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REVIEW

Benoit Petit-Demouliere · Franck Chenu · Michel Bourin

Forced swimming test in mice: a review of antidepressant activity

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Abstract *Rationale:* Among all animal models, the forced swimming test (FST) remains one of the most used tools for screening antidepressants. *Objective:* This paper reviews some of the main aspects of the FST in mice. Most of the sensitivity and variability factors that were assessed on the FST are summarized. *Mechanisms:* We have summarized data found in the literature of antidepressant effects on the FST in mice. From this data set, we have extrapolated information on baseline levels of strain, and sensitivity against antidepressants. *Results:* We have shown that many parameters have to be considered in this test to gain good reliability. Moreover, there was a fundamental inter-strain difference of response in the FST. *Conclusions:* The FST is a good screening tool with good reliability and predictive validity. Strain is one of the most important parameters to consider. Swiss and NMRI mice can be used to discriminate the mechanisms of action of drugs. CD-1 seems to be the most useful strain for screening purposes, but this needs to be confirmed with some spontaneous locomotor activity studies.

Keywords Forced swimming test · Depression · Mouse · Antidepressants · Screening · Strain

Abbreviations

5-HT	Serotonin
8-OH-DPAT	8-Hydroxy-2-(di-*n*-propylamino)tetralin
Atypical	Antidepressants with an atypical activity
BDNF	Brain-derived neurotrophic factor
DRI	Dopamine re-uptake inhibitors
FST	Forced swimming test
MAO-I	Monoamine oxidase inhibitors
NA	Noradrenaline
NOS synthase	Nitric oxide synthase
NRI	Noradrenaline re-uptake inhibitors
SNRI	Serotonin and noradrenaline re-uptake inhibitors
SSRI	Selective serotonin re-uptake inhibitors
TCAs	Tricyclic agents
TST	Tail suspension test

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B. Petit-Demouliere · F. Chenu · M. Bourin (✉)
EA 3256 "Neurobiologie de l'anxiété et de la dépression",
Faculté de Médecine,
BP 53508, 1 rue Gaston Veil,
F44035 Nantes Cedex 01, France
e-mail: mbourin@sante.univ-nantes.fr
Tel.: +33-2-40412853
Fax: +33-2-40412856

Introduction

Half a century ago, antidepressants were discovered by serendipity. In 1954, it was observed that some treatments for tuberculosis were exerting a beneficial effect in the sense of well-being (Selikoff and Robitzek 1952; Bloch et al. 1954). These results set iproniazid as the first antidepressant (Loomer et al. 1957) and the first member of the monoamine oxidase inhibitor (MAO-I) family (Zeller and Barsky 1952). At the same time, imipramine was found to be effective in treating depression (Kuhn 1957; Klerman and Cole 1965). At this point, a completely new approach was exposed: the monoamine theory of depression or biogenic amine hypothesis (Bunney and Davis 1965; Schildkraut 1965; Coppen 1967). The key role of monoamines is not discussed here but it does not fully describe the pathogenesis and aetiology of depression (Heninger et al. 1996; Hyman and Nestler 1996; Nestler 1998; Nestler et al. 2002).

In addition to clinical research, pre-clinical studies were necessary to test new drugs provided by pharmaceutical industry. Depression is defined clinically as a pathological complex of psychological, neuroendocrine and somatic symptoms that cannot be reproduced in animals and especially in mice. Only specific measurable behaviours (endophenotypes) can be assayed to be relevant in human depression (Holmes 2003a). During this 50-year period, numerous animal models of depression have been designed, tested and assessed (Willner 1984; Lucki

1997; Dalvi and Lucki 1999; Holmes 2003b; Cryan and Mombereau 2004). The reserpine effects reversal test, designed by Costa et al. (1960), was the first attempt to screen imipramine-like drugs and led to the isolation of desipramine and the demonstration of its antidepressant effect. To date, few models are commonly used for screening antidepressant effects or studying the mechanisms of action of these molecules. The aim of this paper is mainly to review the characteristics of one of these models: the forced swimming test (FST) in mice, and to discuss the main parameters that influence the sensitivity, specificity and reliability of this model.

