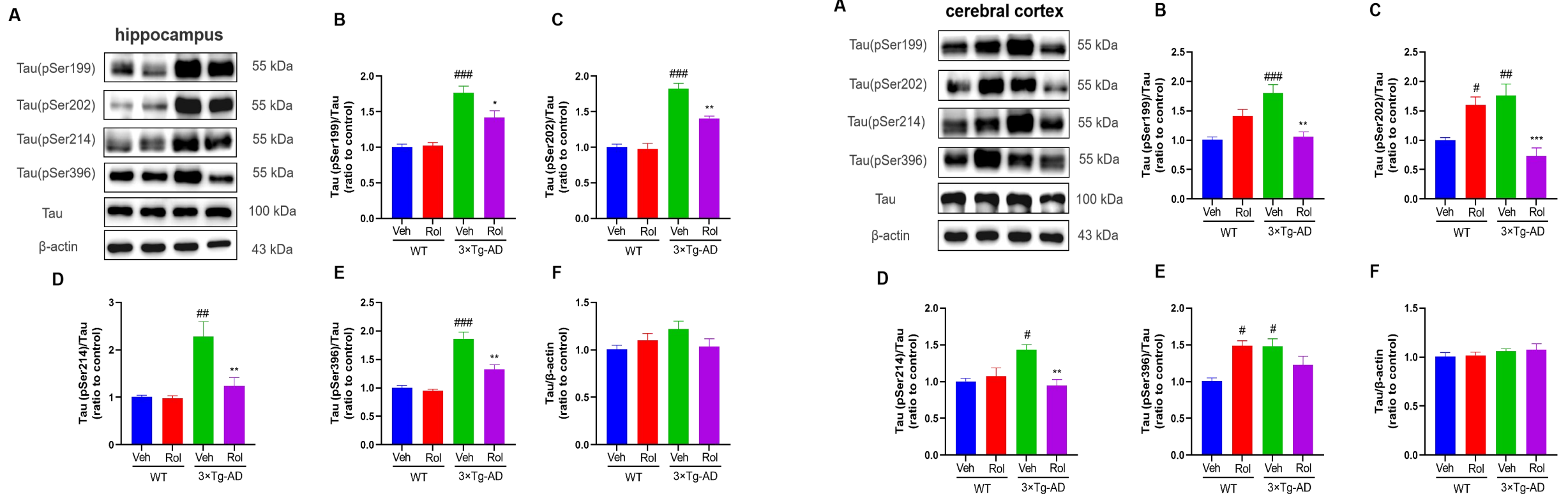


$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. 3 \times Tg-AD + Veh.

$p < 0.05$, ### $p < 0.001$ vs. WT + Veh;
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. 3 \times Tg-AD + Veh.

Effect of Rol on phosphorylated Tau protein in 2/4/10-month-old AD mice

4-month-old mice

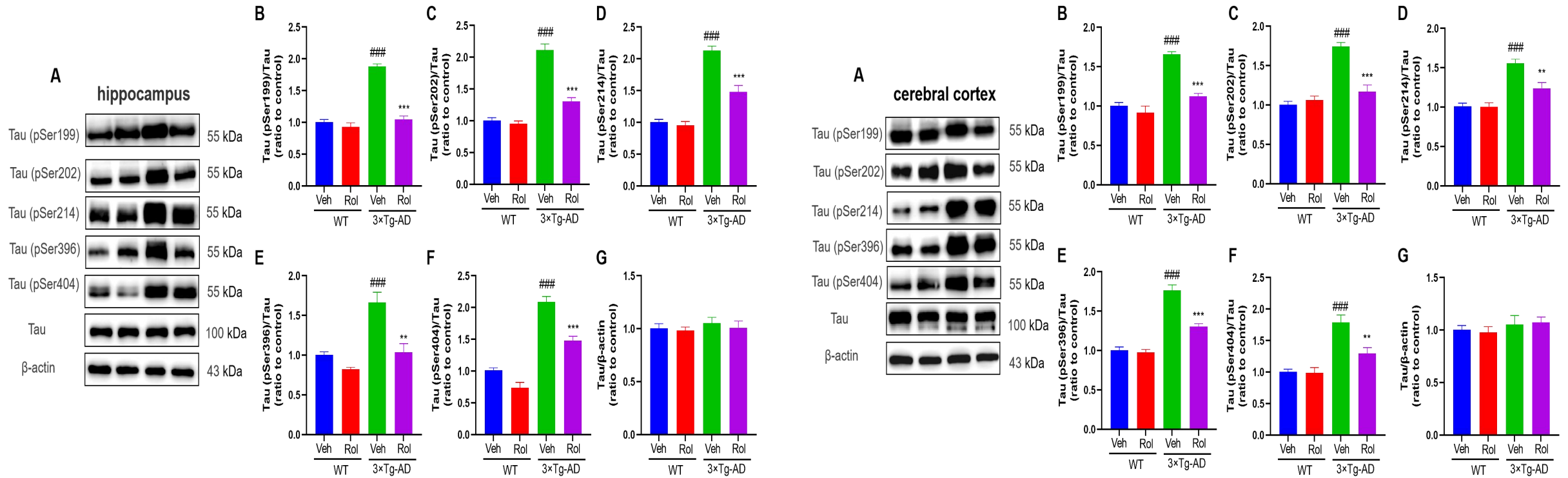


$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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Effect of Rol on phosphorylated Tau protein in 2/4/10-month-old AD mice

