

Administration of High-Dose Tacrolimus Impaired Hippocampal Synaptic Plasticity and Hippocampal-Dependent Memory in Male Wistar Rats

Houzhi Cheng^{1,2,3,4}, Patcharapong Pantiya^{1,2,3}, Thawatchai Khuanjing^{1,2,3}, Titikorn Chunchai^{1,2}, Hiranya Pintana^{1,2}, Chayodom Maneechote^{1,2}, Nipon Chattipakorn^{1,2,3}, Siriporn C. Chattipakorn^{1,2,5}

¹Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Chiang Mai, Thailand, ²Neurophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, ³Cardiac Electrophysiology Unit, Department of Physiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, ⁴Youjiang Medical University for Nationalities, Baise City, Guangxi, China, 533000, ⁵Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

INTRODUCTION

A calcineurin inhibitor such as tacrolimus, an immune suppressant drug, has been associated with cognitive decline in organ transplant recipients (1). Although synaptic plasticity is essential for cognitive function, its alteration following tacrolimus administration remains poorly characterized. Therefore, this study aimed to evaluate the effects of tacrolimus on synaptic plasticity and cognitive function in normal rats, with a focus on calcineurin-related signaling and synaptic protein alterations.

Reference 1. Golenia A, et al. Cognitive Impairment and Anxiety Are Prevalent in Kidney Transplant Recipients. *Kidney & blood pressure research*. 2023;48(1):587-95.

METHODS

Thirty-four-week-old rats
(n=32)

Vehicle
Olive oil

Low-dose
tacrolimus
0.5 mg/kg/day

Medium-dose
tacrolimus
1.0 mg/kg/day

High-dose
tacrolimus
2.0 mg/kg/day

Cognitive test
NOLT and NORT

Sacrifice

Synaptic function
Ex vivo recording

Protein expression
Immunoblotting

Thirty-four-week-old male Wistar rats received either vehicle (olive oil, s.c.) or tacrolimus at doses of 0.5, 1.0, or 2.0 mg/kg/day (s.c.) for 2 weeks. Cognitive performance was assessed using the novel object location and novel object recognition (NOL and NOR) tests. One day later, rats were euthanized, and the left and right hippocampi were collected for ex vivo long-term potentiation (LTP) recordings and immunoblotting analysis, respectively.

