Measuring depression in rodents

How the forced swim test is a controversial but useful tool



This is a chapter from the e-book:

Basic behavioral neuroscience in rodents



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4.1

Introduction

Depression is the world's most predominant mental health problem, affecting approximately over 300 million people worldwide [13]. It is of upmost relevance to be able to investigate this in a preclinical model. Depression in rodents is modeled through a number of ways, but mainly characterized by its core symptoms: episodes of depressed mood, decreased drive and loss of interest and pleasure, with various accessory symptoms. Evidently, modeling such a heterogeneous phenotype is very difficult, if not impossible.

Why do we test depression?

Rodent models of depression have been focused on a specific aspect of its pathophysiology, accompanied by a specific behavioral test. Given the multifactorial nature and heterogeneity of depressive-like symptoms, it can be debated that this is not the most clinically-relevant approach. However rodents were never meant to be a one-on-one comparison to humans, but rather used as a tool to model specific disease-related traits that can be tested and treated in a preclinical setting.

This principle highly applies to the case of modeling depression: By representing a specific feature of depression in a model, and testing this in a behavioral setting, it enables us to achieve a better understanding of an essential biological mechanism, basically serving as *a piece of the puzzle*.

> ### *Early life stress*
> *Early life stress is a way to model adult depression in rodents. Generally, adverse early life experiences are an important risk factor for the development of depression (and other mental disorders). This can be achieved by maternal separation; prolonged separation of pups from the mother, which causes significant amounts of stress [20]. The consequences of this early life stress are expressed in adulthood and persist for life particularly through the HPA (hypothalamic-pituitary-adrenal) axis.*

What tests can we do to measure depression?

The sucrose preference test is a test that measures anhedonia in rodents [21], which is the inability to experience pleasure from rewarding or enjoyable activities, a core depressive symptom. This test is basically a two-bottle choice test that measures the intake ratio of a sucrose (sugar) solution to water, relying on rodents' natural tendency to prefer sweet food. Depressed rodents show a decreased preference towards the sucrose solution [22].

4.2

The forced swim test

A behavioral paradigm to test depression is the forced swim test, also known as the behavioral despair test, which was introduced by Porsolt et al. in the 1970s [23,24]. This test involves placing a rat or mouse inside a cylinder filled with (lukewarm) water, which the rodent naturally tries to escape.

The test is designed to obviously let the animal fail to escape, and as animals give up after a certain period of time, and become immobile, they are removed from the container. Depressed animals give up earlier than non-depressed animals, while it has also been found that swimming behavior is generally increased after administration of (clinically used) antidepressants [25,26], which indicates a positive result in this test.



Mouse test cylinder
25 cm high
13 cm diameter

Rat test cylinder
50 cm high
30 cm diameter

Notice!

Due to the severity of the forced swim test and its impact on animal welfare, this test has come under considerable scrutiny in recent years. It's scientific utility as a depression model is debated, as there is a lack of neurobiological correlation between the behaviors measured in this test, and the human situation.

It is however important to compartmentalize the discussion surrounding the forced swim test, as it still remains an important scientific tool in academia, drug discovery and the research industry where high throughput screening of novel compounds is essential. The forced swim test is still a test with a considerable level of predictive validity, however should definitely not be considered a full spectrum analog of human depression.

The outcomes of the forced swim test are one-dimensional, however the implementation is also relatively simple and inexpensive. This is an extremely important trade-off to consider, but should not devalue the usefulness of the forced swim test as a drug discovery and validation tool.

Protocol suggestion

Preparation

- Fill the swim cylinder about 2/3rd with water, and make sure the water is around 23-25°C (check with a thermometer!)
- Transport the animals, preferably in their home cages, into the testing room and allow the animals to acclimate to this room for a minimum of 30 minutes prior to starting the test.

Pretest

- Place the animals individually into the swim cylinders (up to four cylinders can be utilized for appropriate throughput) and start the timer (video recording is optional in this phase). After 15 minutes of swimming, remove the animals from the water, dry them with a towel and return them to their home cages. If the animals are group housed, ensure that no post-swim animal is placed back into a home cage with animals that still have to undergo the pre-swim. In such instances, a temporary dry cage with fresh bedding is recommended until the animal can be returned to its home cage.

Swim test

- 24 hours after the pretest, the swim test can be performed by again placing the animals in the swim cylinder (which is 2/3rd filled with fresh lukewarm water). It is important to record this session! This session takes 5 minutes, remove the animals from the cylinders after this time and dry them before returning to their home cage or a temporary dry cage.

Setup in EthoVision

Video tracking with EthoVision allows you to detect some behaviors automatically, such as immobility, which is indicative of freezing. The three variations of mobility, immobile, mobile, and highly mobile, indicate the three most important behaviors in the forced swim test:

- Floating (immobility
- Swimming
- Climbing/escaping

There are two ways to detect this with EthoVision, and they can be used alongside each other. First is by tracking the center point of the animal and determining if it is immobile or not. Thresholds can be defined by the user. Second, you can use activity detection. This method might even give you more robust data as it focuses on changes in the arena from one video frame to the next.

Interpretation of the results

In general, a **higher immobility** score represents a more depressive-like phenotype. This can be treated with an antidepressant, like Imipramine, as seen in an example given by Slattery and Cryan (2012), decreasing immobility and increasing climbing (escape behavior) in Sprague Dawley rats [27].

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