

Establishment of an evaluation system using the social defeat stress model

○ Chika Nagao, Masana Kamioka, Kounosuke Sakima, Yoshiyuki Hayashida, Takashi Tashiro, Kousuke Morizumi, Katsuhide Nishi, Naoyuki Hironaka

Research Unit I, Drug Discovery Innovation Center, Non-clinical Business Segment, Mediford corporation

Summary in Japanese

社会的敗北ストレスモデルとは、他個体から継続的に身体的・精神的攻撃を受けることにより、ヒトのうつ病と同様の身体的変化や精神症状、社会的忌避行動等を示すモデルである。本研究では、社会的敗北ストレスモデルを作製し、ケタミンの治療効果を評価した。社会的敗北ストレスモデルは、C57BL/6J マウスを ICR マウスのテリトリーに導入し、ICR マウスから 10 分間攻撃を受けさせる操作を 10 日間実施することで作製した。モデル作製終了翌日に社交性テストを実施し、そのスコアを指標に群分けを行った。社交性テストの翌日よりテールサスペンションテスト（TST）、強制水泳試験（FST）、ショ糖嗜好性テスト（SPT）および臓器重量の測定を実施した。その結果、媒体対照群では正常群と比較して、強制水泳における無動時間の延長、ショ糖嗜好性の低下が確認された。また、臓器重量では副腎の肥大および胸腺の萎縮が確認された。このモデル動物に対するケタミンの効果を検討した結果、ケタミン投与によって強制水泳における無動時間の延長およびショ糖嗜好性の低下が改善され、胸腺の萎縮が抑制された。これらの結果より、社会的敗北ストレスモデルを用いた評価系が確立され、ケタミンの抗うつ効果が示された。

Objective

A social defeat stress animal model, induced by receiving continuous physical and mental aggression from other individuals, shows physical changes, mental symptoms, social repellent behavior like human depression. Therefore, the model would be useful for elucidating the mechanism of the depression and developing new drugs. In this study, a social defeat stress model was established by introducing C57BL/6J mice into the territory of ICR mice and subjecting them to 10 minutes of attacks from the ICR mice for 10 days. A social interaction test (SIT) was performed the day after the model was prepared, and the mice were allocated based on the SI scores for further testing. Starting the day after the SIT, the tail suspension test (TST), the forced swimming test (FST), the sucrose preference test (SPT), and organ weighing were performed. We also evaluated the effects of ketamine using this model.

Materials and Methods

Animals

Stressed mice : C57BL/6J, Male, 6 weeks old
(at the start of model preparation)
Aggressor mice : CrI:CD1(ICR) , Male, 16 weeks old
(at the start of model preparation)

Model preparation

Social defeat stress mice were prepared by introducing C57BL/6J mice into the territory of ICR mice and subjecting them to 10 minutes of attacks from the ICR for 10 days.

Group allocation

Before stress exposure, mice were allocated into a normal group and a stress model group using body weight as an index. After exposing to stress, a social interaction test was conducted, and mice were divided into three groups using the social interaction score (SI score) as an index.

