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PSYCHIATRY MODELS

The following animal models of human psychiatric conditions are available at NDI laboratories for testing potential therapeutics.

PSYCHOSIS

1. BEHAVIORAL SENSITIZATION

One of the few conditions that can precipitate a psychotic state is the chronic exposure to psychostimulant drugs. Both the likelihood of occurrence and the intensity of a psychotic episode increase progressively over psycho-stimulant use. For this reason sensitization to the behavioral and neurochemical effects of amphetamine is considered an experimental model of psychosis. Indeed, amphetamine is one of the few pharmacological compounds that over repeated administration induce sensitization, i.e. an increase of some of its behavioral and neurochemical effects. Sensitization to the effects of amphetamine is also observed after repeated stress, another factor that can precipitate a psychotic state. Antagonism of amphetamine or stress-induced sensitization is considered an index of antipsychotic effect. Our laboratories have extensive experience in measuring both behavioral and neurochemical sensitization to amphetamine and stress.

2. HIGH RESPONDER RATS

High Responder (HR) rats are a model of dopaminergic hyperactivity, which is considered one of the possible causes of psychosis. High Responders, in comparison to their control Low Responder rats, display several neurochemical and electrophysiological parameters indicating higher activity of VTA dopaminergic neurons, and an over-expression of several dopamine mediated behavioral responses. These animals therefore can be used to analyze the ability of test compounds to reduce dopaminergic hyperactivity. The unique feature of this model is that the locomotor hyperactivity of HR rats is selectively reduced by atypical antipsychotics. In contrast typical antipsychotics have similar effects in High and Low Responders.

3. DAT KNOCK-OUT MICE

Mice lacking the dopamine transporter are probably one of the best models of dopaminergic hyperactivity. They have been recently proposed as a model of HD but could be used in general to test compounds that may reduce dopaminergic activity.

BEHAVIOR TESTS OF POTENTIAL ANTIPSYCHOTICS

a) Inhibition of dopamine agonist-induced locomotion

This is one of the most common tests used to screen for potential antipsychotic compounds. It is classically performed by testing whether the compound antagonizes the locomotor stimulant effects of both direct (apomorphine) or indirect (amphetamine) dopaminergic agonists.

b) Catalepsy

This test measures the time of immobility that is induced after the administration of a test compound. Most antipsychotic drugs have cataleptic effects. However drug-induced catalepsy is considered more a predictor of drug side effects rather than therapeutic effects.

c) Inhibition of apomorphine induced stereotypy

Most antipsychotic drugs block the stereotypy that is induced by apomorphine. This effect, generally attributed to dopaminergic receptors in the dorsal striatum, is considered an index of extra-pyramidal side effects of antipsychotics more than a predictor of therapeutic efficacy.

d) Pre-pulse inhibition

This test measures the ability of a compound to "gate" or inhibit environmental information. This response is impaired in schizophrenia. Normal rodents exhibit less of a startle response to a sudden loud sound if it has been preceded by a softer sound. This inhibition is diminished by amphetamine and antagonized by antipsychotic drugs.

NEUROBIOLOGICAL ASSAYS OF ANTIPSYCHOTIC EFFECTS

a) Variation in dopaminergic activity

Most antipsychotic drugs interact with the dopaminergic system and are antagonists of the dopamine D2 receptors. Acutely they increase dopamine release by blocking the auto-receptors, mostly D2. Chronically they inhibit the

activity of dopaminergic neurons by a poorly understood mechanism. Our laboratories can provide a measure of dopaminergic activity by microdialysis, which estimates dopamine release in a target brain area, or by electrophysiology, measuring firing rate of dopaminergic neurons in the VTA.

b) Variation in the expression of Fos-like proteins

A critical component of one major theory of the basis of schizophrenia is that it involves a deregulation of dopaminergic and glutamatergic transmission. One common effect of dopaminergic and glutamatergic drugs is to induce an increase in the expression of Fos-like proteins in the striatum. In particular most antipsychotics modify Fos expression in the striatal complex.

c) Variation in the expression of opioid peptides

Changes in the expression of opioid peptides such as dynorphin and enkephalin in the striatal complex is one of the major effects of dopaminergic agonists. Such effects are antagonized by most antipsychotic drugs.

d) In vitro evaluation of dopaminergic release

The potency and efficacy of a potential antipsychotic compound can be estimated using concentration-response functions in dopaminergic cell cultures. Our laboratories are experienced in measuring extracellular concentrations of endogenous dopamine in primary cultures of dopaminergic neurons. Efficacy and potency in modifying dopaminergic release per se as well as in antagonizing the effect of a dopaminergic agonist can be quantified.

ANXIETY/DEPRESSION

BEHAVIORAL TESTS

a) 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.

b) 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.

c) 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.

d) 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.

e) Light/Dark Preference

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

f) 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).

NEUROBIOLOGICAL TESTS

a) Variation in the release of monoamines

Most modern antidepressants 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.

b) 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. Our laboratories have extensive experience measuring glucocorticoid receptor expression with various techniques, including Northern blot, RNAase protection, in situ hybridization, Western blot, and immunocytochemistry.

We can also provide an in vivo measure of GR translocation to the nucleus and binding to DNA. This constitutes the best available method for measuring the functional activity of GRs in vivo.

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