



Tacrolimus Induces Anxiety- and Depression-Like Behaviors Via Suppressed Hippocampal Serotonin and Dopamine Release in Rats

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Tacrolimus (TAC) is widely used after organ transplantation, yet its effects on mood-related behaviors remain unclear. This study shows that two-week tacrolimus treatment induces anxiety- and depressive-like behaviors in normal rats without affecting locomotion, accompanied by reduced ventral hippocampal serotonin and dopamine release. These findings suggest impaired monoaminergic neurotransmission as a mechanism underlying tacrolimus-related neuropsychiatric adverse effects.

INTRODUCTION

Tacrolimus (TAC), a calcineurin inhibitor, is widely used as an immunosuppressant in patients undergoing organ transplantation (1). Growing evidence suggests that TAC administration is associated with the development of neurological complications particularly cognitive impairment (2). However, the effects of tacrolimus on anxiety- and depression-like behaviors and associated serotonergic and dopaminergic neurotransmitter release remain unclear.

Objective

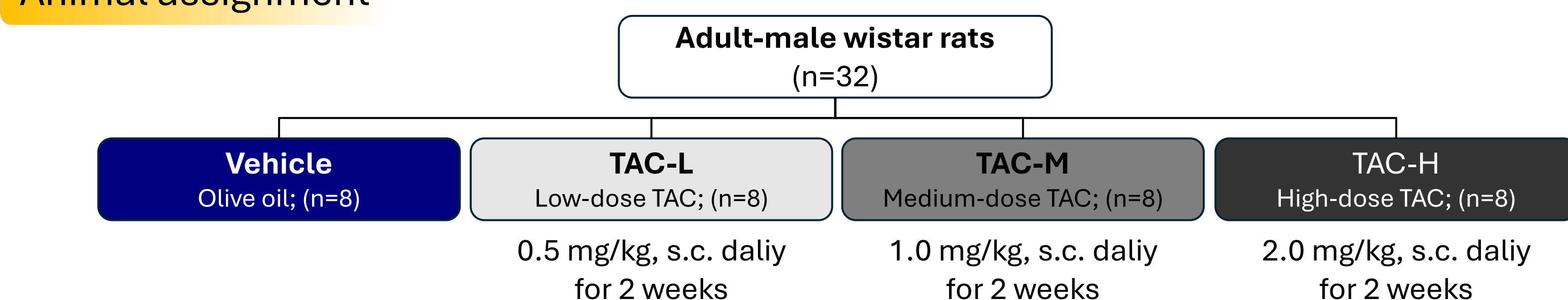
To investigate the effects of TAC administration on anxiety- and depression-like behaviors, as well as associated neurotransmitters release

References

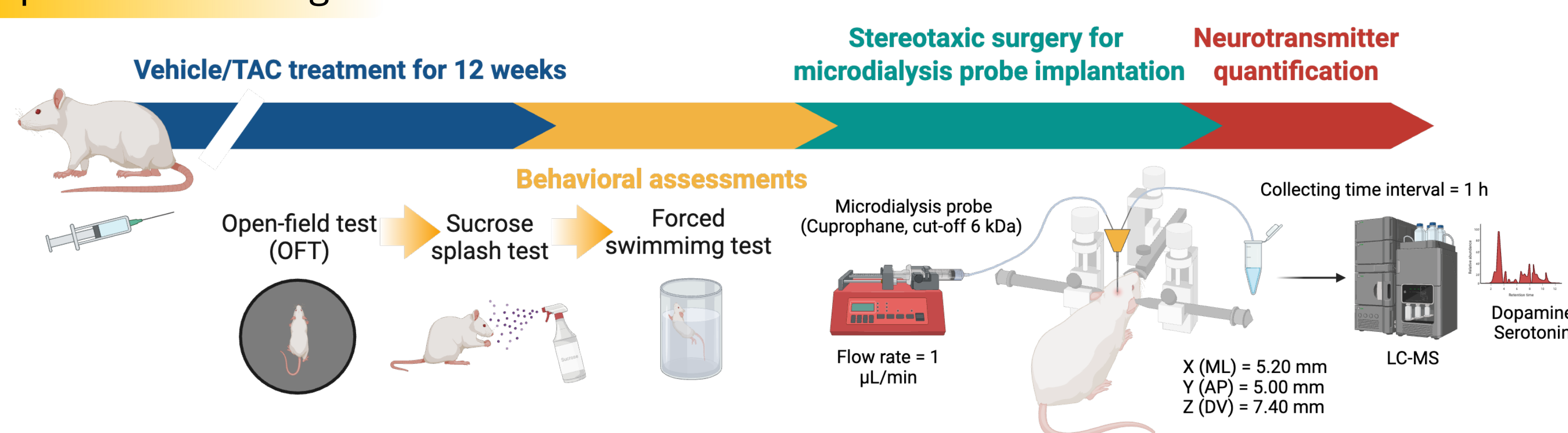
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METHODS