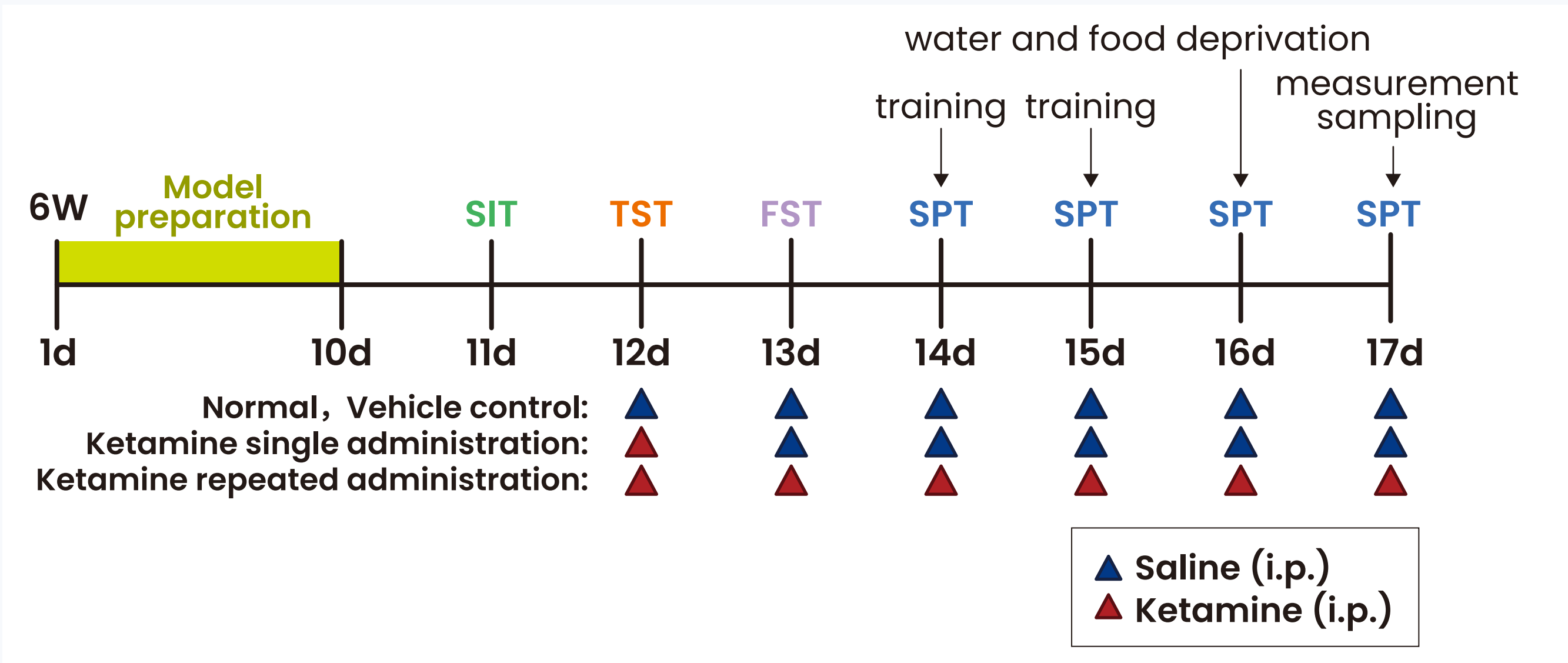
SI score (%) = [time spent in an interaction zone with an aggressor/ time spent in an interaction zone without an aggressor] ×100

Drug administration

Ketamine (10 mg/kg) was administrated intraperitoneally 1 hour before each test.

Group	Dosing article (mg/kg, i.p.)	Number of used animals	Number of adopted animals
Normal	0	16	8
Vehicle control	0	46	8
Ketamine single administration	10		8
Ketamine repeated administration	10		8

