

(第 12 号様式)

## 学 位 論 文 の 要 約 ( 研 究 成 果 の ま と め )

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学位論文名 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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### 学位論文の要約

**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. [Petit-Demouliere et al. 2005] 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. [Bekku N. et al. 2006] Thus, future preclinical screening of new antidepressants should include female animals. **Objectives:** We investigated whether a prior swimming experience affects the immobility duration in a second FST in female mice and whether the test-retest paradigm is a valid screening tool for antidepressants. **Methods:** Female ICR mice were exposed to the FST using two experimental paradigms: a single FST and a double FST in which mice had experienced FST once 24 h prior to the second trial. 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 [Beatty WW. et al. 1986]. 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 [van Waarde A. et al. 2011], 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-HT1A receptor agonist tandospirone, 5-HT2A

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:** The initial FST experience reliably prolonged immobility duration in the second FST. The antidepressants imipramine and paroxetine significantly reduced immobility duration in the single FST, but not in the double FST. Scopolamine and the sigma-1 ( $\sigma_1$ ) antagonist NE-100 administered before the second trial significantly prevented the prolongation of immobility. Neither a 5-HT<sub>1A</sub> nor a 5-HT<sub>2A</sub> receptor agonist affected immobility duration. **Conclusions:** We suggest that the test-retest paradigm in female mice is not adequate for predicting antidepressant-like activity of a drug; the prolongation of immobility in the double FST is modulated through acetylcholine and  $\sigma_1$  receptors.

#### **References:**

Petit-Demouliere B, Chenu F, Bourin M. Forced swimming test in mice: a review of antidepressant activity. *Psychopharmacology (Berl)*. 177:245–255, 2005 DOI:10.1007/s00213-004-2048-7.

Bekku N, Yoshimura H, Araki H. Factors producing a menopause-like depressive state in mice following ovariectomy. *Psychopharmacology (Berl)*. 187:170–180, 2006 DOI:10.1007/s00213-006-0395-2.

Beatty WW, Butters N, Janowsky DS. Patterns of memory failure after scopolamine treatment: implications for cholinergic hypotheses of dementia. *Behav Neural Biol*. 45:196–211, 1986.

van Waarde A, Ramakrishnan NK, Rybczynska AA, Elsinga PH, Ishiwata K, Nijholt IM, et al. The cholinergic system, sigma-1 receptors and cognition. *Behav Brain Res*. 221:543–554, 2011. DOI: 10.1016/j.bbr.2009.12.043.

なお、この学位論文の内容は、以下の原著論文に既に公表済である。

A test-retest paradigm of the forced swimming test in female mice is not valid for predicting antidepressant-like activity: participation of acetylcholine and sigma-1 receptors. *J Pharmacological Sciences*, 123(3):246-255, 2013. DOI: 10.1254 / jphs.13145FP