Animal assignment



Experimental design



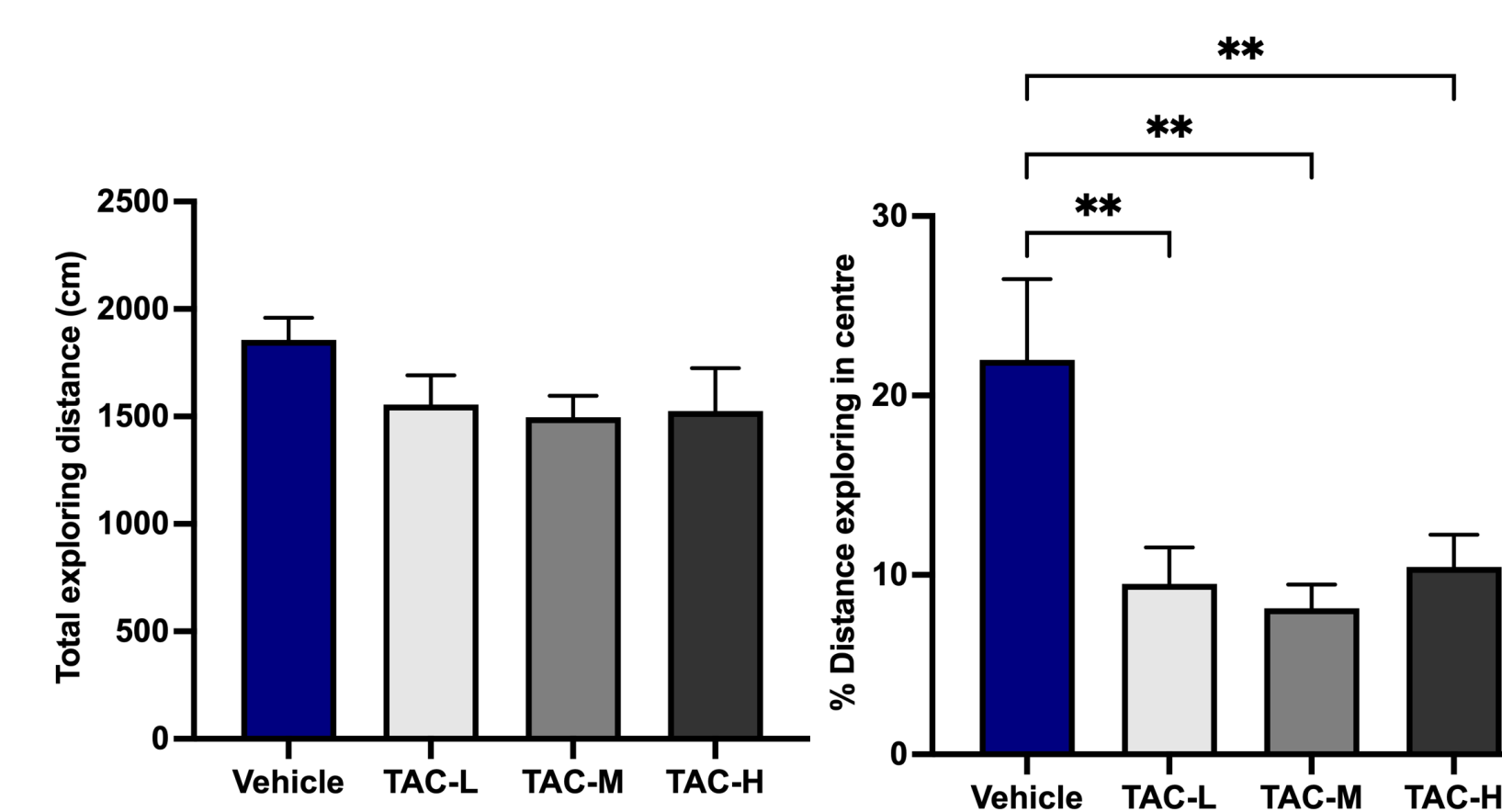
Adult male Wistar rats received either vehicle (olive oil, s.c.) or TAC at doses of 0.5, 1.0, or 2.0 mg/kg/day (s.c.) for 2 weeks. At the end of the treatment period, behavioral assessments were conducted, including the open-field test, sucrose splash test, and forced swimming test. Subsequently, rats were implanted with a microdialysis probe targeting the ventral hippocampus (AP; 5.00, ML; -5.20, DV; -7.40). Dialysate samples were collected at a flow rate of 1 µL/min and quantified using LC-MS analysis.