10-month-old mice



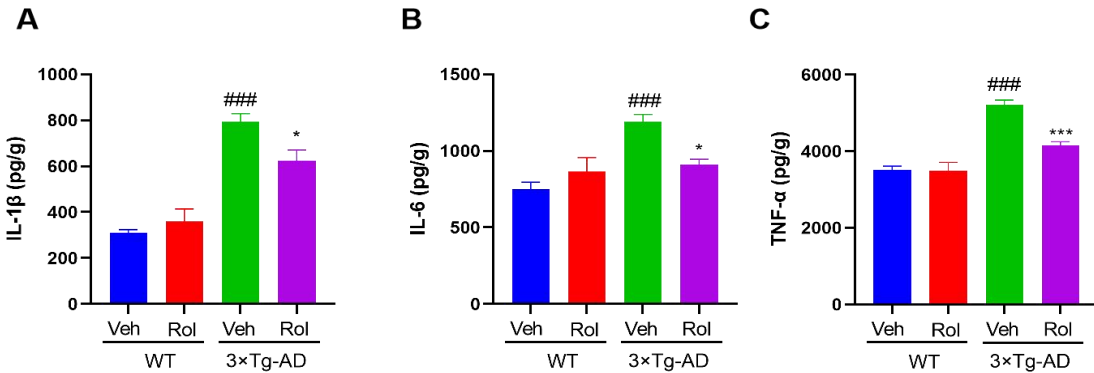
$p < 0.001$ vs. WT + Veh;
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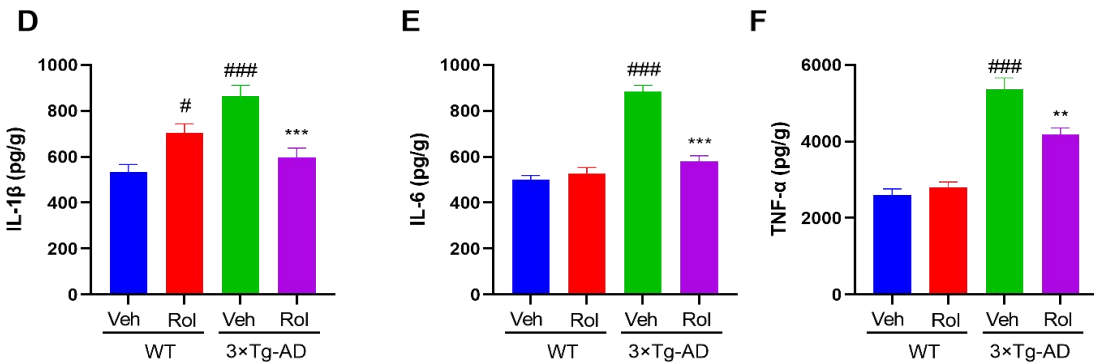
Effect of Rol on neuroinflammation in 4/10-month-old AD mice

4-month-old mice

hippocampus



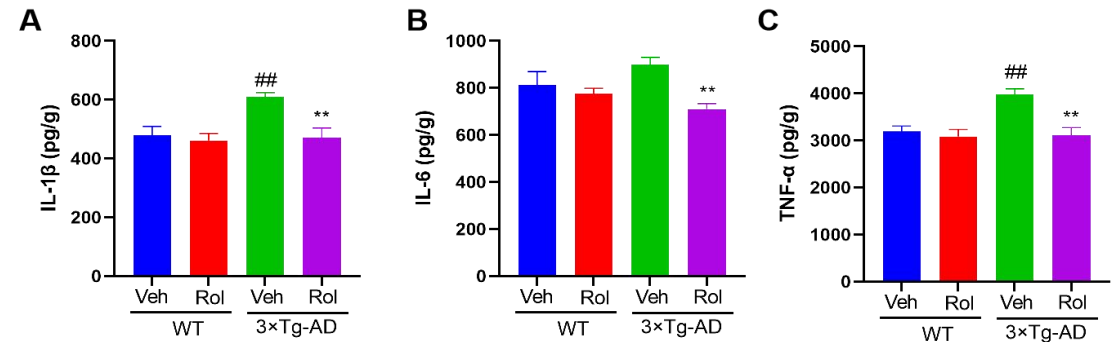
cerebral cortex



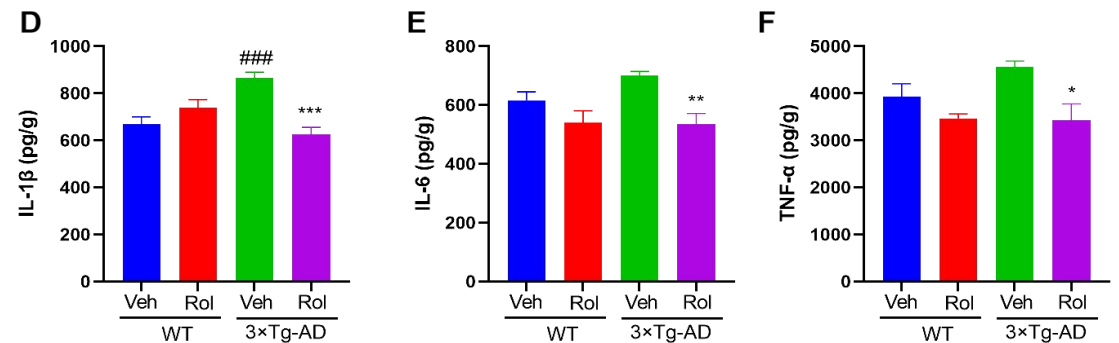
$p < 0.05$, ### $p < 0.001$ vs. WT + Veh;
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10-month-old mice