ACKNOWLEDGEMENTS

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CONTACT



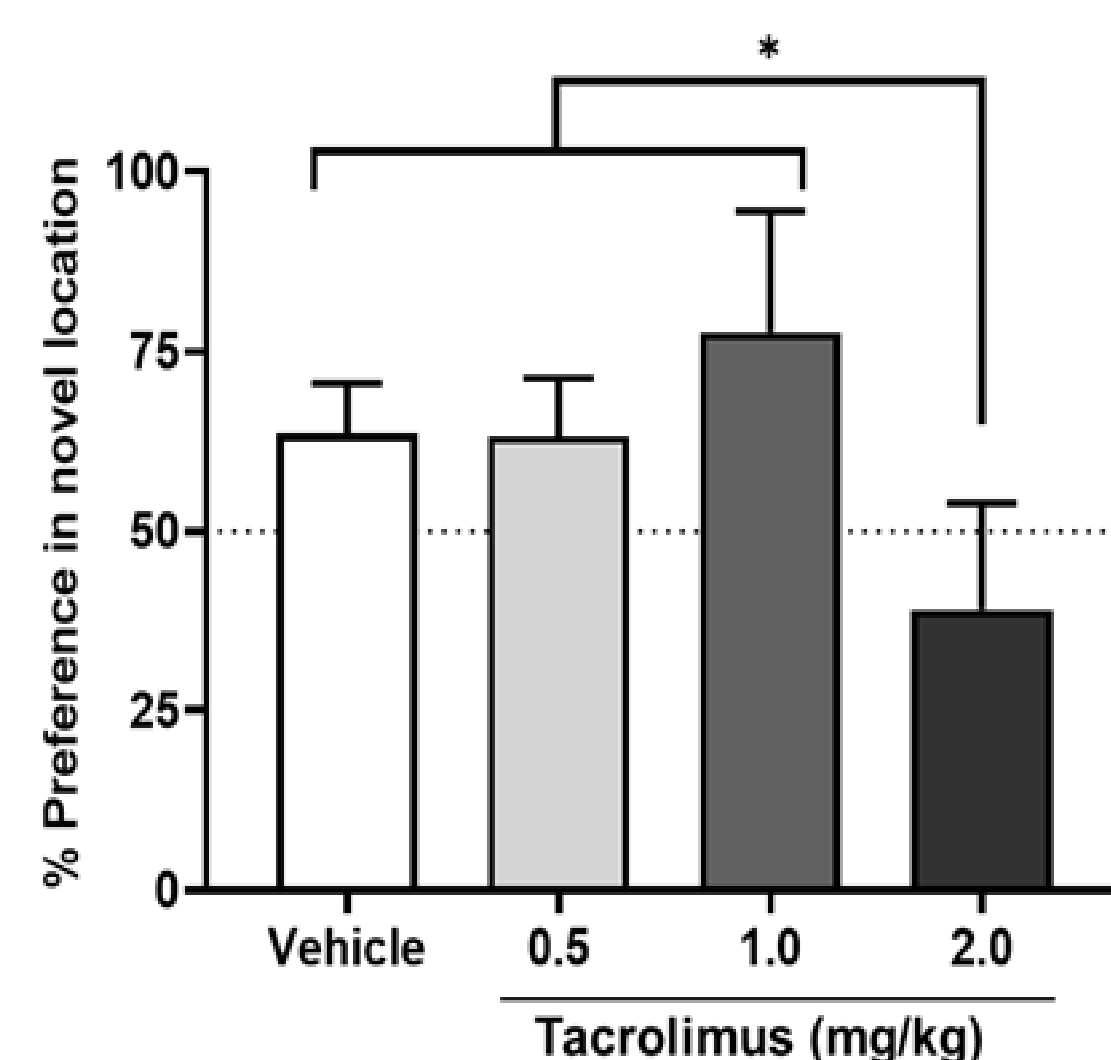
Houzhi Cheng, MS.
Neurophysiology Unit,
Cardiac Electrophysiology Research and Training Center,
Faculty of Medicine,
Chiang Mai University, Thailand
Email: Houzhi_cheng @cmu.ac.th