RESULTS

Anxiety-like behavior

TAC treatment at all doses did not alter overall locomotor activity, as total distance traveled in the open-field test was unchanged. In contrast, TAC at all doses significantly reduced center exploration, indicating increased anxiety-like behavior.

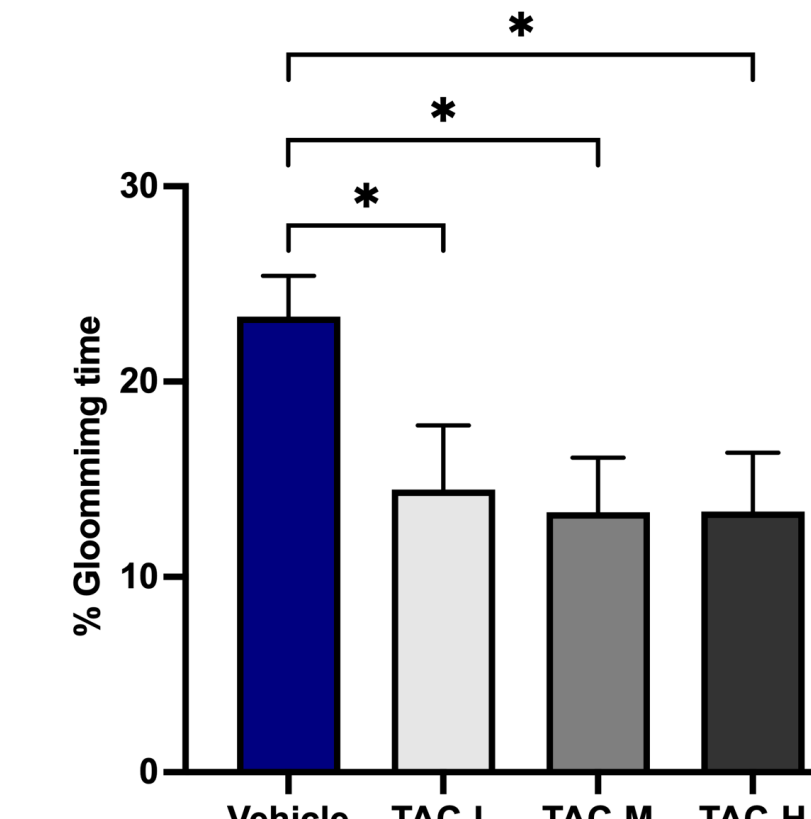
Open-field test



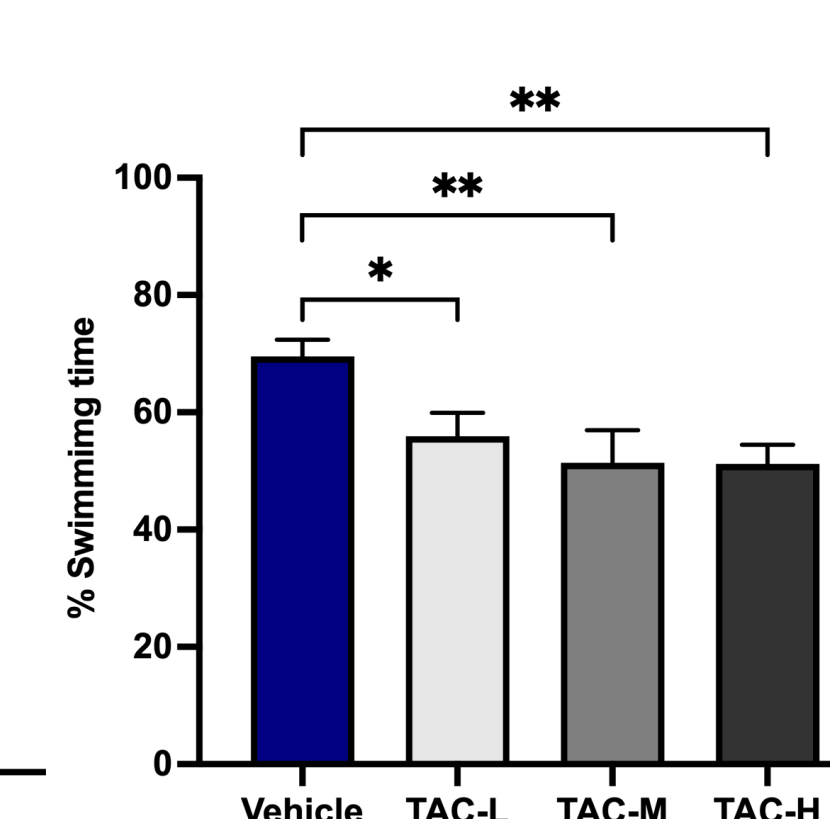
Depression-like behavior

TAC at all doses significantly reduced center exploration, indicating increased anxiety-like behavior. Depressive-like behaviors were also found, as shown by decreased % grooming time in the sucrose splash test and increased % swimming time in the forced swimming test.