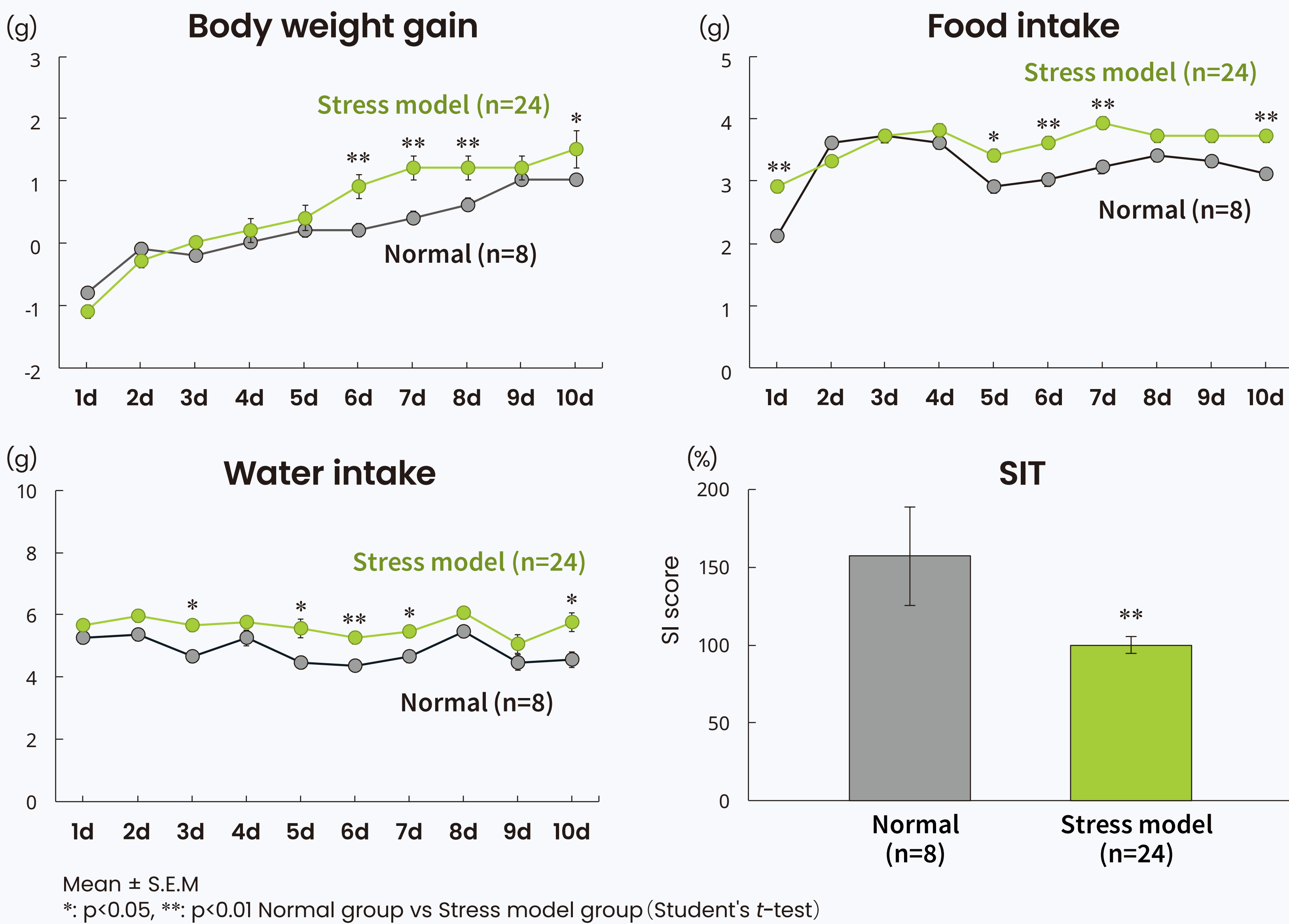
Experiment schedule



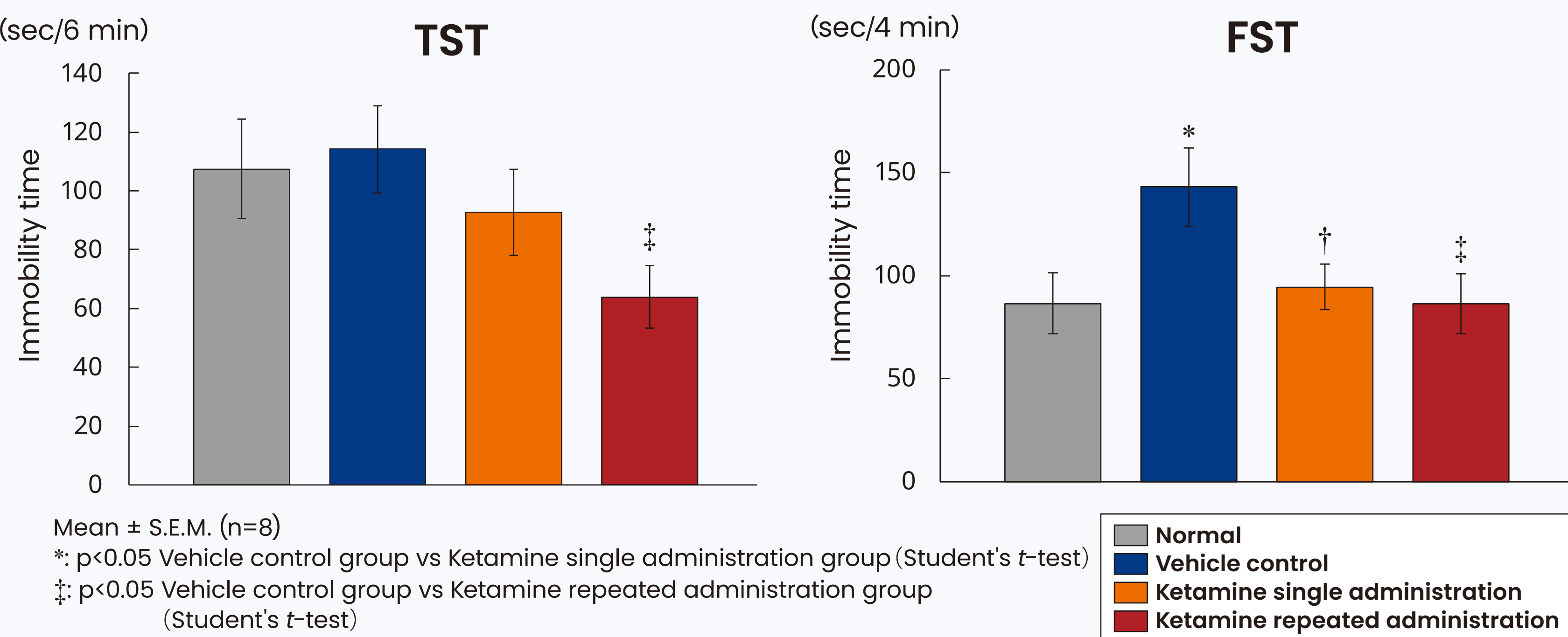
Measurement items

- Body weight gain
- Food intake
- Water intake
- SI score in the SIT
- Immobility time in the TST
- Immobility time in the FST
- The percentage of sucrose preference
- Organ weight (spleen, adrenal gland, thymus)

