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ANXIETY AND DEPRESSION MODELS

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

ANXIETY TESTS

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).

Ultrasonic Vocalization

Ultrasonic vocalization (USV) by rodents can occur under anxiety producing conditions. It is regarded as a "universal" anxiety measure, i.e. is sensitive to both typical and atypical anxiolytics, and occurs in response to aversive stimuli (e.g., following air puff or shock) and in classical conditioning paradigms.

Light-enhanced startle

The startle response exhibited by rodents to a loud sound is increased by the simultaneous 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.

Light/Dark preference

Activity in light and dark portions of a divided box is recorded. Increased avoidance of the lighted portion reflects elevated anxiety, while little or no preference for either the lighted or dark halves of the box reflects decreased anxiety.

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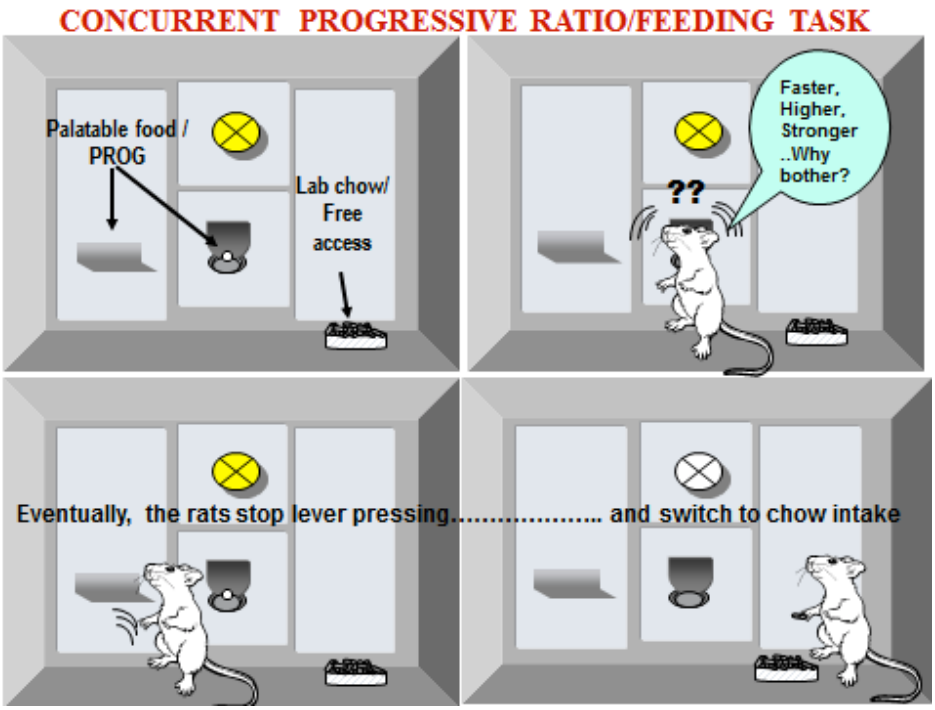
DEPRESSION TESTS

**(NEW) Effort-related choice behavior

There is growing recognition of the importance of motivation in depression, as well as a realization that depressives with major motivational symptoms are particularly resistant to treatment. In clinical tests, people with major depression show a reduced likelihood of selecting high effort alternatives when assessed in a test of effort-related decision making. Recently this behavior has been modeled in rats, using tetrabenazine, and this depression-like behavior is reversed by bupropion.

In this model, preferred food choices that result from extra effort in a lever-pressing task are reduced by drug treatment (e.g., tetrabenazine), even while food-seeking behavior overall remains constant. Potential anti-depressants with varying pharmacological profiles are tested for their ability to reverse this behavior.



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Forced swim test (Porsolt test)

This is 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. Antidepressant drugs increase swim time and reduce the length of time spent immobile. Strain of animal must be considered as the behavioral effects of some drugs have been shown to vary between in-bred and out-bred mice. For example, imipramine has been shown to be effective in CD1 mice while failing to show effects in NMRI mice.

Tail suspension test

The tail suspension test is a model of depression that measures the length of time an animal, usually a mouse, will struggle to escape while being suspended by its tail. Thus, the tail suspension test is sometimes referred to as a "dry land" version of the forced swim test. As with the forced swim test, antidepressant drugs increase the amount of time the animal spends struggling, and reduce the length of time spent immobile. Strain of animal may also be important in this test, as, for example, imipramine has been shown to be effective with NMRI mice but not with CD1 mice. The tricyclic antidepressants, such as amitriptyline and phenelzine, as well as SSRIs, are generally ineffective in this model.

Chronic mild stress

Chronic mild stress involves long term exposure to mild aversive stimuli or environmental conditions, such as food or water deprivation, soiled cage, tilted cage, or altered light/dark conditions. This model may represent anhedonia in depression. Sucrose consumption is often used as an index of anhedonia after the chronic stress treatment. All classes of antidepressants have been shown to be effective in this model, while anxiolytic and neuroleptic drugs have not. However, the results of chronic mild stress studies are sometimes difficult to replicate across laboratories.

Schedule induced polydipsia

This paradigm is conducted in a test chamber equipped with a food pellet dispenser and a water bottle. In a typical setup, the food pellets are delivered every 60 seconds, while a sipper tube for the water bottle is always available. Rats are food deprived before testing, but not water deprived. Thus, rats readily consume the food pellets when they are delivered. During the 60 seconds in

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Schedule induced polydipsia (continued)

between food pellet deliveries, rats tend to drink water from the water bottle. Over time, water consumption in this task develops into polydipsia. Once a baseline level of polydipsia is achieved, antidepressant effects are indicated by a reduction in water intake. A particular advantage of this task is that repeated administration of antidepressant drugs is necessary to lower water intake. Thus, this model can be used to assess response time to antidepressant drugs, a major clinical concern.

IN VIVO MICRODIALYSIS

Most modern antidepressant agents target the serotinergic 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.

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