also reflect increased arousal, and behavioural changes observed from the first to the second FST exposure could also mirror cognitive processes and interindividual differences in stress coping[10-12]. In general, many biological factors affect behavioral performance during the FST and might influence the evaluation of potential antidepressant drugs. For mice, these factors include strain[13,14], gender[15], age[16], and susceptibility in swimming[17].

Strain

Strain is one of the most important parameters to consider in the FST[14]. The influence of the strain of rodent on behavior in the FST has been more extensively characterized in mice than rats, where more than a tenfold difference in baseline immobility has been observed between different strains, including inbred strains (BALB/cJ, DBA/2J, C57BL/6J, A/J, FVB/NJ, C3H/HeJ, 129/SvemJ, etc.) and outbred strains (Swiss-Webster, CD-1, CF-1, NIH Swiss, NMRI, etc.)[3, 14, 18].

In general, inbred strains demonstrated lower variability than outbred strains[14]. Different strains showed different baseline immobility and swimming. BALB/cJ and C57BL/6J inbred male mice had lower immobility than the NMRI outbred male mice, and C57BL/6J mice had the highest swimming distance among the three strains[19]. Moreover, the C57BL/6J mice had almost highest immobility among the inbred strains, and more reliable than the others[13,14,19]. This might explain why so many depression-related transgenic mice were based on the genome of C57BL/6J mouse strain[20,21].

Mice strains not only differ in baseline activity, but also differ in responsiveness to drugs in the FST[8]. Lucki *et al.* demonstrated that the DBA/2J and C57BL/6J inbred mice showed greater sensitivity than other strains to desipramine. Nicotine increased swim distance in C57BL/6J and BALB/cJ mice, but did not affect NMRI mice[19]. Different antidepressant drugs probably exert their effects in the FST through partly different mechanisms. On the other hand, outbred mice strains are more responsive to antidepressants in the FST than inbred strains[8]. The most frequently used out strains, CD-1[22], NMRI[19] and Swiss[23], respond positively to most of the antidepressants when subjected to the FST[8]. The strain background is a critical variable in determining baseline performance and the sensitivity to different types of antidepressant drugs in the mouse FST.

Gender

Behavioral strategies in the FST can vary significantly with animal gender. Firstly, gender-specific immobility differences were shown to exist in many mice strains. For example, male WT mice showed significantly less immobility during the night phase in comparison to female mice[24]. Secondly, gender-specific immobility in FST was also existed in genotype mice. Lydia *et al.* found that early-life interventions were able to improve the time and frequency of episodes of immobility, being more evident in the female gender of both old NTg and 3xTg-Alzheimer's disease mice[16]. In addition, there were differences in the circadian characteristics of immobility induced by FST in WT, Clock$^{\Delta 19}$, Per1, and Per2 mutant mice, and all four genotypes showed gender-specific differences in the level of immobility[24].

C57BL/6J mice are commonly used as the genetic background for many knockout and transgenic mice lines[12,15,20,25], and studies found female C57BL/6J mice to be more sensitivity to antidepressants in the FST. Females C57BL/6J naïve mice tended to show a greater response to antidepressant amitriptyline treatment than males, and female stress-naïve mice are more sensitive to the rapid and the sustained (at 24h) antidepressant-like effects of ketamine, which may be due to altered sensitivity to the drug or variations in metabolism or consumption[15,26]. Moreover, The residual (i.e., after withdrawal) antidepressant effects mediated by PAM-2 or N,6-dimethyltricyclo[5.2.1.0^{2,6}] decan-2-amine enantiomers were only observed in female mice[27,28].

Age

Evidence suggested that there was a strong difference between younger and older mice groups in the FST. Older (8 to 12 month old) naïve male C57BL/6J mice had lower immobility than their younger (2 to 3 month old) counterparts[29]. There was also a significant difference in immobility between 22-month-old mice, 17-month-old mice and 11-month-old mice[30]. Shortly, older C57BL/6J mice had decreased immobility. Moreover, transgenic mice also showed age-depended behavioral performance in the FST. The long persistence of immobility found in males 17-month-old (late-stages of disease) 3xTg-AD mice was different to that at 12 months of age (beginning of advanced stages)[16].

Sensitivity to some antidepressants is also profoundly altered by the age of mice. Tricyclics, noradrenaline reuptake inhibitors and serotonin reuptake inhibitors exhibited stronger effects in 4-week-old Swiss mice than 40-week-old mice[8,31]. Social isolation, as well as treatment with reserpine, an antihypertensive and antipsychotic drug, increased FST immobility in 17–21 day-old Swiss-Webster mice but not in 26–30-day-old mice[32,33].

Mice Susceptibility in Swimming

It was recently found that the mice susceptibility in swimming proficiency is another important factor influencing the mice FST. It has been reported that male mice that are genetically selected for long attack latency

(LAL) and short attack latency (SAL) display differences in the structural and functional properties of postsynaptic serotonergic-1A (5-HT 1A) receptors[34] and that they also show divergent behavioral responses during the FST, such as higher immobility in LAL and lower immobility in SAL mice[35]. Moreover, our group found that individual ICR mouse performed differently in the forced swim pre-test, resulting in two different mouse substrains: short immobility mice (SIM) and long immobility mice (LIM), and the SIM substrain showed a greater susceptibility to forced swimming. In other words, leaned helplessness is present in the SIM substrain but not the LIM substrain in our experimental conditions.

Sensitivity to some antidepressants is also profoundly altered by the mice susceptibility in swimming. Acute administration of the full 5-HT 1A receptor agonist, 8-OH-DPAT (5 mg/kg), induced a significant decrease in immobility and an increase in swimming activity in LAL mice, but it did not affect them in SAL mice[34]. Our study also showed that short-term abscisic acid administration had antidepressant-like effects only in the SIM substrain, as indicated by decreased immobility and increased swimming in the FST. This result highlighted the importance of the forced swimming pre-test, which is used to screen out the SIM substrain in preclinical antidepressants studies. Along with the positive correlation of pre-test performance with FST in immobility, these results suggest that mice sensitivity to forced swimming was positively correlated with drug sensitivity, further confirming that mice sub-strains grouping is necessary[17]. These results also suggest that susceptibility in swimming is strongly related to mouse genetic background.

Conclusion

Mice sensitivity to the FST can be influenced by many factors including: preconditioning before the FST, schedule and routes of treatment, dosage and type of the drugs as well as experimental design and laboratory environmental effects[8]. In the present Mini Review, we analysed the variables of biological factors: strain, gender, age, and susceptibility, and highlighted their importance in the FST and antidepressants screening.

The detailed characterization of strain, gender, age, and susceptibility related changes in behavior of mice will provide researchers with useful information for designing behavioral experiments, interpreting results, and understanding the neurobiological basis of related behavioral changes[29]. Especially, our previous results suggest that dividing ICR mice into drug-sensitive and drug-insensitive groups may not only allow easier screening for anti-depressant drugs, but also provide opportunities for identifying drugs that are effective in patients with drug-resistant depression if drugs can be developed that are also effective in the LIM group. Many factors affect behavioral performance during the FST and might influence the evaluation of potential antidepressant drugs[17]. In this Mini Review, sensitivity to the antidepressants is profoundly altered by all the biological factors, which suggested that neuropharmacological mechanism of drug action is critical for the interpretation of FST results[36]. Antidepressant drug belongs to diverse chemical class with different acute pharmacological effect and mechanisms of action[37], and the type and dose of drug as another important factor of mice FST should be considered. Due to the high sensitivity of the test to biological variability, the FST should be standardized and the above-mentioned factors should be considered during study design and execution.

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