RESULTS

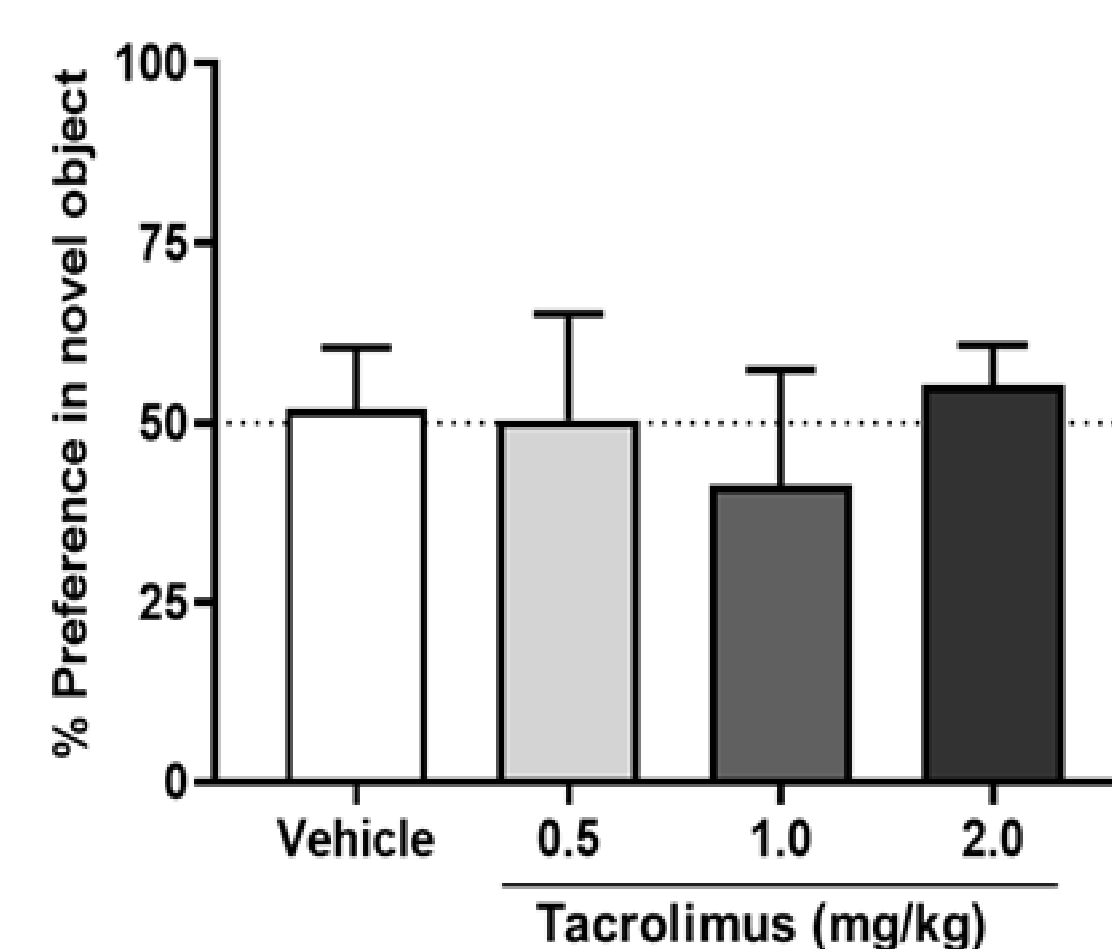
Cognitive behavior

High-dose tacrolimus significantly reduced preference for the novel location, indicating impaired hippocampus-dependent spatial memory. In contrast, preference for the novel object did not differ among groups, suggesting preserved recognition memory.