Porsolt et al. (1977) described "a new behavioural method for inducing a depressed state in mice". The idea arose out of some learning experiments they were doing with rats in a water maze. Most rats were finding the exit within 10 min but they noticed that other rats ceased struggling altogether and remained floating passively (Porsolt et al. 1979). To describe this new behavioural model in mice, the following procedure was adopted "1 h after a single i.p. injection mice were dropped into the cylinder (height 25 cm, diameter 10 cm, 6 cm of water at 21–23°C) and left for 6 min. Because little immobility is observed during first 2 min, only that occurring during the last 4 min was counted. The duration of immobility occurring in each minute was scored. A mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water making only movements necessary to keep its head above water" (Porsolt et al. 1977). Male CD (Charles River) mice of 20–25 g, were housed ten to a cage with free access to food and water.

In the same paper, Porsolt tested a large range of antidepressants and showed a reduction of immobility of mice with all of them. The other usual clinical therapies were also effective (e.g. electroconvulsive shock or selective deprivation of REM sleep) (Porsolt et al. 1977, 1979).

The goal of the present paper is to summarize the advantages and drawbacks of the FST in mice, as well as the factors of variability of the test through an extensive review of the litterature.

FST validity, advantages and drawbacks

To evaluate the validity of an animal model, many criteria have to be explored. For example, we could consider reliability and different types of validity: predictive, face, construct, etiological, concurrent and discriminant. Undoubtedly, the more types of validity a model satisfies, the greater is its value, utility and relevance to the human condition. To establish the value of a model in basic neurobiological research, few of these parameters have to be satisfied (Geyer and Markou 2000). It was argued that there are only two criteria that a model must satisfy to establish its value in basic neurobiological research: reliability and predictive validity. Nevertheless, the process of construct validation is valuable in further development and refinement of the model; however, in practice it is difficult to determine this validity in animal models of depression (Geyer and Markou 2000; Willner and Mitchell 2002).

As semantic issues seem to exist between some authors (Geyer and Markou 2000; Willner and Mitchell 2002), it is fundamental to have a clear definition of used terms. For example, predictive validity and construct validity have not the same meaning for Willner and Mitchell than for Geyer and Markou. Predictive validity for Willner and Mitchell is assessed by whether a model correctly identifies antidepressant treatments without making errors of omission or commission, and whether potency in the model correlates with clinical potency. For Geyer and Markou, an animal model has predictive validity to the extent that it allows one to make predictions about phenomena based on the performance of the model. The narrow sense to refer to the ability of the model to identify drugs with potential therapeutic value in humans appears limited for Geyer and Markou. It does not include the identification of any variables that influence both the experimental preparation and the modelled phenomenon in similar ways. This wider definition includes much of what Willner and Mitchell would discuss under the rubric "construct validity". Bearing in mind this opposition, predictive value in our paper will accord to the definition of Willner and Mitchell.

Construct validity does not represent the same concept for these authors. Geyer and Markou defined it as the accuracy with which the test measures that which it is intended to measure. For Willner and Mitchell, it is a means of bringing the theoretical accounts of both the disorder itself and the disordered behaviour exhibited by the model into alignment. It includes neurobiological mechanisms, aetiology or psychosocial mechanisms. We will use this definition of construct validity that includes etiological validity previously evocated (Geyer and Markou 2000).

Reliability refers to the consistency and stability with which the variables of interest are observed, and is relevant to both independent and dependant variables (Geyer and Markou 2000).

Willner used a third parameter to describe some animal models of depression: face validity (Willner 1984).

Face validity for an animal model of depression, represents the analogy between the model and the disease (i.e. how well they apparently resemble the human depressive state). It refers to the phenomenological similarity between the behaviour exhibited by the animal model and the specific symptoms of the human condition. This criterion is often criticized because of its non-scientific aspect. It sums up specific patterns of depression and the model should not show features that are not seen clinically. Although it appears to be useful to validate models, such a criterion is actually not necessary (Geyer and Markou 2000). Because the pharmacotherapy of depression typically requires chronic drug treatment to obtain a full response, face validity (Willner 1984) takes account of the necessity, or not, to use chronic administration to have an antidepressant effect and the specificity

of observed features. Irrespective to how it responds to acute antidepressant treatment, to have face validity, an animal model if depression must respond to chronic treatment (Willner and Mitchell 2002).

These types of validity are discussed below for the FST. For other types of validity, the FST was estimated to have a lack of convergent validity and a possible etiological validity (Geyer and Markou 2000).