hippocampus

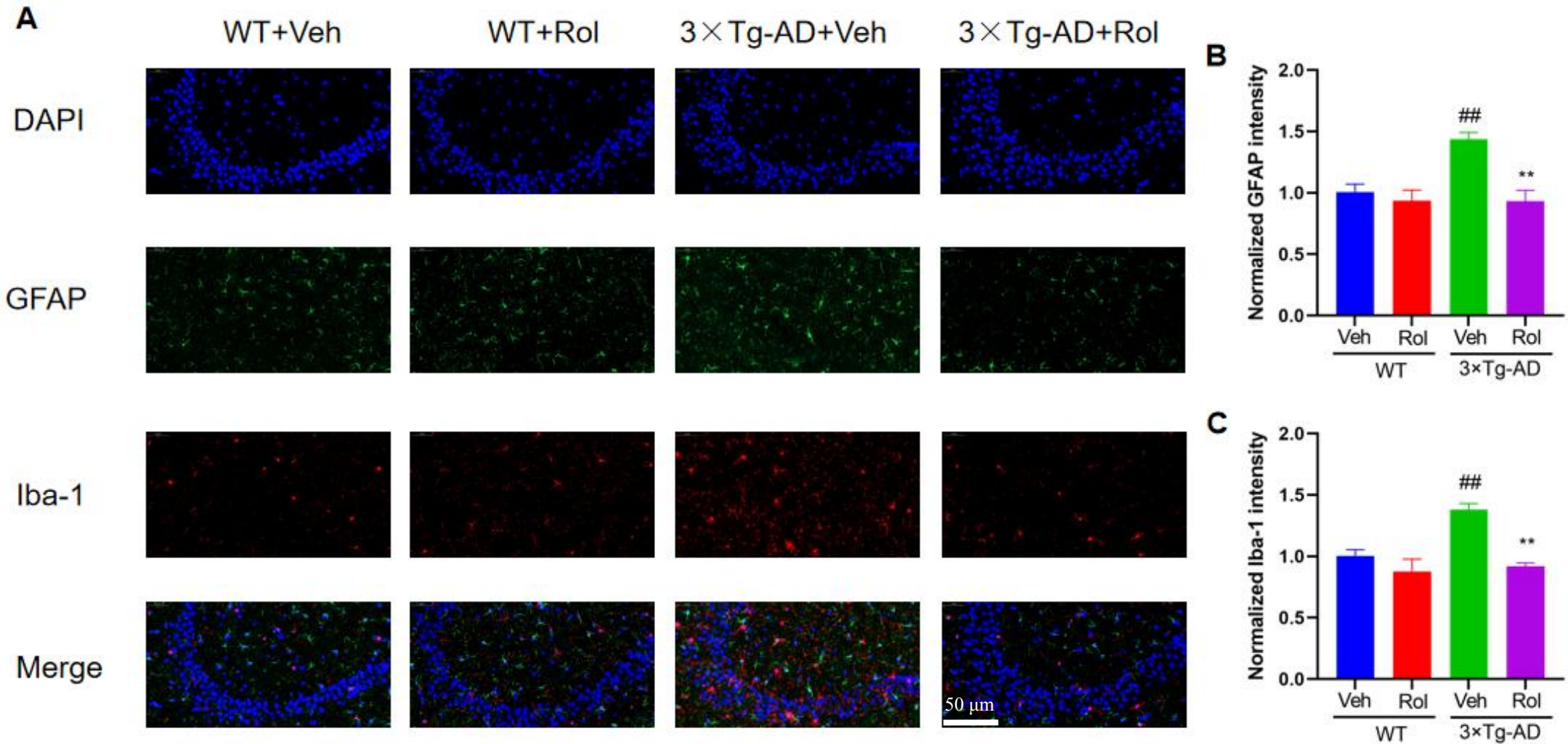


cerebral cortex



$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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Effect of Rol on neuroinflammation in 10-month-old

