Two Mouse Models with Predictive Validity for Treatment of Bipolar Disorder: Amphetamine/Chlordiazepoxide-Induced Hyperactivity and Prepulse Inhibition of Acoustic Startle

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Introduction

Bipolar disorder is a brain disease associated with severe mood swings characterized by mania and depression and in severe cases psychosis. In humans, the anticonvulsant drugs valproate and carbamazepine are often used as mood stabilizers to decrease the manic symptoms of the disease (Arban et al., 2005; De Leon, 2001). Valproate is thought to be effective in treating both the mania as well as the depression associated with bipolar disorders (Ketter et al., 2006).

Animal models for bipolar disorders are scarce. Hyperactivity-based studies are often used to simulate the manic phase of the disease. For example in the baseline of a rodent-amygdala (ANPH) and chlordiazepoxide (CDP) increased head dip and arm entries in the open field, and mice. This effect is attenuated by lithium, valproate and carbamazepine which increases the time mice spend in the Y-maze in a manner which is sensitive to anticonvulsant drugs such as lithium, carbamazepine and valproate (Lamberty et al., 2001). In mice, AMPH or AMECICP-induced activity in the Open Field is also sensitive to anticonvulsant drugs. However, this model is sensitive to the mood-stabilizer levetiracetam as well as the doses of both CDP and amphetamine (Arban et al., 2005; Gould et al., 2006).

There are several mouse models going to a process through which the brain filters information. It has been shown that patients suffering from mood disorders have deficits in their sensorimotor gating (Thibaudeau et al., 2000). Lamotrigine, which is used as an anticonvulsant drug also increases prepulse inhibition in mice (Hervey et al., 2003).

Hypotheses

- C7T/CD mice can be used as a mouse model for mania as measured by AMPH/CDP-induced hyperactivity.
- Lithium, valproate and carbamazepine enhance PPI in C7T mice and thus provide another tool for pre-psychosis associated with mood swings.

Methods

Male C7T/CD mice from Jackson Laboratories (Bar Harbor, Maine) were used in this study. Upon receipt, mice were assigned unique identification numbers (tail marker) and were group housed in polyethylene cages with filter top. All animals remained housed in groups of four during the remainder of the study. Mice were maintained in a 12:12 h light-dark cycle with a light on at 06:00 h (L:12h). The room temperature was maintained at 22±1°C and the relative humidity was maintained at 50±10%. Mice were fed ad libitum (oats, sunflower seeds, and peas) and water were provided ad libitum for the duration of the study. Prior to testing, all mice were maintained on a regular basic, handled, and weighed to ensure adequate health and stability. In each test, animals were randomly assigned across treatment groups. Animals were not disturbed between test days.

Locomotor activity in an open-field environment

The open field chamber was equipped with infrared detectors (C5R Inc., St Albans, VT) surrounded by infrared photobeam sources (16 x 16 x 16). The enclosure was configured to be the open field chamber a center and perimeter zone and the planned beams were set to measure activity in the center and the periphery of the OF chamber. Distance traveled was measured from consecutive beam breaks and total score for activity. Mice were injected with vehicle, Lamotrigine, Valproate or LiCl and placed in the holding cages for 30 min following which they were exposed to water, chlordiazepoxide, d-amphetamine or d-amphetamine/CDP mixture and placed in the OF chamber for a 60 min test session.

Sensorimotor gating is a process through which the brain filters information. It has been used as a tool for the assessment of deficiencies in sensory-motor gating. Mice were placed in the Prepulse Inhibition chambers (Med Associates) for a 5 min session of white noise (70 dB) and prepulse stimuli presented at random within each block. The prepulse stimulus was presented at 200 ms before the startle stimulus, which was presented at 40 ms and responses recorded for 100 ms from startle onset. Responses were sampled for 40 ms and responses recorded for 100 ms from startle onset. These data provide two potential models for screening novel compounds that target mania and psychosis that underlie bipolar disorder.

Statistical analysis

Data from OF and PPI were analyzed using analysis of variance (ANOVA) followed by Fisher’s LSD post hoc test when appropriate. An effect was considered significant if p < 0.05

Figure 1: Time course for the effects of valproate and CDP on amphetamine-induced locomotor activity

Figure 2: Valproate decreases locomotor activity induced by amphetamine/CDP mixture, but not by amphetamine alone.

Figure 3: Open Field traces for the effects of VPA on amphetamine and mixture-induced activity

Figure 4: Lamotrigine and Lithium chloride decrease amphetamine/CDP-induced locomotor activity

Figure 5: Lamotrigine increases PPI

Figure 6: Lithium and valproate increase PPI

Mice were pretreated with vehicle or valproate (400mg/kg) for 30 min. They were then injected with amphetamine (4 mg/kg) or amphetamine + CDP (2.5 mg/kg) and activity was monitored for 60 min.

Mice were pretreated with vehicle, d-amphetamine (400 mg/kg) or d-amphetamine + CDP (2.5 mg/kg) for 30 min prior to test. Repeated measure ANOVA found a significant treatment effect. Lamotrigine significantly increased PPI compared to vehicle. Data represent mean ± SEM of 8 mice/group.

Mice were pretreated with vehicle or Lamotrigine (27 mg/kg) for 30 min prior to test. Repeated measure ANOVA found a significant treatment effect. Mice pretreated with vehicle or lamotrigine showed a significant increase in activity compared to vehicle. Data represent mean ± SEM of 8 mice/group.

References