Reliability

The FST is currently a popular model, due to the low cost of the experiments and because it is arguably the most reliable model available (Holmes 2003b). Moreover, it has been reported to be reliable across laboratories (Borsini and Meli 1988).

Predictive validity

To evaluate predictive validity, correlating potencies between a model and the condition it models is possible (Willner 1984). In a comparative review of drug effects on immobility time in mice, Borsini and Meli adopted a limit of 20% reduction of immobility to consider an antidepressant effective on the test. They show that 94% of antidepressants decrease the immobility time in mice (Borsini and Meli 1988). In this study, they found that 83% of classes of drugs decrease immobility time in the mouse. This lack of specificity may be largely explained by methodological considerations. Some authors changed the scoring method, other authors recorded animal movements by using automated devices. Moreover, false positive effect of motor activity enhancing drugs would have been detected with an actimeter, where psychostimulant drugs could reduce immobility without antidepressant effect (Porsolt et al. 1978). Nevertheless, the FST is a suitable model to detect antidepressants due to the fact that it detects the majority of antidepressants and discriminates antidepressants from neuroleptics and anxiolytics (Borsini and Meli 1988).

Together, these data provide us with a broad spectrum of antidepressant effects with good reliability and some answers to the lack of specificity of the test, which has been discussed (Schechter and Chance 1979).

Face validity

A second characteristic of the FST is that acute drug treatments are effective in this model and do not correspond to the clinical time course of their action. One of the main arguments increasing the face validity is that chronic treatments reinforce the effects of antidepressants on immobility. It showed several differences between chronic and subchronic treatment of a SSRI, fluoxetine, in the FST with BALB/c mice weighting 25–35 g (Dulawa et al. 2004). Four days of treatment were ineffective, whereas 24 days were effective at 10 mg/kg per day and 18 mg/kg per day administered in drinking water. This delay of action provides further data to increase the face validity of FST in mice, even if their experimental paradigm was not the original method for the FST. (Dulawa et al. 2004). Moreover, we have to consider that some authors using standard methods showed that fluoxetine was effective acutely at 16 mg/kg in the FST with CD mice (Da-Rocha et al. 1997). This shows the preponderant place of methodological parameters in behavioural studies (e.g. strain, pretest session).

In addition, from an ethical point of view, this animal experiment requires only a single exposure to the stressful stimulus (Thierry et al. 1986). The used dose in the test as well as in other tests in mice are high doses compared to human but the pharmacokinetic parameters in mice are very different (i.e. half-life is about 1 h for mice compared to several hours in human). Face validity for the FST with mice is not strong; chronic administration remains to be fully studied in order to increase this face validity.

Construct validity

The construct validity of the FST is difficult to establish and questionable. Indeed, the onset of immobility observed during the test is hard to interpret. Porsolt et al. (1978) described this state as a behavioural despair "reflecting a state of lowered mood". He had also dissociated hypothermia induced by forced swimming from immobility occurring in these conditions and also from drug-induced hypothermia in rats (Porsolt et al. 1979). The anthropomorphic interpretation was assessed and replaced by other assumptions: a shift from active coping to passivity, a means to conserve energy (Arai et al. 2000; Holmes 2003b) or a psychological concept of "entrapment" described in clinical situations (Cryan and Mombereau 2004). This passive behaviour could also be considered as unwillingness to maintain effort in this inescapable situation. Immobility may be seen as an adaptative response to an inescapable situation. This strategy could be perceived as a successful coping rather than a failure of coping (West 1990).

Immobility observed in the swim test seems not to be related to behaviour in the tests used in anxiety models (elevated-plus maze, hole-board test, locomotor activity) (Hilakivi et al. 1989). Even if the onset of immobility remains hard to interpret, the aetiological part of construct validity could be highly relevant. The stress leading to the behavioural despair may be involved in the aetiology of some types of depression in humans (Geyer and Markou 2000). Nevertheless, the FST has a very little construct validity due to this acute and non-ecologically relevant stressor that produces this behaviour (Willner and Mitchell 2002).

To summarize, FST has strong predictive validity, good reliability, some face validity and poor construct validity. In a review of the causes of immobility in the FST, West (1990) concluded that FST "no longer appears to be a

valid model of depression. Nonetheless the forced swim test is still likely to be useful in understanding antidepressants treatments". This point of view should be moderated by a consideration on "what is a valid model of depression?"