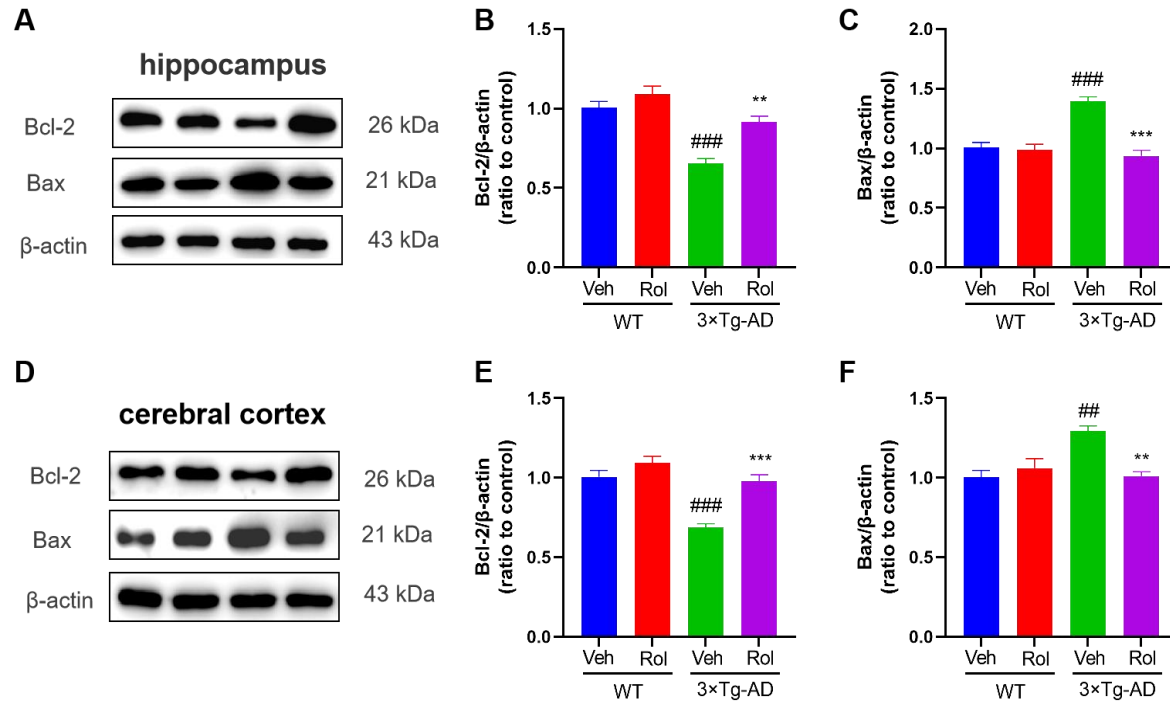


× 400 magnifications; scale bar represents 50 μ m

^{##} $p < 0.01$ vs. WT + Veh; ^{**} $p < 0.01$ vs. 3 × Tg-AD + Veh.

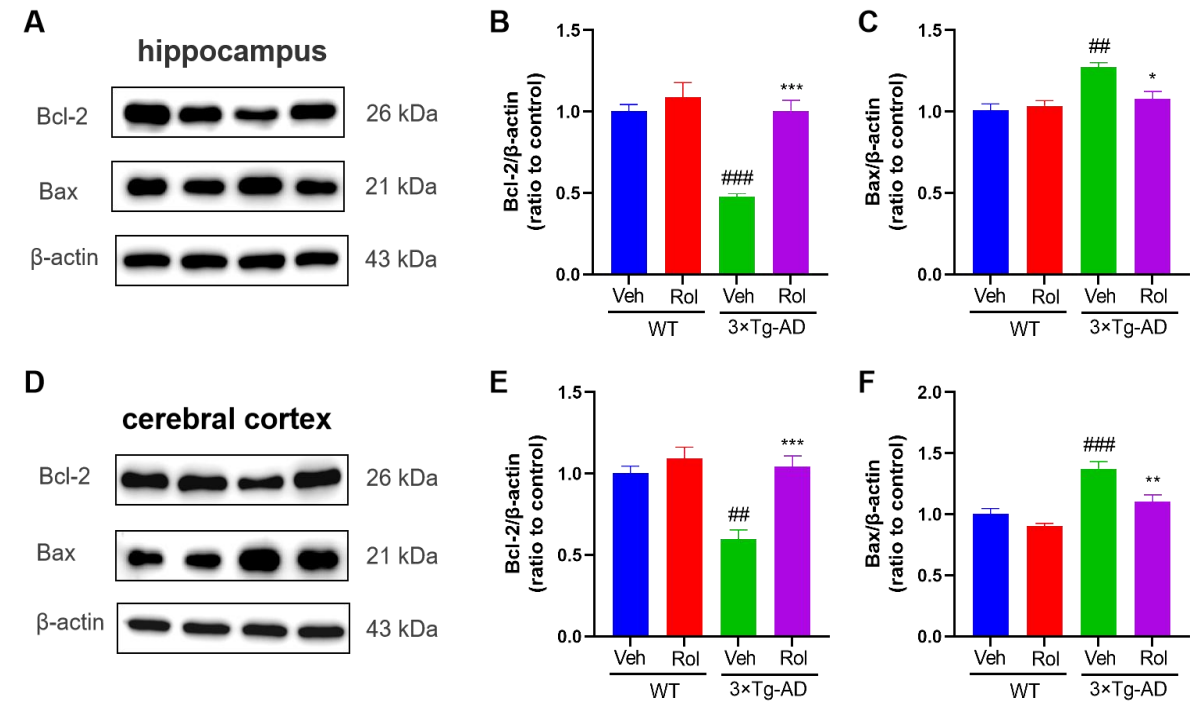
Effect of Rol on apoptosis in 4/10-month-old AD mice

4-month-old mice



$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
** $p < 0.01$, *** $p < 0.001$ vs. 3 \times Tg-AD + Veh.

