

Schizophrenia Models

The following animal models of schizophrenia are available at NDI laboratories for testing potential neuroleptics.

Behavioral outcomes

Pre-pulse inhibition

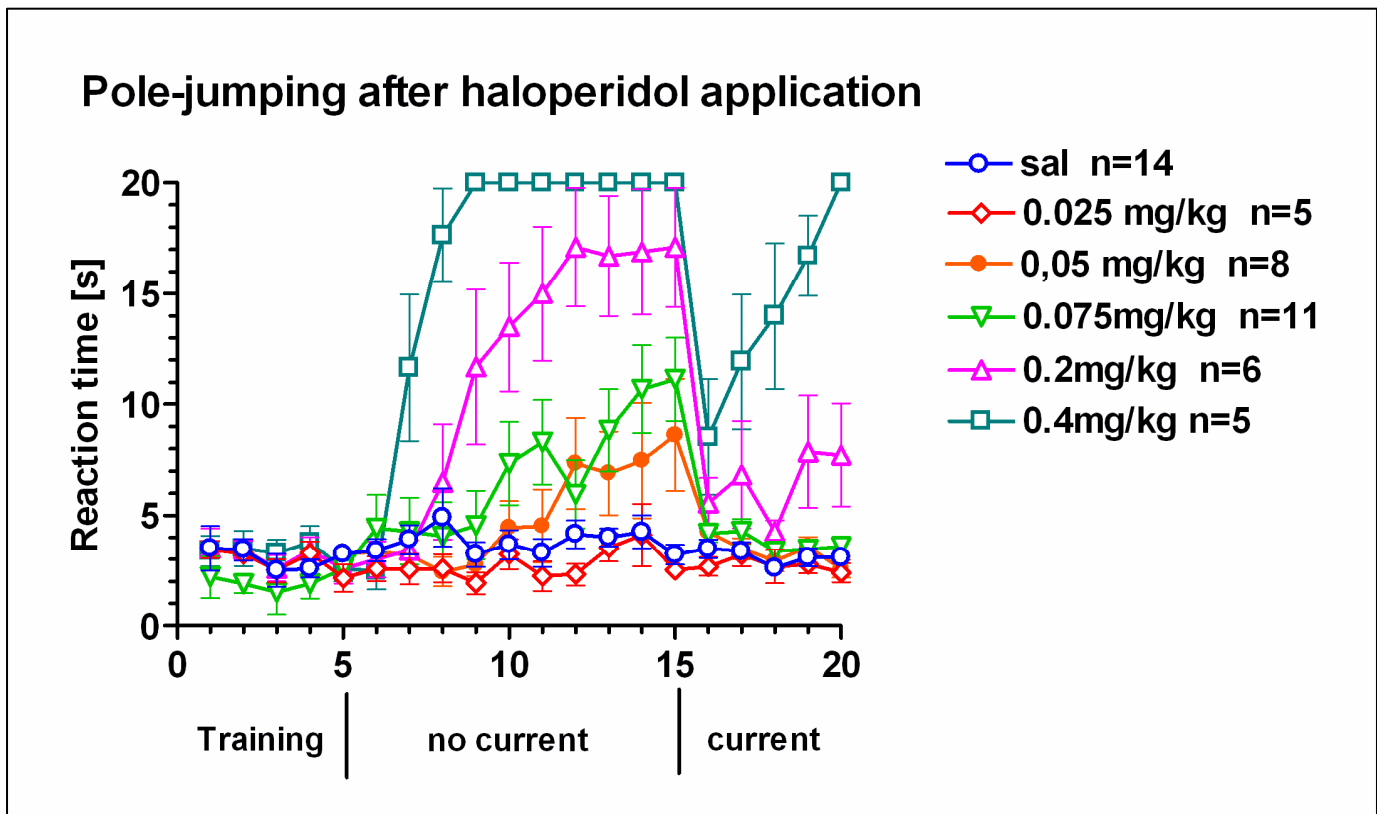
This test is the most commonly used behavioral assay of schizophrenia, although anti-psychotics other than neuroleptics may also show positive effects in this model. This test measures the ability of a compound to "gate" or inhibit environmental information. This response is impaired in schizophrenia. In a normal rodent this response is modeled by the animal's reduced (inhibited) "startle" response to a sudden loud sound if that sound has been preceded by a softer sound. This normal inhibition is diminished by amphetamine, an effect which is antagonized by concomitant administration of most neuroleptics, as well as other antipsychotic drugs.

Inhibition of a learned response

A more specific model of impaired inhibition involves a learned conditioned response. An active avoidance response by rats (jumping off a pole to avoid a shock) is inhibited (measured as increased latency to make the jump), and this inhibition is thought to be similar to the withdrawn or depressive behavior characteristic of schizophrenia. The basic paradigm of this test is as follows: rats are trained to learn a conditioned avoidance reaction (pole-jumping), where the conditioned stimulus (CS) is a sound and the unconditioned stimulus (UCS) is an electric current. The CS-UCS interval is 4 s. and training requires 8 - 10 sessions. Trained animals jump quickly to the CS, in less than 4 seconds. Then the animals are injected with various doses of a test compound (as an example, data with haloperidol are shown below). Thirty min later, performance is tested without current, i.e. the previously learned response is tested. As shown with haloperidol, avoidance reaction time increases dose- dependently. Finally the animals are again

presented with the CS-UCS combination, as a control condition. Animals injected with therapeutic doses of haloperidol (.05, .075 mg/kg, which increased latency to jump in the previous CS-only condition) show normal latencies in the presence of the electric current, i.e. their learned response is not inhibited. However animals injected with higher doses of haloperidol that affect motor functions are impaired at performing the conditioned response.

This model does not distinguish between the classical and atypical antipsychotics, the latter being more effective in treating the negative symptoms of schizophrenia. However it is specific, in that it controls for compounds that have strictly motor effects.



Reduction of social inhibition

A newer model for testing anti-schizophrenic compounds measures the reduced social interaction that normally follows injection of low doses of ketamine in rodents. The rationale for this test is that it focuses on one of the cardinal negative symptoms of schizophrenia, social withdrawal. This model has recently been validated in an extensive series of experiments (Becker at al., 2004, *Progress in Neuro-Psych. and Biological Psych.*, 28: 1267-1277). The main advantage of this test is that it reveals efficacy of compounds that directly reduce a negative symptom seen in schizophrenics.

A downside is a risk of false positives, from compounds that are anxiolytic.

Inhibition of amphetamine-induced activity

This is one of the most common tests used to screen for potential antipsychotic compounds, including neuroleptics. The rationale for the test is the clinical fact that most anti-psychotic drugs will reduce behavioral stereotypys. With rodents this test is performed by examining whether a test compound antagonizes the locomotor stimulant effects of the indirect dopamine agonist amphetamine. The test occurs in a simple open-field box, with automated recording of a variety of measures, including wall-climbing attempts, rearing, distance traveled, time spent in different types of movements, time spent within specified areas of the apparatus, etc. A baseline locomotion test is performed 1 day prior to drug dosing and then up to 4 hours post D -amphetamine/test-drug dosing.

The advantages of this test are speed and low cost. The disadvantage is lack of specificity for type of symptoms; for example a positive test compound may be one that reduces locomotor side-effects, rather than reducing the principal symptoms of schizophrenia.

Side-effect measures

Extra-pyramidal side effects are often seen in neuroleptics, and the extent of these side-effects is measured the rotarod and catalepsy tests (the latter being latency to remove paws gripping a rod).

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.

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