When pre-clinical tests were created to study the depressive state, the first role for models of depression was to predict antidepressant potency. Moreover, the validity of these tests was largely based on an empirical observation, namely that the two major groups of antidepressants, MAO-I and tricyclic drugs (TCAs), are active (Bourin 1990).

The FST, as described by Porsolt et al. (1977), has been designed to be "a primary screening test for antidepressants". For this purpose, FST is a good model for screening antidepressants, maybe the best one. FST shows a strong sensitivity to monoamine alterations, but it should not be forgotten that other antidepressants treatments, such electroconvulsive shock, are efficient (Porsolt et al. 1977). To summarize these ideas, we can consider that "The FST models a very specific cluster of stress-induced behaviours that have no direct, empirical relation to depression symptoms in humans, but which are nonetheless exquisitely sensitive to monoaminergic manipulations" (Holmes 2003b). Additional possibilities for the FST should be considered on a more neuropharmacological point of view. This test also provides a useful model to study neurobiological and genetic mechanisms underlying stress and antidepressant responses (Porsolt 2000; Lucki et al. 2001; Nestler et al. 2002).

Moreover, new approaches of research for antidepressant treatments continue to use the FST as a preliminary test. For example, some authors work on neurotrophic factor that could potentially be used in the treatment of depression. They used the FST and showed that brain-derived neurotrophic factor (BDNF) infusion in the ventral tegmenta area resulted in 57% shorter latency to immobility relative to control animals, in the FST in rats (Eisch et al. 2003). This use of the FST had already been described previously with a 70% decrease in the immobility time compared to vehicle-infused controls after BDNF infusion (Siuciak et al. 1997). Other ways of investigation for depression use the FST as model of depression. Acute antidepressant treatment attenuates swim stress-induced corticosterone release in the rat (Baez and Volosin 1994). NK2-receptor antagonists, K^+ channel openers and K^+ channel blockers were considered for their antidepressant-like properties in the forced swim test (Guo et al. 1996; Redrobe et al. 1996; Slattery et al. 2004). Nitric oxide synthase (NOS) or neurosteroids have been tested in the FST with mice to look for an antidepressant-like effect (Harkin et al. 1999; Khisti et al. 2000). Many studies keep using the FST, not only for screening for antidepressant effects, but for a more neuropsychological purpose. This utilization of the FST differ from the monoaminergic purpose it is often used. Nevertheless, this model of depression is not only linked to monoamine. The uncontrollable stress involved during the test may implicate many mechanisms of reaction that could be considered as possible investigation ways. The fact that electroconvulsive seizures are effective in the test argues for its ability to pick up broader mechanisms of action (Nestler et al. 2002). The relevance of using the FST for this new ways of research needs clinical correlations to validate also the FST for this utilization. The development of clinically effective antidepressant

Table 1 Summary of some modifications tested on the FST in mice

Factor	Sensitivity	Variability	Reference
Acute vs chronic administration		X	Dulawa et al. (2004)
Age of mice		X	Bourin et al. (1998a); David et al. (2001a)
Automated device/water waves	X		Browne (1979); Denenberg et al. (1990)
Circadian rhythm		X	Dubocovich et al. (1990)
Cylinder diameter	X		Sunal et al. (1994)
Depth of water	X		Aley and Kulkarni (1989)
Environment of the laboratory		X	Crabbe et al. (1999)
Food restriction		X	Cabib et al. (2000); Cabib et al. (2002)
Gender		X	Alonso et al. (1991); David et al. (2001b); Voikar et al. (2001)
Housing of animals		X	Karolewicz and Paul (2001)
Isolation of animals			Hilakivi et al. (1989); Yates et al. (1991)
Interval of observation	X		Sunal et al. (1994); Lucki (1997)
Observer		X	–
Revised scoring	X		Lucki (1997)
Scoring on categorized behavior			Schramm et al. (2001)
Side preference in rotation		X	Krahe et al. (2002)
Strains		X	Lucki et al. (2001); Voikar et al. (2001); Bai et al. (2001); David et al. (2003)
Test / retest		X	Alcaro et al. (2002)
Time between treatment and FST	X		–
Water temperature	X		Arai et al. (2000); Taltavull et al. (2003)
Wheel water tank	X		Nomura et al. (1982)

drugs with novel mechanisms should give answers to this question.