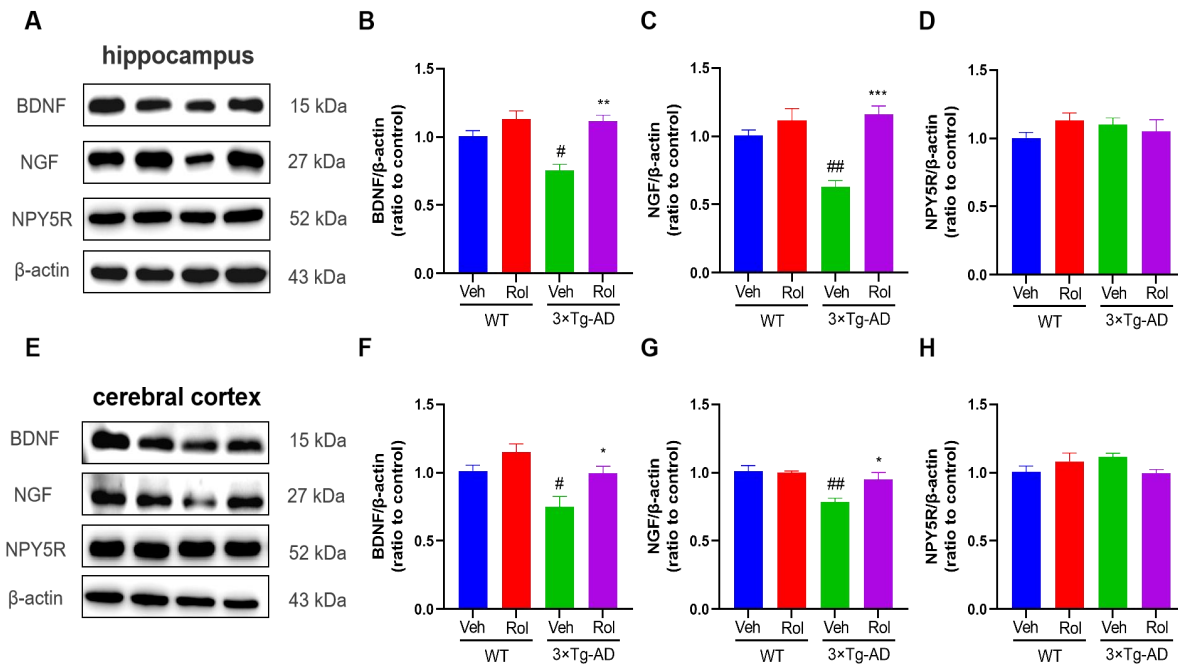
10-month-old mice



$p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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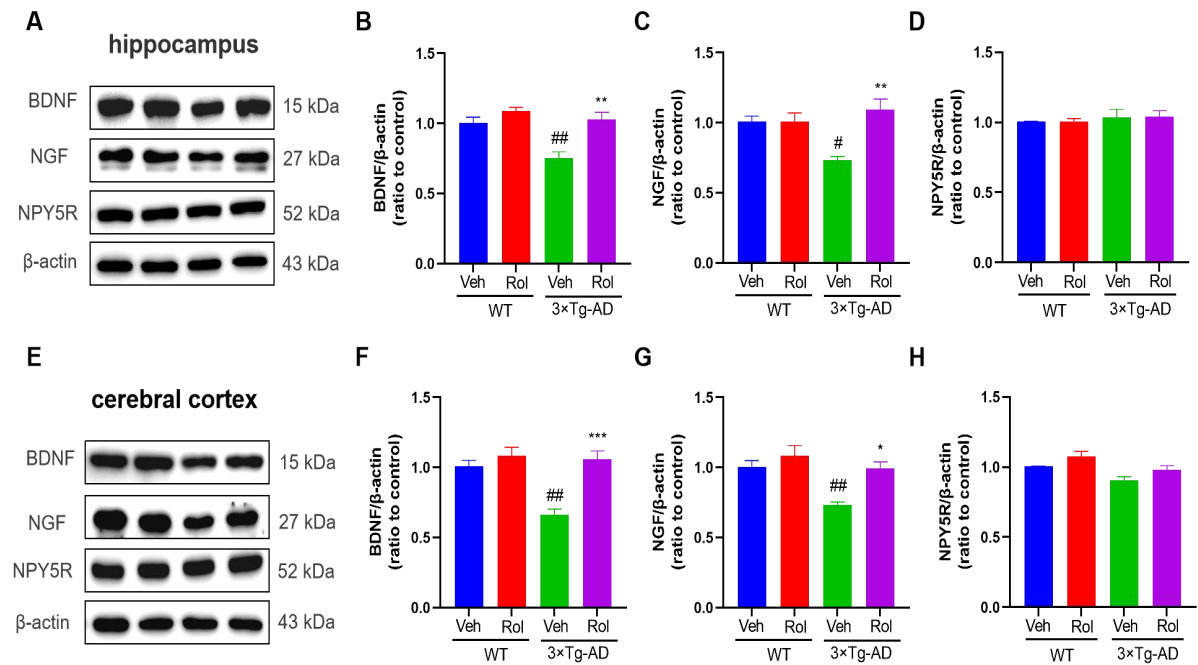
Effect of Rol on BDNF/NGF/NPY5R in 4/10-month-old AD mice

4-month-old mice



[#] $p < 0.05$, ^{##} $p < 0.01$ vs. WT + Veh;
^{*} $p < 0.05$, ^{**} $p < 0.01$, ^{***} $p < 0.001$ vs. 3 × Tg-AD + Veh.