Sucrose splash test



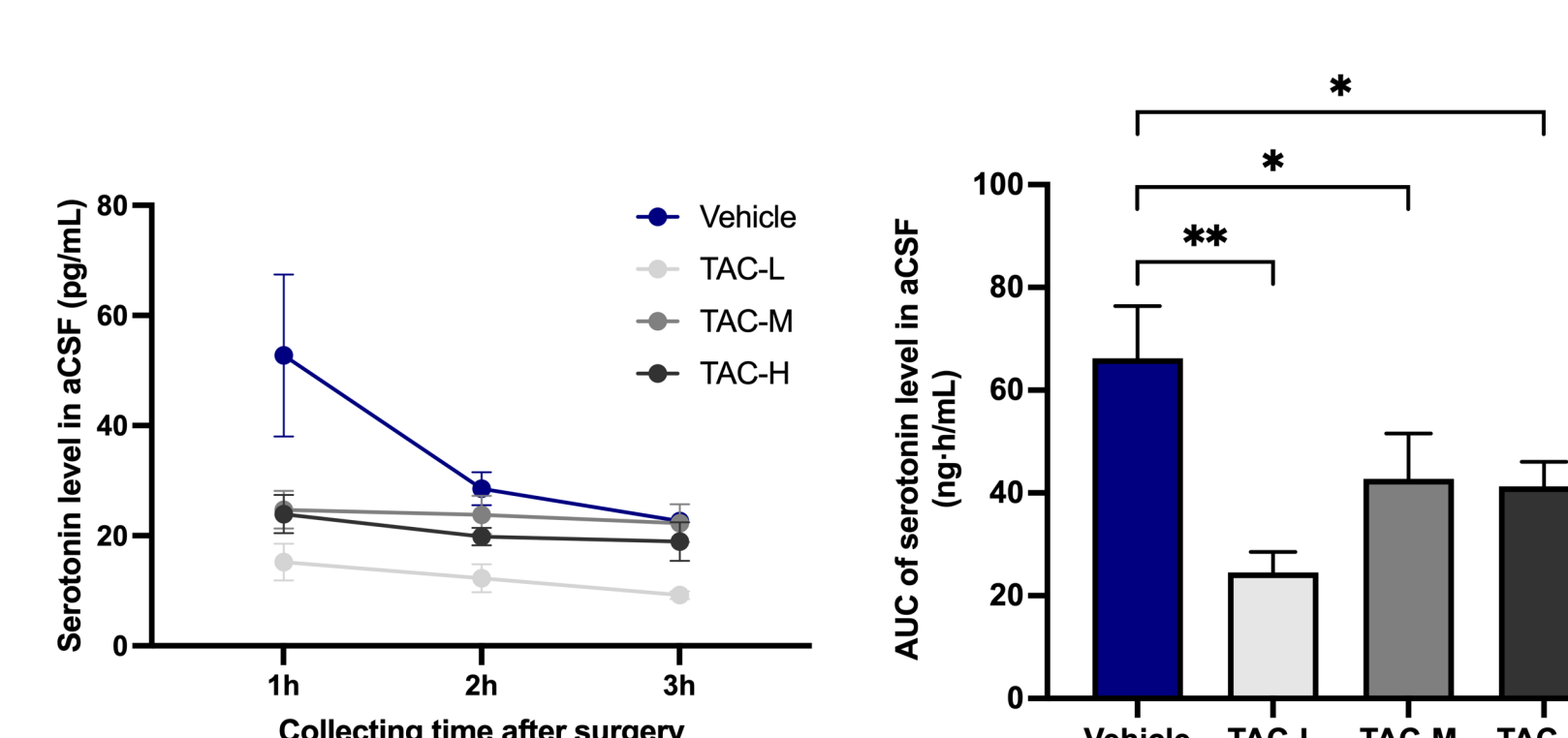
Forced swimming test



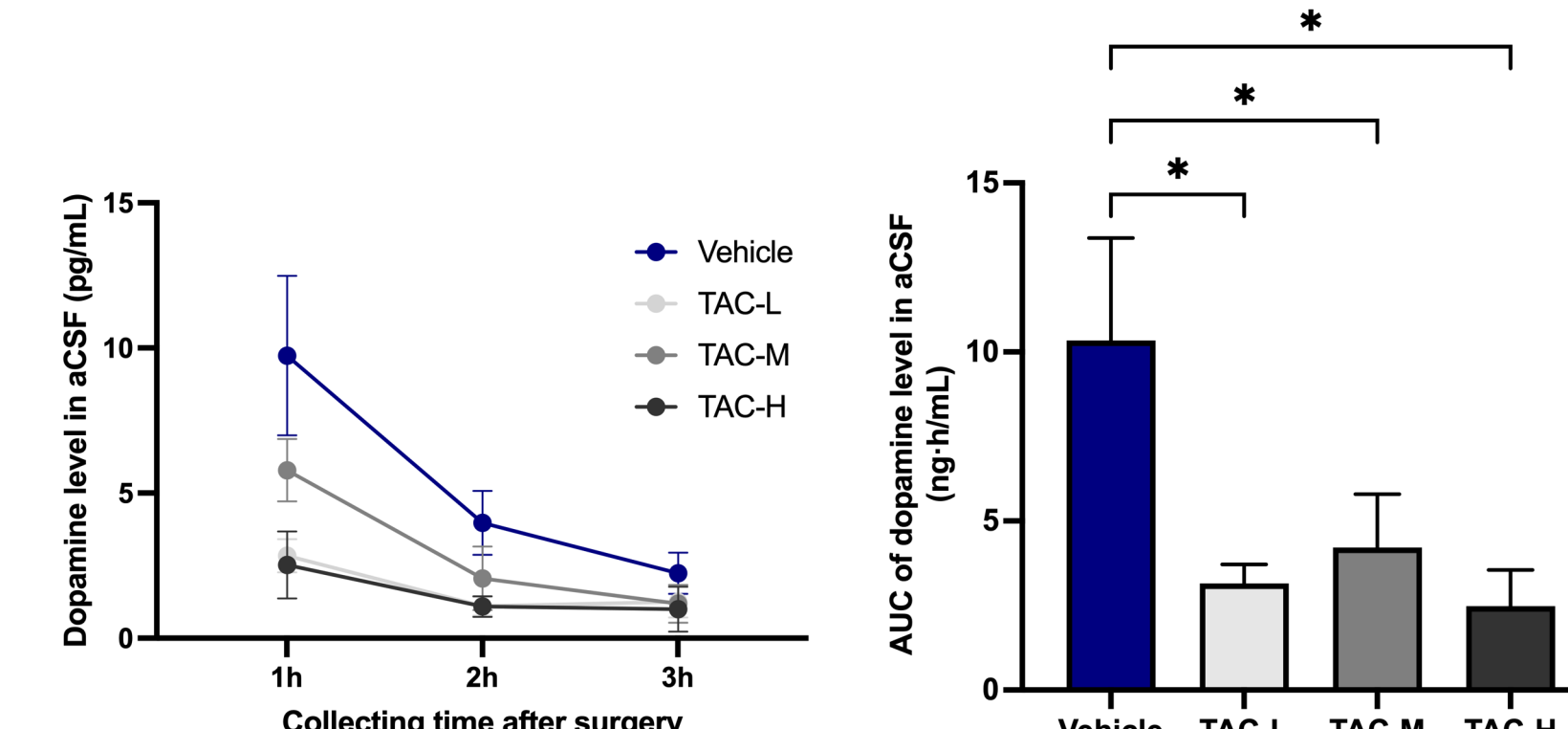
Extracellular neurotransmitter levels

Microdialysis experiment revealed that all doses of TAC markedly reduced extracellular serotonin and dopamine levels across sampling time points, with corresponding decreases in the area under the curve for both neurotransmitters.

Extracellular serotonin levels



Extracellular dopamine levels



CONCLUSION

TAC administration induces behavioral deficits associated with reduced central serotonergic and dopaminergic neurotransmission in a dose-independent manner, highlighting a potential neurobiological mechanism underlying TAC-related neuropsychiatric adverse effects and its clinical significance for mood disturbances in patients receiving calcineurin inhibitor.

ACKNOWLEDGEMENTS



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