Spatial memory



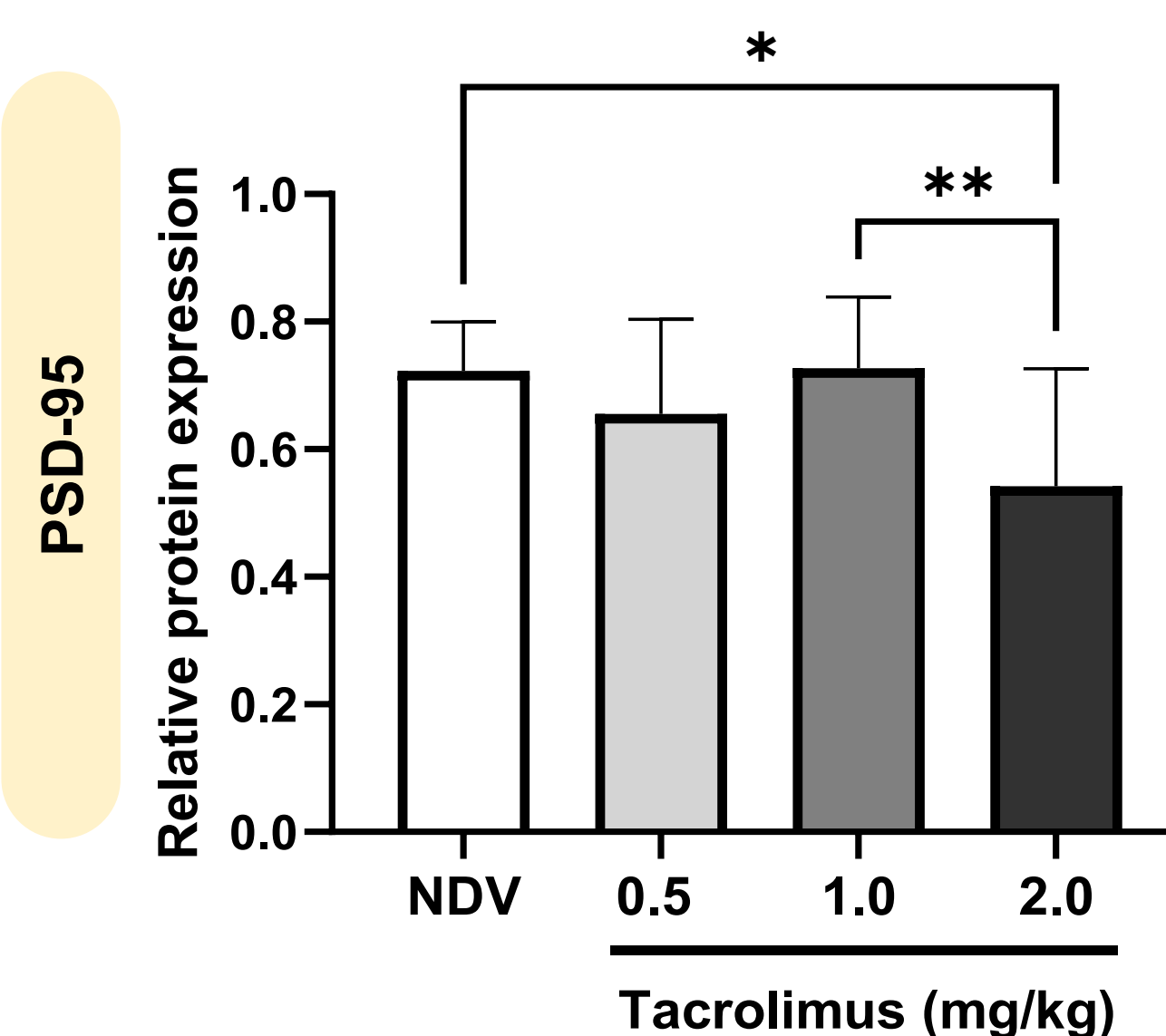
Recognition memory