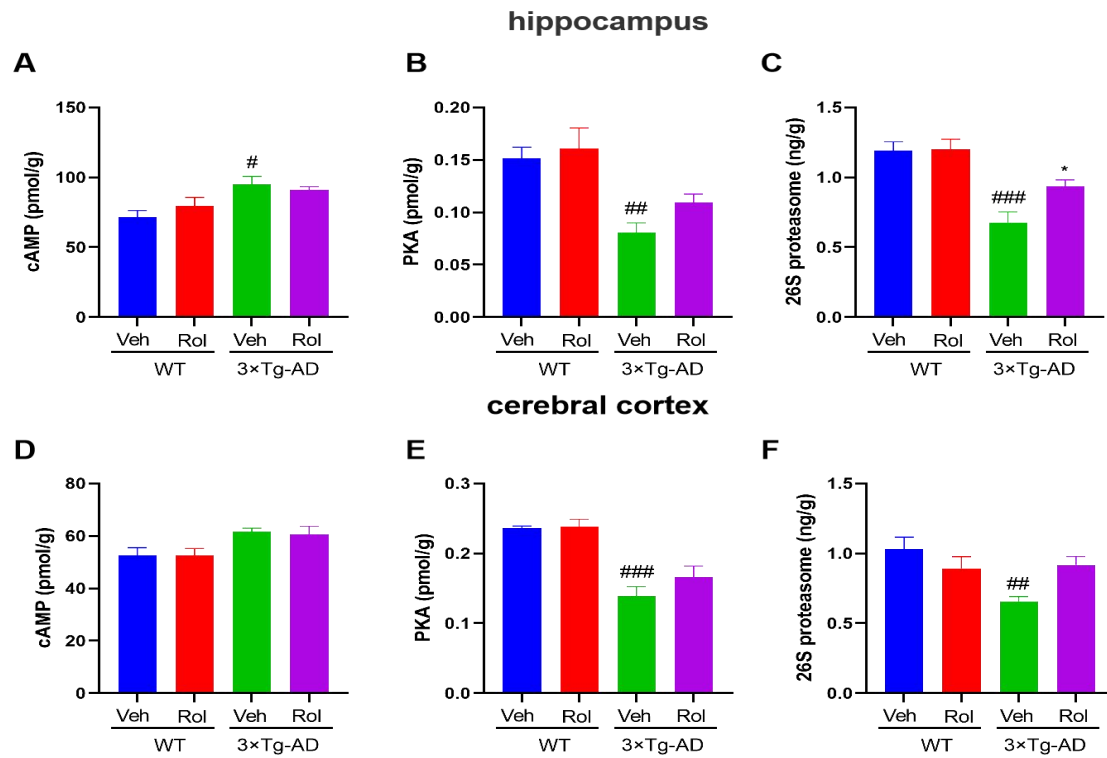
10-month-old mice



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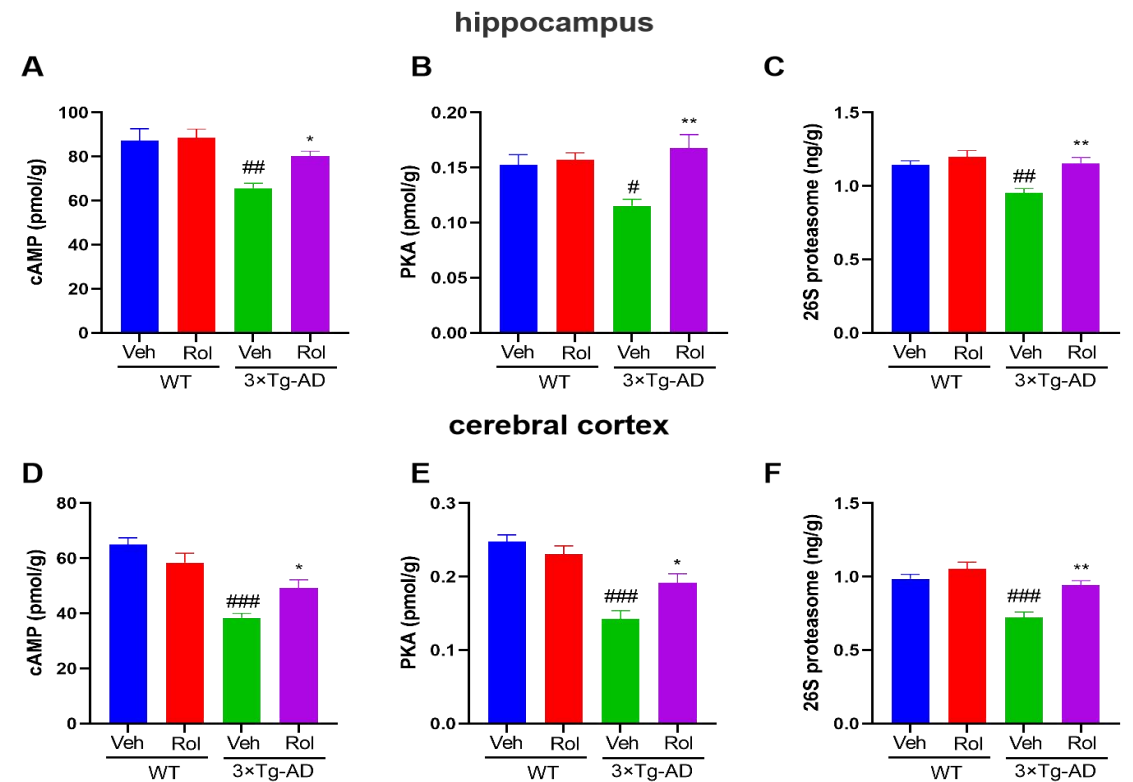
Effect of Rol on cAMP/PKA/26S signaling pathway in 4/10-month-old AD mice

4-month-old mice



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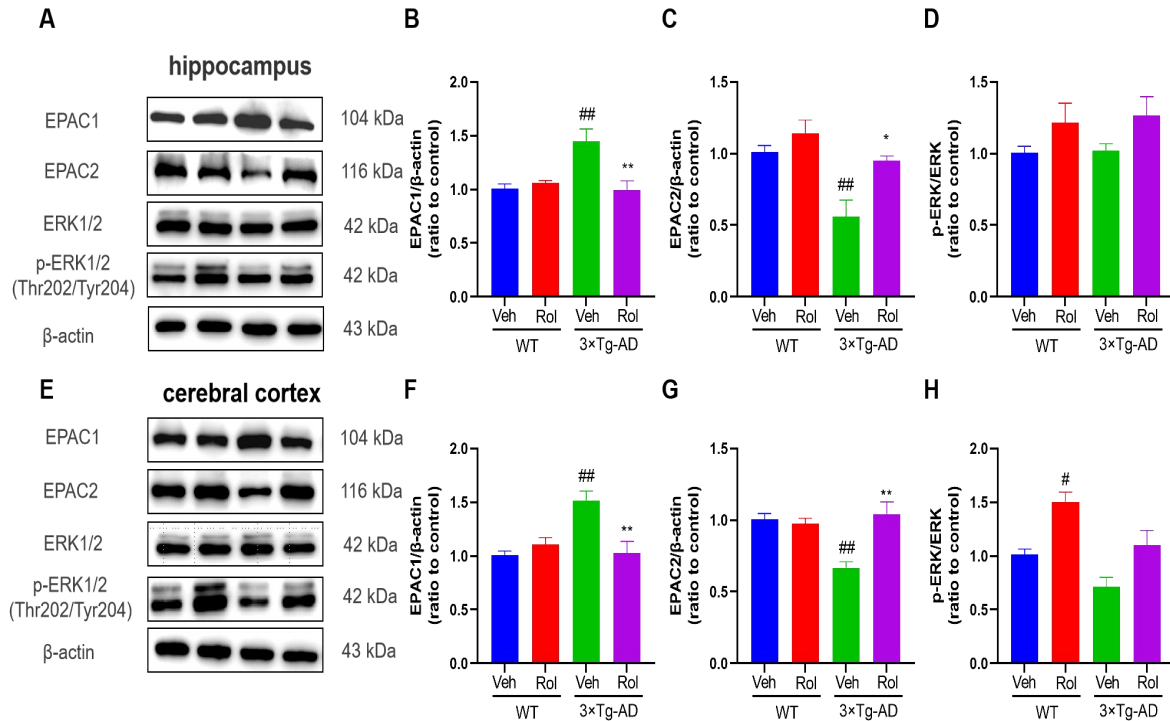
10-month-old mice



