（第３号様式）

# 学　位　論　文　要　旨

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論　文　名　強制遊泳実験のテスト再テストパラダイムは雌マウスでは抗うつ薬効果の予測に妥当性が不十分である：不動時間の延長に対するアセチルコリンおよびシグマ受容体の関与

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学位論文要旨

***Rational:*** The forced swimming test (FST) in mice and rats is widely used to predict the antidepressant property of candidate drugs because of the simplicity and reproducibility of the procedure. The FST, however, is performed differently in mice and rats: mice are forced to swim once for 6 min, whereas rats are forced to swim for 15 min on the first day, followed by a 5- to 6-min retest 24 h later. The experimental protocol in rats does not take into account the possibility that drug effects could result from deteriorated memory processes that affect the immobility in the second trial. Several investigators have used the rat FST protocol in mice to minimize between-group variations and maintain the consistency of immobility time, but exposing mice to the FST twice does not exclude the possibility that actions of the drug on memory processes may be involved in antidepressant-like effects of the drug. On the other hand, gender differences exist in the prevalence of mood disorders and the effectiveness of antidepressants. Nevertheless, numerous studies have used the FST to investigate the behaviors of male rodents, while few studies have examined the responses of female rodents. The focus on male animals may be attributed to endocrine changes during the estrous cycle that complicate the analysis of data from female animals. We have previously reported no significant difference in the duration of immobility among the four estrous stages in female ICR mice. Thus, future preclinical screening of new antidepressants should include female animals. ***Objectives:*** In the present study, we used female mice as subjects and investigated whether the initial FST experience affects the duration of immobility in the second trial and clarified the mechanism underlying the differences between the single and double FSTs. ***Methods:*** Female ICR mice were exposed to the FST using two experimental paradigms. The

first exposed naïve mice to a single FST and the second used female mice that had experienced the FST test one time 24 h prior to the second FST. To investigate whether the immobility duration involved learning and memory processes in female mice following the pre-exposure we evaluated the amnesic effect of scopolamine. Because memory consists of three different components (memorization, memory retention, and retrieval), we used three different injection times: 30 min before the first FST, immediately after the termination of the first FST, and 30 min before the second FST. In the present study, we compared its effect with that of methylscopolamine, which does not cross the blood-brain barrier, to distinguish between central and peripheral actions. As current evidence indicates that sigma-1 receptors modulate central cholinergic activities and play an essential role in mediating memory deficits, we also examined the effect of the sigma-1 receptors agonist (+)-pentazocine and sigma-1 receptors antagonist NE-100 on the immobility duration in the second FST. We also assessed the drug effects of 5-$HT_{1A}$ receptor agonist tandospirone, 5-$HT_{2A}$ receptor agonist (-)-2,5-dimethoxy -4-iodo-amphetamine hydrochloride (DOI) and antidepressant imipramine, paroxetine on the immobility duration in both mice exposed to the FST once and mice exposed to the FST twice. ***Results:*** An experience of FST for 10 min or 15 min reliably prolonged the duration of immobility during the second trial (24 hrs later) compared with the duration in a single FST. Among three different injection timings, only at 30 min before the second trail, scopolamine significantly prevented the prolongation of immobility. (+)-pentazocine failed to show any significant effect on the prolongation of immobility, but NE-100 prevented it in a dose-dependent manner. Neither tandospirone nor (-)-DOI affected the duration of immobility, whereas imipramine and paroxetine significantly reduced it in the single FST, but not in the second test. ***Conclusions****:* Female mice displayed a prolonged duration of immobility in a second FST, and this phenomenon was prevented by scopolamine or NE-100 administered prior to the second trial. This suggests that acetylcholine and sigma-1 receptors may play a role in the response to the test-retest paradigm. Since antidepressants failed to show any significant effect on the immobility time of female mice exposed twice to the FST, we propose that the test-retest paradigm is inadequate for detecting antidepressant-like activity of a drug, possibly because the repetition of the FST may involve an episodic-like memory process that cannot be eliminated.


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| キーワード（３～５） | Forced swimming test<br>Female mice<br>Acetylcholine receptors<br>Sigma-1 receptors<br>Antidepressants |