Another point is the utilization of the FST for genetically modified animals that is applicable to study mechanisms of action of antidepressant on the test. For example, the decrease of immobility observed after paroxetine administration in wild-type mice is absent in 5-HT1B knockout in the test (Gardier et al. 2001). Other data with knock-out mice can be useful to determine the role of NA or 5-HT in the test; for example with mice lacking serotonin transporter (Holmes et al. 2002) or dopamine-beta-hydroxylase deficient mice (Cryan et al. 2001). This new employment of the test permits to better know the mechanisms of action of drugs on the FST involving or not the monoamine, i.e. for new possible therapies for example, BDNF+/– mice (MacQueen et al. 2001) or inducible BNDF knock-out (Monteggia et al. 2004).

Modifications of the FST

There have been many modifications of the FST but improvements of the test are often poorly validated (Bourin et al. 2001). Many parameters have been assessed in order to increase the sensitivity, specificity and reliability of detection of antidepressant activity. The following list describes some of these modifications of FST (Table 1). The two columns of Table 1 separate each modification between variability and sensitivity. A "variability factor" is assessed to check what parameter could increase or decrease reliability of the test between different laboratories.

Sensitivity factors

Automated device/water waves Different procedures have been elaborated to automate the FST. Video-tracking, computer analysis or wave analysis were used to score the immobility of rodents. From the data set, one can extract full or partial turns, clockwise or counter-clockwise rotations, total activity, and speed of swimming clockwise and counter-clockwise (Denenberg et al. 1990). Another author used an apparatus consisting of a transparent plastic cylinder (10×20 cm) containing 7 cm of water (23°C). Movement by the animal created a waveform in the water, resulting in a converted digital signal (Browne 1979). The ease of use of these systems appears not to counterbalance the cost of the equipment. Few studies use an automated video-tracking device, and mainly as a confirmation tool (Eisch et al. 2003). Nevertheless, some automated devices employed in FST studies were reported to be reliable for antidepressant screening (Yoshikawa et al. 2002).

Cylinder diameter To test this parameter, mice were forced to swim for 15 min in tanks of 10 (the original diameter of the Porsolt's forced swimming chamber), 20, 30, and 50 cm diameter in 20 cm deep water. Modifications of this parameter provide a way to distinguish the antidepressant drugs from caffeine, anticholinergics, and antihistaminics, which gave a false positive response in 10 cm diameter cylinders. The selective effect of antidepressants, namely, the rotatory locomotor activity during swimming can also be studied (Sunal et al. 1994). In our laboratory, we use a cylinder with the closest available diameter to the original test's diameter, associated with a check of variation of locomotor activity that can discriminate false-positive effects (Porsolt et al. 1978).

Depth of water This parameter had to be considered as mice should not sense a limit under the level of water. Their tails should not touch the bottom of the cylinder or the behaviour of the mice would be altered. Increased depth of water decreases the time spent immobile. No paper clearly described this process in mice; this parameter was shown to alter the behaviour of the rat (Borsini and Meli 1988; Detke and Lucki 1996). The original description of the FST by Porsolt et al. (1977) explains that 6 cm of water is sufficient. But mice can sense the bottom of the cylinder with this level of water. In our laboratory, the water level is at least 10 cm. Some modifications of Porsolt's paradigm have often been used; one of the most quoted is the method of Aley and Kulkarni (1989). They measure immobility in a glass jar (21×12 cm) containing 12 cm of water maintained at 22±1°C, during a 6-min period. It is important to consider that the only main modification of the original test is the increased depth of water. This procedure is consistent with the one we use and should be considered as the actual standard method.

Interval of observation/scoring Porsolt's paradigm has been modified by some researchers in order to increase the sensitivity or the specificity of the FST. Some authors have created a totally new analysis procedure for scoring immobility. The observation interval can be separated into 5-s parts in which the main behaviour is scored (Lucki 1997). Analysis of the behaviour of the mice can be totally different with categorization of a specific behaviour (Schramm et al. 2001). Some authors made a series of observations at 30 s. intervals and the mouse was rated as immobile (score 0) or not (score 1) for each observation period (Borsini and Meli 1988).