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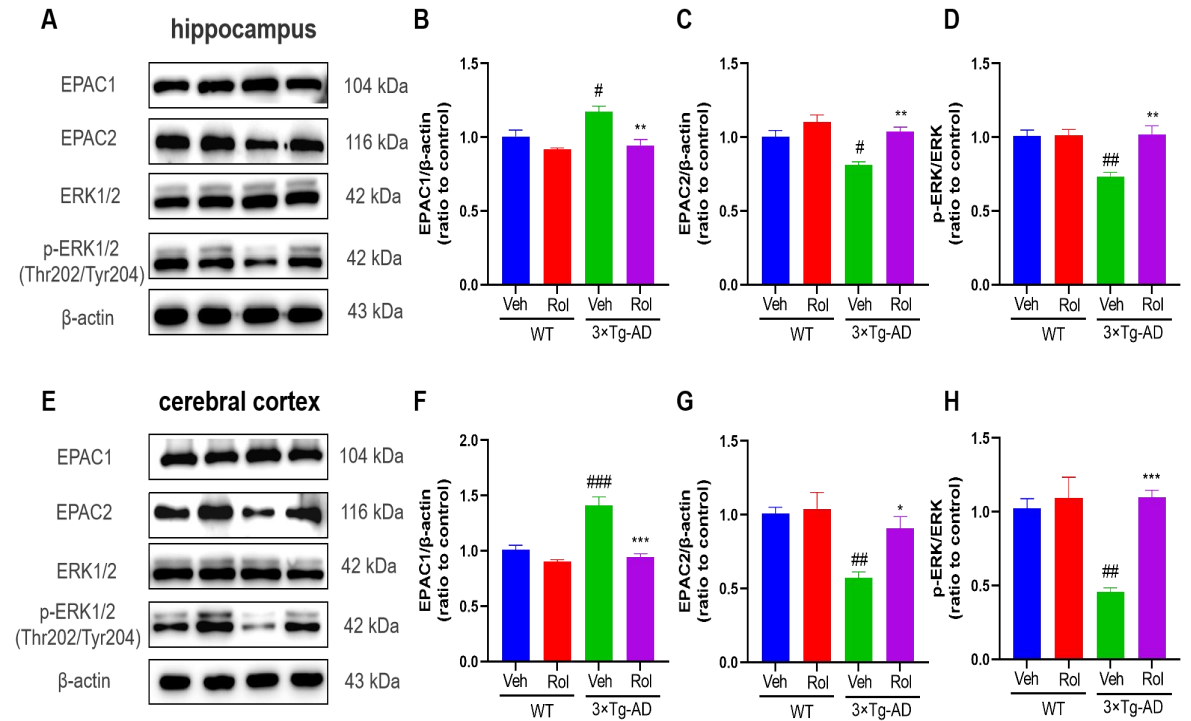
Effect of Rol on cAMP/EPAC/ERK signaling pathway in 4/10-month-old AD mice

4-month-old mice



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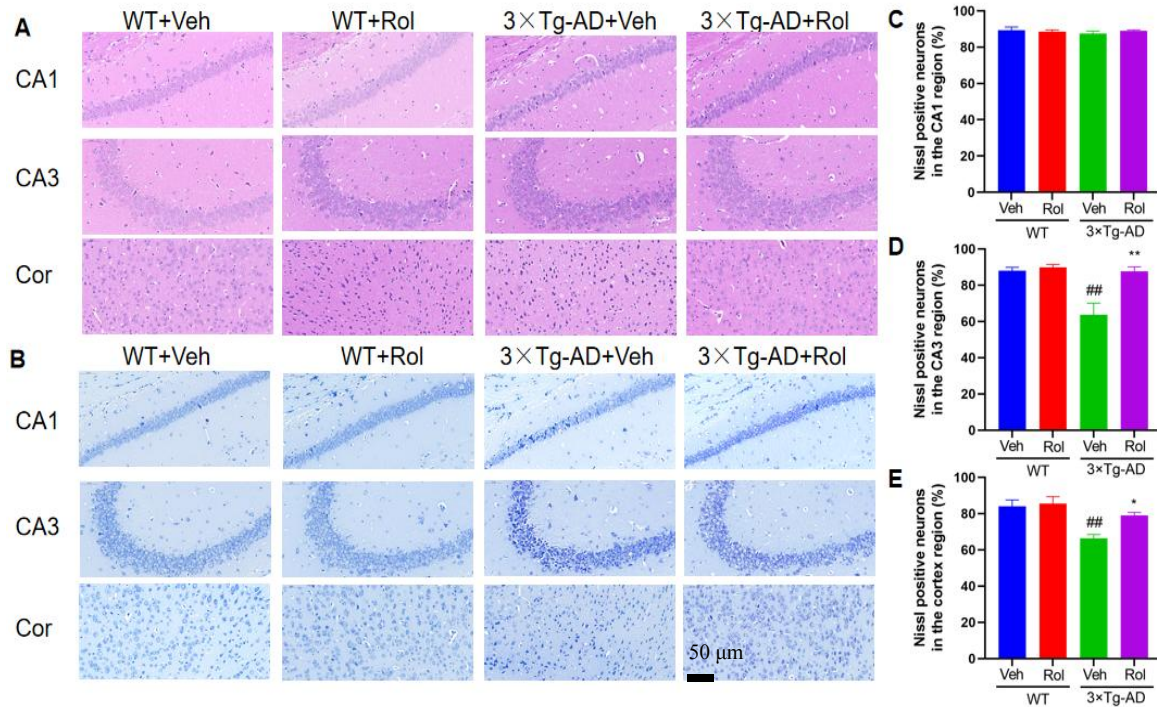
10-month-old mice