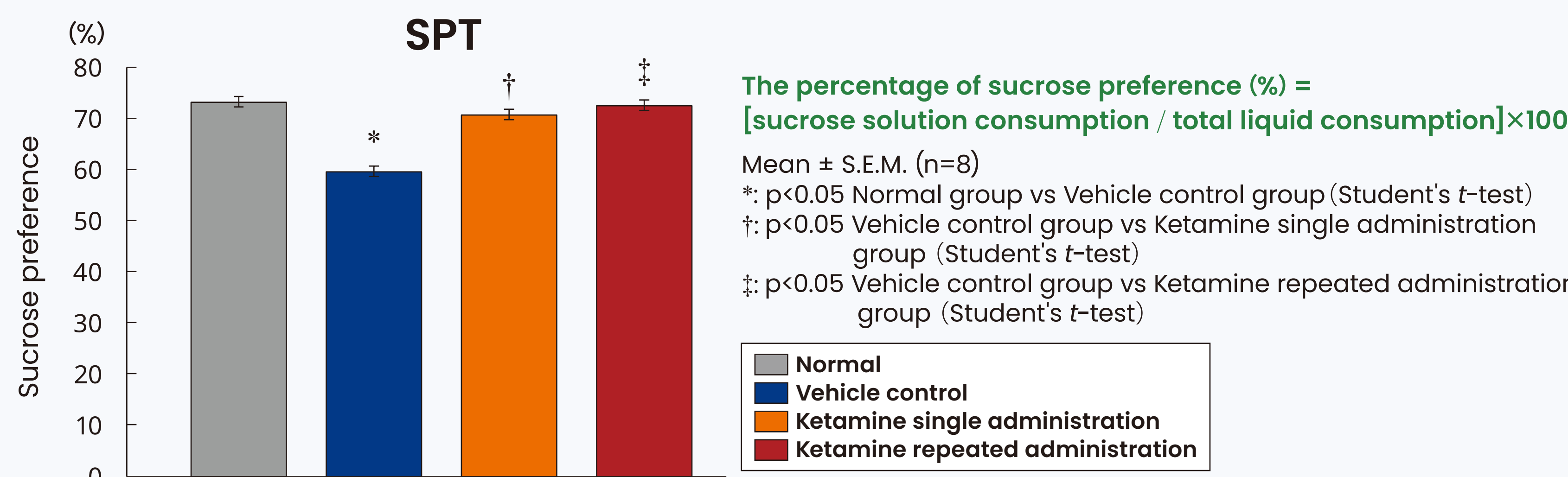
Results



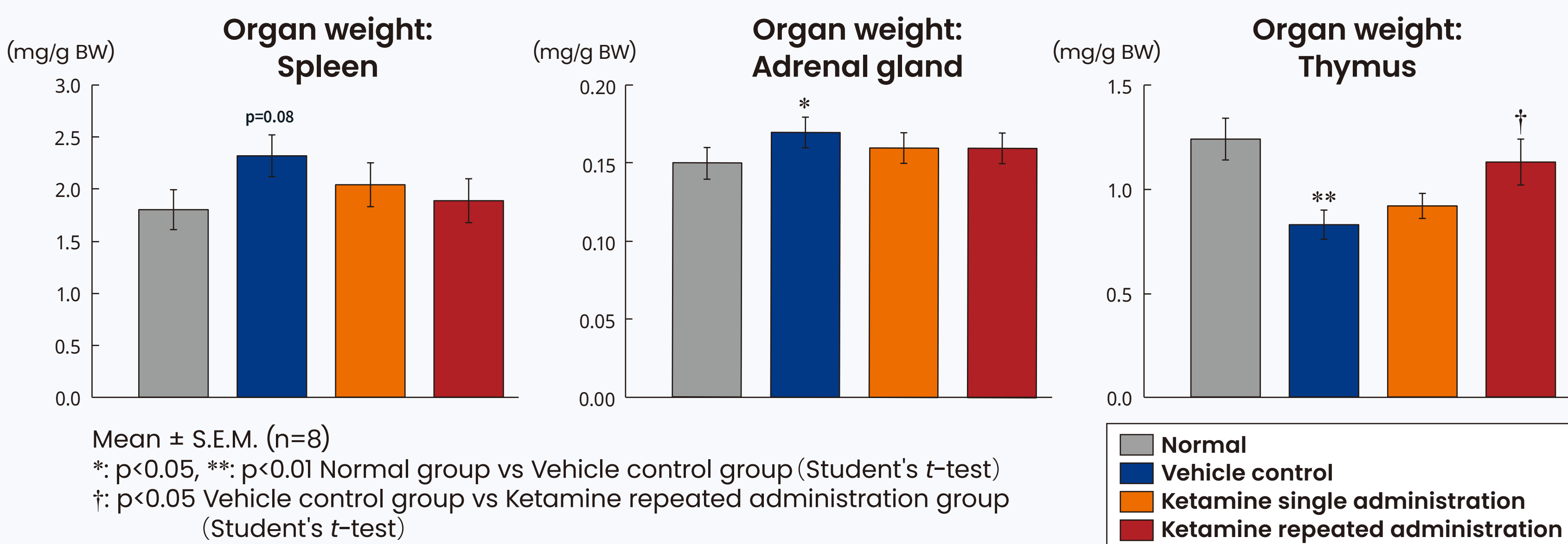
- During the model preparation period, body weight gain, food intake and water intake were significantly increased in the stress model group compared with those in the normal group.
- SI score was decreased in the stress model group compared with those in the normal group.



- No significant difference was observed in the immobility time between the normal group and vehicle control group in the TST. The immobility time was significantly shortened in the ketamine repeated administration group compared with those in the vehicle control group.
- The immobility time in the FST was significantly prolonged in the vehicle control group than in the normal group. The immobility time in the ketamine groups were significantly shortened than in the vehicle control group.



- The percentage of sucrose preference was significantly decreased in the vehicle control group compared with those in the normal group.
- The ketamine administered groups showed significantly higher values than the vehicle control group and suppressed the decrease in the percentage of sucrose preference.



- No significant difference in spleen weight between the normal group and vehicle control group, but the spleen tended to become enlarged due to stress. The ketamine administration groups also showed a lower weight.
- The vehicle control group showed significant hypertrophy in the adrenal glands and significant atrophy of the thymus compared with the normal group.
- Thymic atrophy was significantly suppressed by ketamine repeated administration group compared with those in the vehicle control group.