Time between treatment and FST This factor is not often considered but may explain some of the differences between FST results. Two possibilities seem to be available: acute injection 1 h before the FST as described by Porsolt et al. (1977) or acute injection then the FST when the maximal effect is intended. This requires a time-course study of the drug effect.

Water temperature The influence of water temperature on immobility time of the mice was studied. An effect of water temperature was revealed; a higher temperature (35°C) resulted in shorter immobility time after 10 min of forced swimming (Arai et al. 2000). Other data suggest

that immobility, which develops rapidly during forced swimming in cold water, may result from dramatic inhibition of neural functions because of severe brain hypothermia (Taltavull et al. 2003). Currently, most studies use warmer water between 23°C and 28°C. In our laboratory, we choose a temperature between 23°C and 25°C.

Wheel water tank Some authors have tried to measure immobility time in another way. A wheel was immersed in the water tank. Mice placed on this apparatus keep turning the wheel vigorously; when they abandon their attempts to escape from the water, the wheel stops turning. The number of rotations of the water wheel is counted. All antidepressants tested increased the number of rotations as tranquillizers, anticholinergics and antihistaminics were not effective. It was suggested that this water wheel test was more appropriate as screening test for antidepressants than Porsolt's test with regard to both objectivity and specificity (Nomura et al. 1982).

Variability factors

Acute versus chronic administration The effectiveness of acute treatment is a particularity of the FST. Useful for a screening test, it appears to decrease the face validity of this model, as the clinical time course requires chronic administration to be active. Experiments were made to find out the effects of chronic administration on the FST. Subchronic or acute effects were increased by chronic administration (Dulawa et al. 2004).

Age of the mice This parameter should be considered in parallel with weight. Our team has already shown a strong difference between younger and older mice groups. Sensitivity to some antidepressants is profoundly altered. Tricyclic, noradrenaline reuptake inhibitors (NRI) and serotonin reuptake inhibitors were more active in 4-week-old mice than 40-week-old Swiss mice (Bourin et al. 1998; David et al. 2001a). In our laboratory experiments, we choose mice weighting 20–25 g.

Circadian rhythm An effect of circadian rhythm was shown in response to antidepressants in the FST. FST was carried with three strains of mice: C3H, C57BL/6J and ND/4. Immobility time was scored at noon (1200–1400 hours) and midnight (0000–0200 hours). For C3H/Hen mice, duration of immobility was greater at midnight (Dubocovich et al. 1990). Another study did not show any difference between the FST made at noon (1100–1200 hours), early dark (2000–2100 hours) and at midnight (0100–0200 hours) for BALB/c and C57BL/6J mice (Raghavendra et al. 2000). Genetics studies on the Clock gene, implicated in circadian rhythm, revealed an effect of this parameter on immobility time (Easton et al. 2003). Studies in our laboratory are only made between 0800 and 1200 hours to avoid any risk of behavioural modification throughout the experiments.

Environment of the laboratory Interactions with laboratory environment have been studied in several strains of mice on few behavioural tests (open field, elevated plus maze, water maze, alcohol preference) (Crabbe et al. 1999). Despite standardization, there were systematic differences in behaviour across three different laboratories. In our opinion, FST is less sensitive to variation of laboratory environment (noise, air temperature, light, atmosphere pressure).

Food restriction Food restriction can strongly modify behavioural responses, as shown with amphetamine or the FST. The authors used FST for two sessions with two groups of DBA/2 mice. One group was isolated and food restricted, the other group was isolated but had free access to food. Immobility time was significantly decreased in the food-restricted group compared to the other group (Cabib et al. 2000; 2002).

Gender Differences of sensitivity between male and female mice were revealed by some studies depending on the strain used. David et al. (2001b) described a different sensitivity to antidepressants in the FST related to gender. Imipramine and paroxetine were active on CD1 male and female but at different doses. Another study showed a difference between male and female mice but only in some strains; FVB females, for example, had a shorter floating time than males (Voikar et al. 2001). Sexual differences have also been described in another study of immobility, which was higher in males than in females (Alonso et al. 1991).