$p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs. WT + Veh;
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Effect of Rol on neuronal morphology in 4/10-month-old AD mice

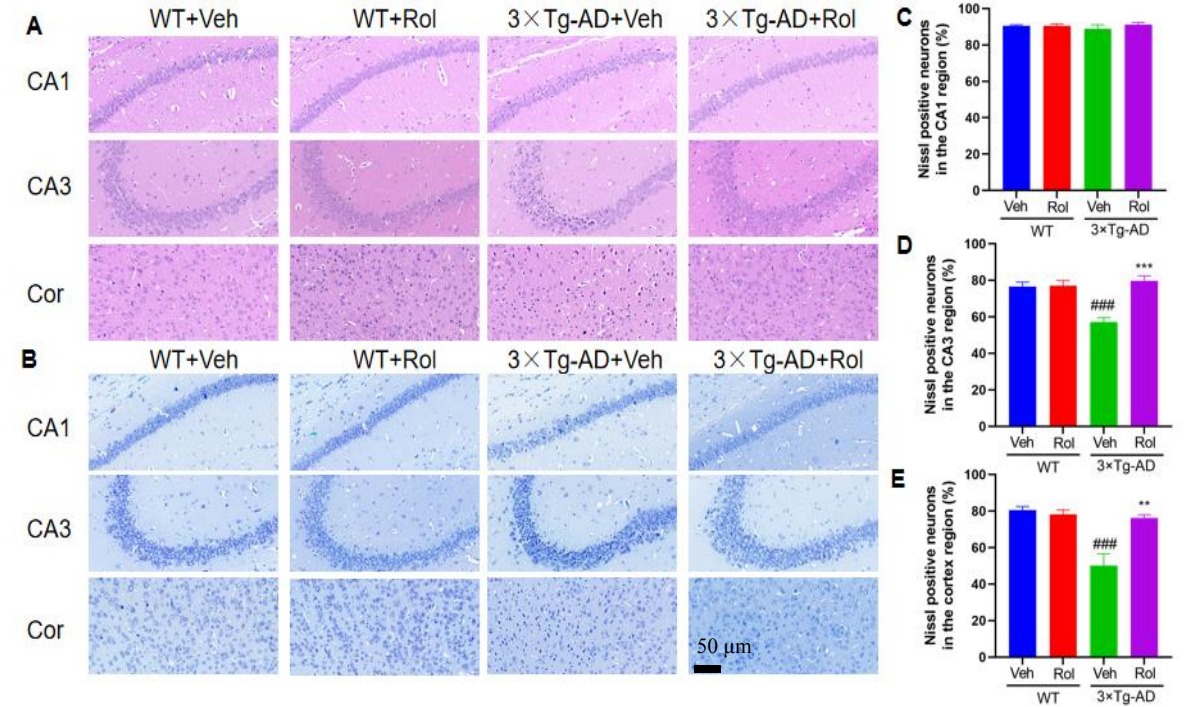
4-month-old mice



× 400 magnifications; scale bar represents 50 μm

$p < 0.01$ vs. WT + Veh; * $p < 0.05$, ** $p < 0.01$ vs. 3 × Tg-AD + Veh.

10-month-old mice



× 400 magnifications; scale bar represents 50 μm

$p < 0.001$ vs. WT + Veh; ** $p < 0.01$, *** $p < 0.001$ vs. 3 × Tg-AD + Veh.

1

Rol treatment reversed or alleviated cognitive and memory decline and anxiety-like and depression-like behaviors in 4- and 10-month-old $3 \times$ Tg-AD mice, possibly associated with the neuroprotective effects of Rol.

2

Rol treatment differentially inhibited A β deposition and Tau phosphorylation in 2-month-old, 4-month-old and 10-month-old $3 \times$ Tg-AD mice, improved neuronal environment, exerted anti-inflammatory and anti-apoptotic effects, and exerted protective effects on neurons.

3

The neuroprotective effect of Rol may be related to the inhibition of PDE4B and PDE4D-induced activation of cAMP/PKA/26S and cAMP/EPAC/ERK signaling pathways.

Shortcomings: There are multiple splice variants of PDE4B and PDE4D, and the functions of different splice variants in different brain regions need to be further investigated.

Prospects: This experiment revealed the neuroprotective mechanism of Rol in animal models of AD, providing a theoretical basis for the use of PDE4 inhibitors for the prevention and treatment of AD patients and their concomitant depression. Targeted development of efficient and low-risk PDE4 subtype-selective inhibitors will be the focus of future research.



Thanks for watching