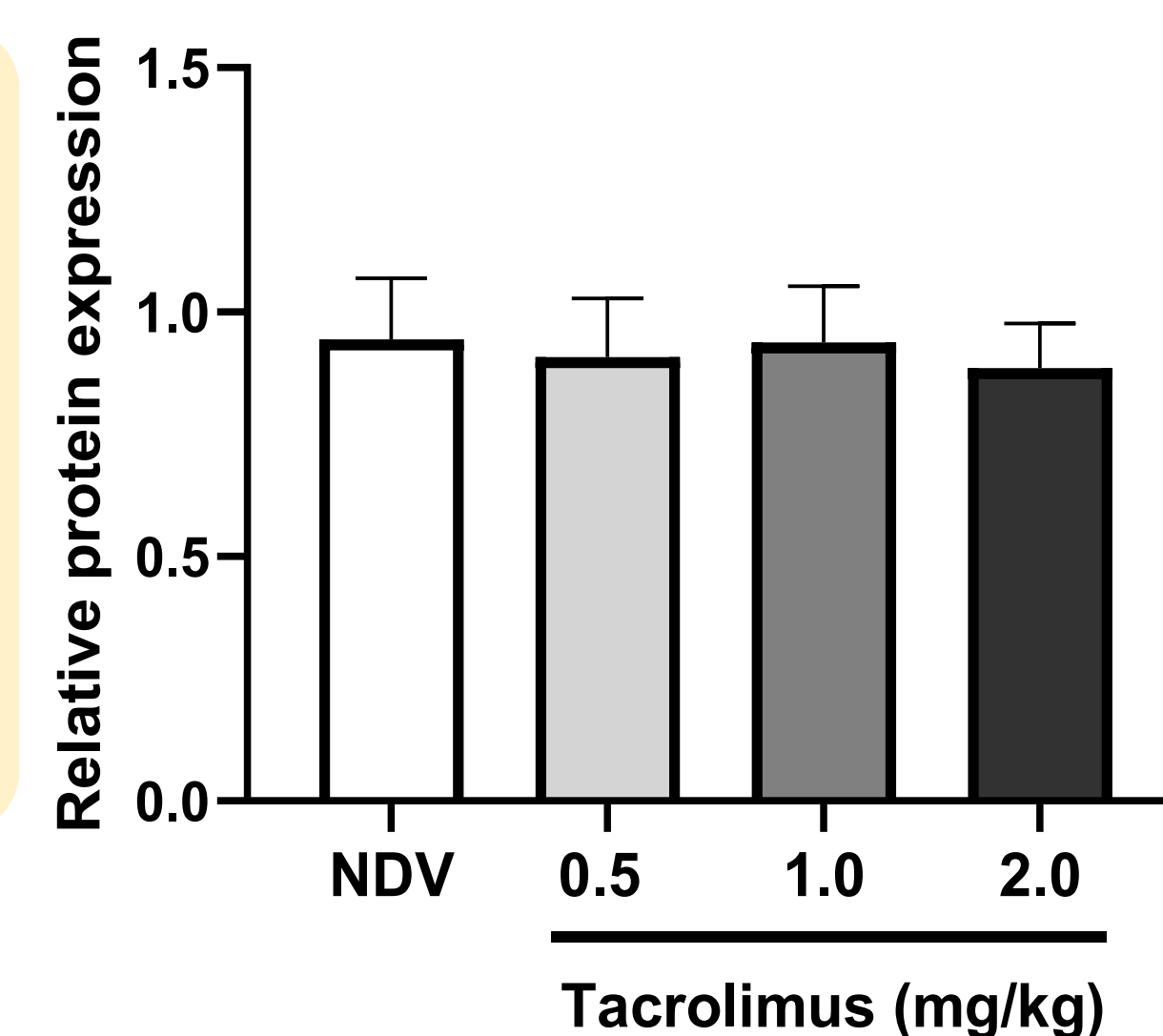
Synaptic and calcineurin related molecules