Housing of animals/isolation of animals All studies have shown that housing was a critical parameter. In the above mentioned study of Cabib (see food restriction section), a group of DBA/2 mice was isolated for 13 days and compared with group-housed mice in the FST. They showed a significant increase of the immobility time in the isolated group (Cabib et al. 2002). Yates et al. (1991) linked this difference with the age of the mice. After having isolated mice for 24 h prior to a 15-min FST, they showed an increase in immobility time in 17- to 21-day-old Swiss Webster mice but not in 26- to 30-day-old mice. In another study, the immobility time in the FST was shortened in NIH Swiss mice isolated for 2 or 5 days, suggesting an improved ability to cope with stressful situations (Hilakivi et al. 1989; Yates et al. 1991). Isolation seems to have strain-dependent effects on the FST, but none of these studies had the same isolation time. If isolated for a longer period (8 weeks), mice displayed lower levels of immobility time when exposed to this test (Karolewicz and Paul 2001). Nevertheless, isolation, e.g. for surgery, had to be specified in methods of a paper, as it may modify dramatically immobility time of the FST.

Observer The most important source of variability (and the best way to consider in order to increase the sensitivity of the FST), with identical environmental parameters, is the observation. Like all behavioural studies, the observer is

the main actor of the test and reproducibility between laboratories is a matter that affects all these tests. The scoring of the immobility time should be strongly considered and assessed by all teams. The mouse is judged to be immobile when it makes only movements necessary to keep its head above water. It can move in the cylinder but without struggling movements. The analysis of active behaviours in the FST has strengthened the possibility of replicating the experiments.

Side preference in rotation A study was made on side rotational preference of mice during the FST. Krahe et al. (2002) concluded that side preferences of spontaneous rotational behaviour may account for inter-individual differences.

Strains Strain is one of the most important parameters to deal with (Lucki et al. 2001). Important differences exist between strains in both immobility observed and effects of imipramine (Porsolt et al. 1978). Genetic background could modify response by providing an inappropriate baseline level of behaviour (Holmes 2003a). There is a maximal tenfold difference in baseline immobility scores in control animals between strains and baseline level does not correlate with antidepressant sensitivity (Lucki et al. 2001). Several gender dissociations suggest the strain and task specificity (Voikar et al. 2001). Intra-strain and inter-strain comparisons indicate that the biological substrates mediating performance in the FST and the tail suspension test (TST) are not identical. For example, in NIH-Swiss mice, a 7-fold difference in baseline immobility was observed between the FST and TST. By contrast, the baseline immobility in C57BL/6 mice was similar in both procedures (Bai et al. 2001). There is a continuum of variation in basal responses from almost no time spent immobile by DBA/2J mice to more than 210 s of immobility in a 360-s test session with Balb/cJ mice (O'Neil and Moore 2003). In one of our studies, we have shown that drug sensitivity is genotype dependent. FST results have shown that Swiss mice were the most sensitive strain to detect serotonin (5-HT) and/or noradrenaline (NA) treatment. The use of DBA/2 inbred mice may be limited, as an absence of antidepressant-like response was observed in the FST (David et al. 2003). Control mice from the same breeders with comparable housing conditions should have the same immobility time in all laboratories. However, a gene-environment interaction is possible and may account for some difference between laboratories (Wahlsten et al. 2003). For example, in our data set, animals of the same strain that received no treatments do not have the same immobility time (for CD-1 from 135 s to 223 s of immobility time).

Test/retest This method is used normally for rats. In a first session, the animal is able to discover the test, rat usually explore the water surface and dive. In a second session were they will be scored, rats are familiarized to the test and do not try to dive. Mice do not have this behaviour and this explain the easy use of mice that do not need a second session. This second session has been assessed for the construct validity of the FST. Memory process was involved to explain immobility of the rat. The absence of second session with mice removes this problem and simplifies the test. In their experiments, Alcaro et al. (2002) evaluated behavioural responses to FST in naive animals and in animals pre-exposed to the FST 14 days before the test session. They showed a major effect of the pre-session FST in mice on immobility time with a dramatic increase after pre-exposure. For Andreatini and Bacellar (2000), "this test showed a very low intra-class correlation coefficient in the test-retest design, which suggests a poor reliability of these measures". These results suggest that the behavioural parameters of the behavioural despair are not stable. Therefore, they are possibly more related to state than trait characteristics, this test is not appropriate to evaluate trait characteristics which are supposed to be stable over time without treatment. Some authors use the test/retest paradigm to avoid variations and to maintain consistency in the immobility time between different groups (Hirani et al. 2002).

Discussion

Many antidepressants have been tested with the FST on mice. Some results available for all classes of antidepressants with different strains of mice are reviewed here.

