

Anxiety and Depression Models

The following animal models of anxiety and depression are available in the laboratories of NDI neuroscientists for testing potential therapeutics.

Behavioral tests

Forced swim test

This is probably the most frequently used test of learned helplessness, a classical model of depression. The test measures the time an animal remains immobile when immersed in a water-filled cylinder from which escape is not possible. Reduction in the time during which the animal is immobile is considered a predictor of antidepressant effects, at least for some types of compounds.

Tail suspension test

In this test the time it takes an animal to stop squirming and turning when it is suspended by the tail is measured. Longer times are considered an indicator of an antidepressant effect.

Defensive burying

This test has been used for testing anxiolytics but is also sensitive to antidepressants. Defensive burying is one of the spontaneous reactions of rodents when exposed to an aversive stimulus. In the test, rodents are confronted with a weakly electrified rod placed in their cage, and react by pushing cage bedding toward it and attempting to bury it. Longer times of activity in this effort are considered an indicator of an antidepressant effect.

Light/Dark Preference

Activity in light and dark portions of a box is recorded. Avoidance of lighted portion reflects elevated anxiety while little or no time in the dark area reflects limbic disruption.

Maternal separation

Rapidly becoming the “gold standard” for evaluating anxiolytics, this test measures the number of “squeaks” made by guinea pig pups when temporarily separated from their mother. A reduction in the number of “squeaks” over a five-minute separation time has been predictive of clinical efficacy in reducing anxiety.

Elevated plus-maze

Rodents prefer to explore the enclosed 2 arms of a plus-maze elevated above floor level, compared to the un-enclosed 2 arms. Reduction in this preference by a test compound is considered predictive of an anxiolytic effect. This test is typically conducted using adult rodents and is considered supplemental to the maternal separation test (above).

Light-enhanced startle

The startle response exhibited by rodents to a loud sound is increased by the presence of a light of higher than normal intensity. This enhanced response is thought to reflect heightened anxiety, as it is blocked by antagonists directed to discrete brain areas implicated in anxiety.

Neurobiological tests

Variation in the release of monoamines

Most modern antidepressants target the serotonergic and noradrenergic systems, but most of them also act on the dopaminergic system. Using *in vivo* microdialysis to measure drug-induced release of noradrenaline, serotonin and dopamine in target brain regions provides an index of the spectrum of action of a test antidepressant compound.

Evaluation of GR receptors

One of the common effects of most antidepressant drugs is to modify the expression of brain glucocorticoid receptors (GR). Brain glucocorticoid receptors are one of the major targets of glucocorticoid hormones. A deregulation of the functional activity of these hormones is considered one of the possible biological bases of depression. Measurement of glucocorticoid receptor expression in response to a test anti-depressant provides a biochemical measure of the compound's actions. Measurement can be accomplished by Northern and Western blots, RNAase protection, *in situ* hybridization, immunocytochemistry, and *in vivo* by assaying GR translocation and binding to nuclear DNA.

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