PSD-95 protein expression was significantly reduced in the high-dose tacrolimus group compared with the vehicle group. Although calcineurin protein expression remained unchanged, FKBP12 expression was significantly increased in all tacrolimus-treated groups.

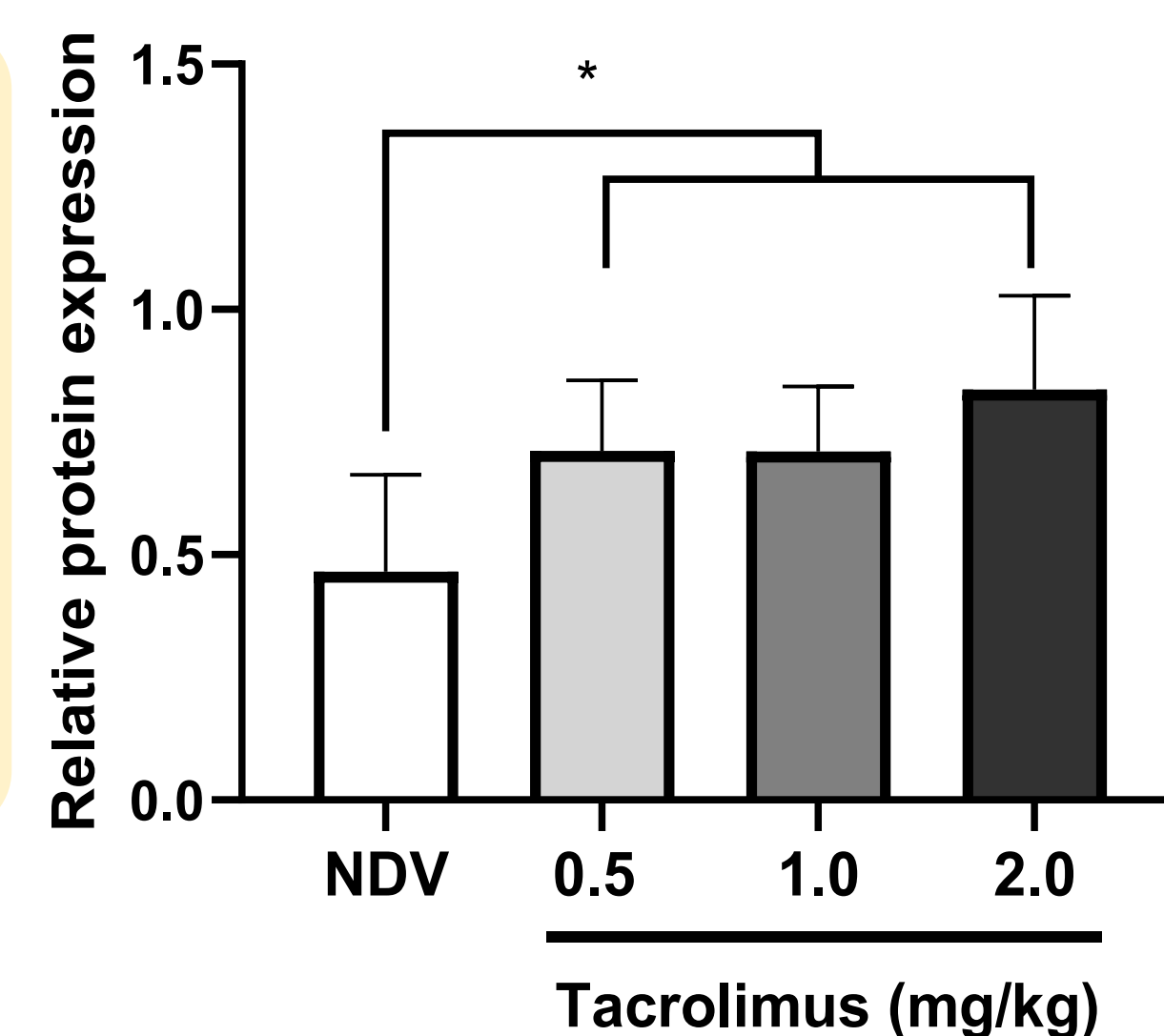
Post-synaptic protein



Calcineurin