In the literature, the lowest control immobility time was obtained with FVB/NJ (13 s) mice and highest with ddY (220 s).

Table 2 summarises the results for three inbred strains and four outbred strains that are compared over their results in the FST. A more detailed version of this table, with more antidepressants and strains, is available as Electronic Supplementary Material (ESM).

Inbred strains have been found very defective in the FST with antidepressants. Only one type of antidepressant (DRI), bupropion, was significantly effective in the FST with C57BL/6Rj. For C57BL6j and DBA/2, no positive result coupled with a locomotor test was found in papers we analysed. Outbred strains of mice are more responsive to antidepressants in the FST than inbred strains. These four outbred strains may be used for at least three classes of treatments. The most frequently used strains, CD1, NMRI and Swiss, have positive results with most of the antidepressants in the FST. HaM/ICR seems to be very responsive to drugs in the FST but it is a rare strain. Only one paper was found to use this strain on the FST (De Graaf et al. 1985). There are many differences between strains; DBA/2, for example, does not have an appropriate response to the FST. This strain should not be used for behavioural studies with the FST. CD-1 is not useful to discriminate different mechanisms of action in the test. It could be used as a screening model but, to recommend this strain, we need to know if Dopamine Reuptake Inhibitors (DRI, e.g. bupropion), NRI and MAO-I are effective in the

Table 2 Antidepressant effects on the FST with different strains of mice (taken from the literature)

	Inbred			Outbred			
	C57 BL/6Rj	C57 BL6J	DBA/2	CD-1	HaM/ICR	NMRI/EC	Swiss/Janvier
Atypical				*	+	*	*
DRI	*		−	+	+	−	−
NRI	−	+	−	+	+	−	*
SNRI							*
SSRI	−		−	*	+	*	*
MAO-I				+			−
TCAs	−		−	*	+	*	*

*, treatment is effective and locomotor activity was tested without significant variation
+, treatment is effective but locomotor activity was not tested
−, treatment has no potency and does not increase locomotor activity
Different categories of drugs are listed in the first column. For example, DRI includes bupropion, nomifensine or amineptine. Atypical antidepressants include mianserin, iprindole and others. A positive result, represented by a star, signifies that at least one study showed a significant effect of one drug of the considered category. For a more detailed table, Electronic Supplementary Material is available with all drugs and effects reported in different studies

FST with CD-1 without increasing spontaneous locomotor activity of the animals.

Even with a very precise binding of antidepressants, it is often difficult to understand the mechanisms of action of antidepressants. Some of our previous works showed that dopaminergic activity compounds are not easy to be active on the FST. On the other hand, the binding or the drug activity at the synaptic level is only an indirect understanding of the activity of drug in a whole animal. It was showed in our lab (David et al. 2003) as well as in Lucki's laboratory that depending on the strain, the effect size is quite different (from 0% effect for desipramine in C3H/HeJ to almost 60% of decrease of immobility time with BALB/cJ) (Lucki et al. 2001).

FST was designed by Porsolt as a primary screening test for antidepressants. It is still one of the best models for this procedure. This is a low-cost, fast and reliable model to test potential antidepressant treatments with a strong predictive validity. However, the low face and construct validities should not forbid the use of this model for neurophysiological studies. It has a great sensitivity with all the antidepressant classes and all the mechanisms of action of treatments could be determined, but clinical correlations should be considered very carefully. Studying the method of action of an antidepressant is different from studying aetiology and how to cure depression.

For this reason, some authors decided to abandon the term "model" of depression. They prefer the word "test", which corresponds to an examination of a critically key aspect of either the response to stress or to antidepressant drug action. It could help to reconsider their true role in the process of discovery of novel antidepressants (O'Neil and Moore 2003).

We totally agree that the FST is "a very specific cluster of stress-induced behaviours that have no direct, empirical relation to depression symptoms in humans" (Holmes 2003b). Care must be taken on the strain used for the test and all the experimental parameters involved. For a screening test, CD-1 can be a good strain to use to find out if a treatment has an antidepressant-like activity.

Despite their intrinsic limitations, the full potential of animal models of depression has not yet been realized and they represent an under-explored opportunity for drug development. Such opportunities arise from the molecular dissection of the biological features of the models (Wong and Licinio 2004).

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