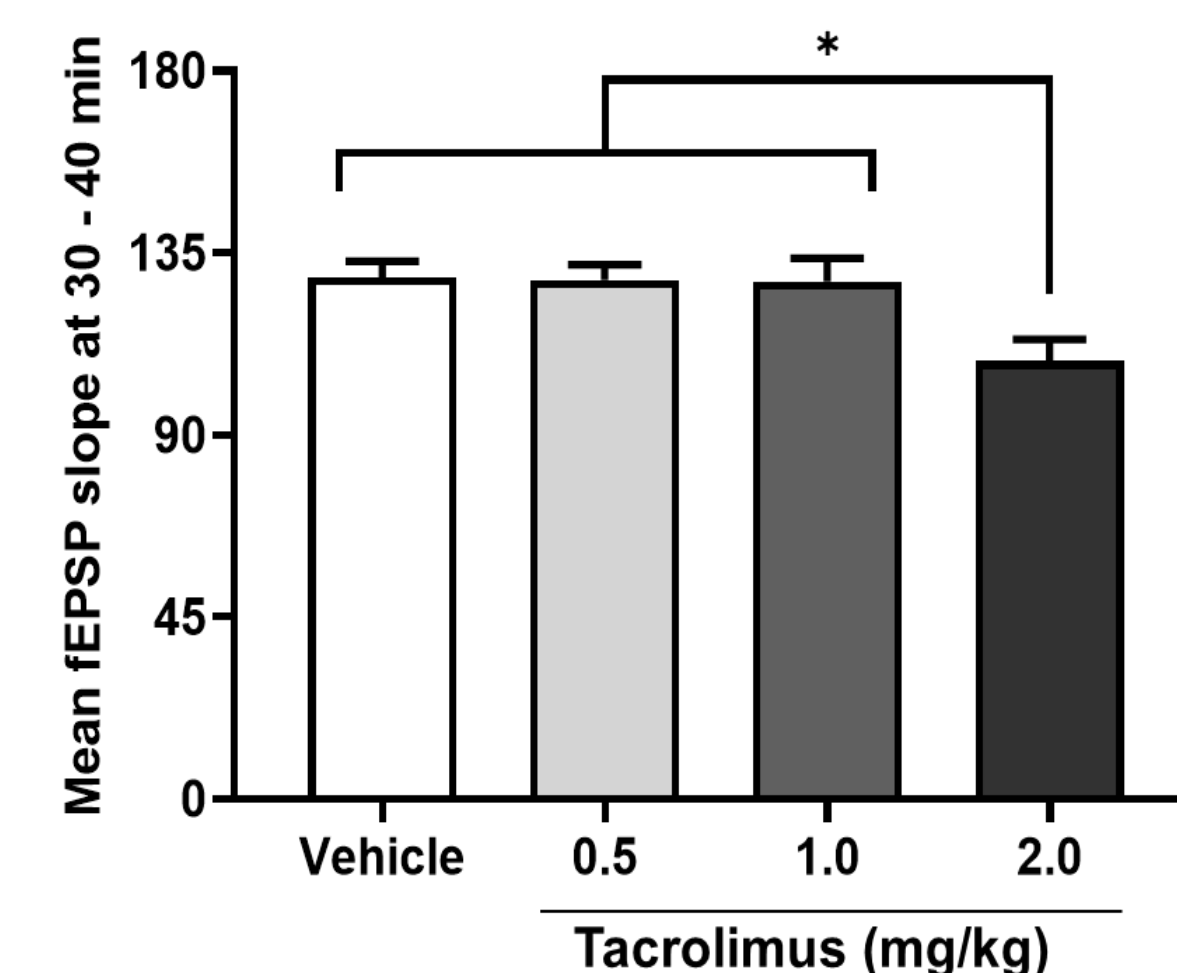
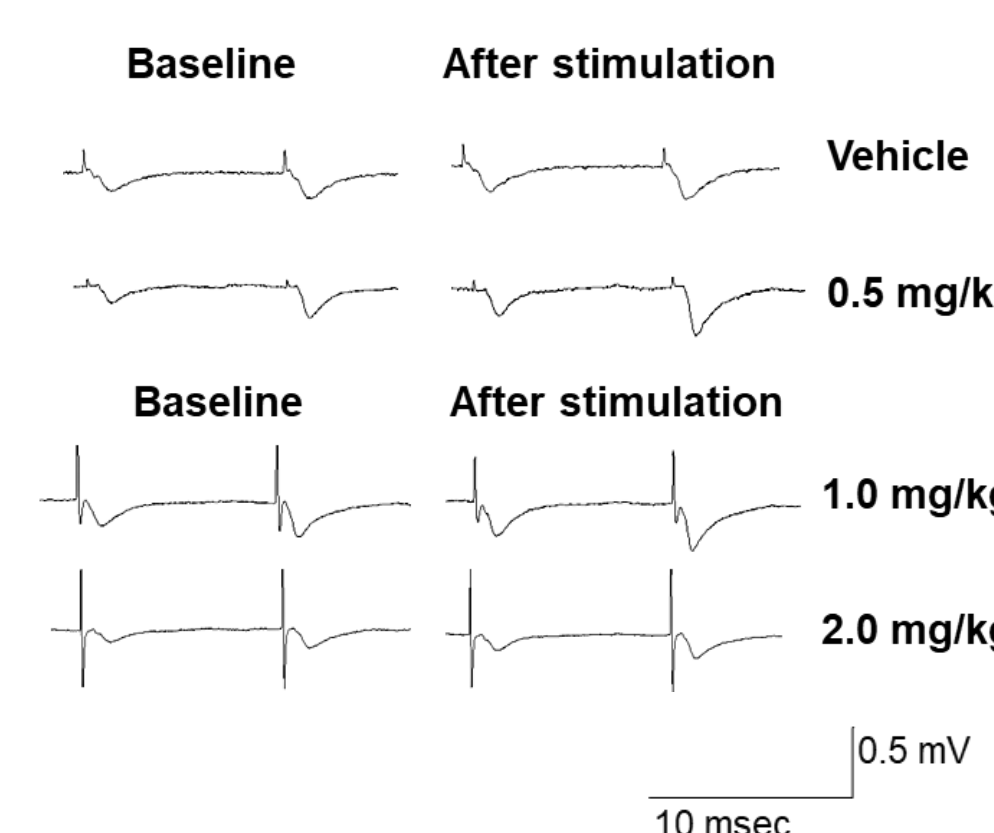
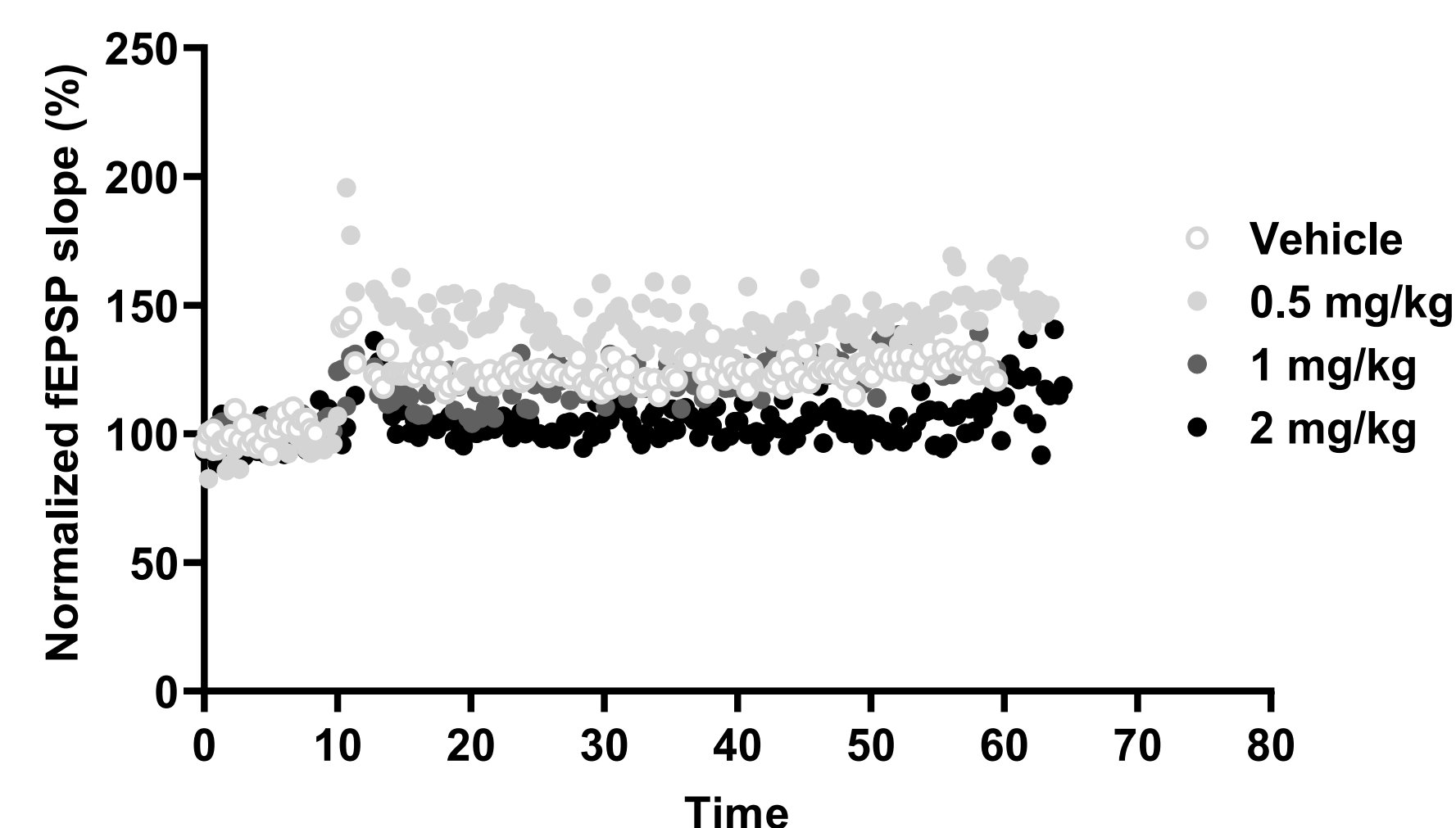
FKBP12



Synaptic plasticity

High-dose tacrolimus markedly reduced the field excitatory postsynaptic potential (fEPSP) slope compared with other groups, indicating impaired synaptic plasticity.

Electrophysiological detection of LTP



CONCLUSION

High-dose tacrolimus impaired hippocampal synaptic plasticity and spatial memory in rats, accompanied by changes in calcineurin-associated pathways. The findings underscore the importance of optimizing tacrolimus dosing and developing targeted strategies to mitigate neurotoxicity while preserving its immunosuppressive efficacy in clinical settings.