Preclinical Psychopharmacological Properties of JZP-4, a Novel and Potent Mood Stabilizer

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Introduction

Anticonvulsants are among the most widely used pharmacological agents for CNS disorders. Applications range from epilepsy, essential tremor, neuropathic pain, bipolar disorders and drug withdrawal (Foreman et al., 2008; French et al., 2003; Leach et al., 2002; Theodore et al., 2007). However, due to many adverse effects of these compounds, there remains a need for drugs without specific side effects and their associated tolerability.

Lamotrigine, a better tolerated, anticonvulsant has been shown to be used in the treatment of epilepsy, Lennox-Gastaut Syndrome and bipolar II (Bowden, 1998; Goldsmith et al., 2003, Leach et al., 2002; Theodore et al., 2007). Although lamotrigine is an established antiepileptic drug used to treat depression, mania, anxiety and pain (Foreman et al., 2008; French et al., 2003; Leach et al., 2002), JZP-4 (3-(5-(1H-1,2,4-triazol-1-yl)-1,2,4-triazol-1-yl)pyridine-2-amine) is structurally related to lamotrigine but has no thiophene ring and therefore is a pyridine rather than a triazine ring (Figure 1). JZP-4 is a potent calcium and sodium channel blocker that is currently in clinical trials as an anticonvulsant and moodstabilizer.

Compared to Lamotrigine, JZP-4 has lower half life making it pharmacokinetically possible to achieve therapeutic levels with shorter titration periods (Elzer et al., in press).

The current study focuses on evaluating the efficacy of JZP-4 in mice and rats models of mania, depression and anxiety.

Methods

Animals

Male C57 (6 weeks old) mice from Charles River Laboratories were used in the Four Plate Test, Male/WF 180 (4 weeks old) from Jackson Labs were used in the elevated plus maze and amphetamine/bischofitepynomethylcellulose hyperactivity tests. Male Sprague Dawley rats (250g) from Harlan were used in the rot forced test and locomotor tests. Upon receipt, all mice and rats were acclimated to the laboratory for one week. Mice were used for open field tests and subjected to light cycles in the exposure room at least 1 hour before the test. All mice were put on a 15 mg/kg dose of amphetamine (designated with amphetamine salts) prior to testing. Data are expressed as mean ± SEM.

Open Field

The open field test (OD) is used to assess both anxiety-like behavior and motor activity. The open field chambers are plexiglas square chambers (27.3 x 27.3 x 20.3 cm; Med Associates Inc., St Albans, VT) surrounded by infrared photobeam sources (16 x 16 x 16). Distance traveled is measured from consecutive beam breaks. Measurements of activity are defined as an index of motor activity (Figure 2).

Following pre-swim, animals were placed back in the same chamber for a 5-minute test session. Pretreatment time for all compounds was 30 min. The frequency of swimming, climbing and spending time in open arms was automatically recorded by the computer. Mice were injected with lamotrigine, JZP-4, diazepam, 45% cyclodextrin or Jazz Pharmaceuticals, Palo Alto, CA and PsychoGenics Inc., Tarrytown, NY, USA

Four Plate Test

The four plate test is an animal model of anxiety in which simple ongoing behavior (exploration of novel surroundings) is superseded by the demands of mild electric footshock. Antidepressant treatment has been shown to be effective in this species (Morley-Forster, 2006). The four plate apparatus (Bioscre, Chisle France) consists of a cage (150 x 150 cm) divided by four identical rectangular metal plates (14 x 15 cm), separated by a 4-cm gap. The plates are connected to a computer (2009) which tracks the movement of the animal over a 5 min period. Rates were injected with either water, desipramine, 0.5% hydroxypropylmethylcellulose (HPMC), JZP-4 or lamotrigine (i.p) 30 min prior to testing. Data represent mean ± SEM.

Statistical Analysis

Data were analyzed either by analysis of variance or student's t-test followed by Dunnett's test. All animals were tested once. The time spent, distance traveled and entries in each arm were automatically recorded by the computer. Mice were injected with lamotrigine, JZP-4, diazepam, 45% cyclodextrin or Jazz Pharmaceuticals, Palo Alto, CA and PsychoGenics Inc., Tarrytown, NY, USA

Elevated Plus Maze

The elevated plus maze test assessed anxiety. The maze (Hamilton Kinder) consists of two closed arms (16 x 16 x 16 cm in length) and two open arms (6 x 31 cm) forming a cross, with a square center platform (6 x 6 cm). All visible surfaces were made of black acrylic. Each arm of the maze was placed on a support column 35 cm above the floor. Antibiotic black powder was used to block the visual access to the animals. The arms of the plus maze are approximately 30 cm apart. The arms are divided into two equal parts by a 1-cm gap. The arms leading to the open field are called the closed arm of the maze. The maze was placed in the center of the elevated plus maze facing the closed arm for a 5-min run. All animals were tested once. The time spent, distance traveled and entries in each arm were automatically recorded by the computer. Mice were injected with lamotrigine, JZP-4, diazepam, 45% cyclodextrin or Jazz Pharmaceuticals, Palo Alto, CA and PsychoGenics Inc., Tarrytown, NY, USA

Rats were injected with water, desipramine, 0.5% hydroxypropylmethylcellulose (HPMC), JZP-4 or lamotrigine (i.p) 30 min prior to a placing in the locomotor activity chambers. Data represent mean ± SEM.

Summary

- JZP-4 showed higher potency and efficacy than lamotrigine in the mouse amphetamine/CDP-induced hyperactivity model of mania. In addition, JZP-4 (1 mg/kg) significantly increased immobility and increased climbing behaviors in the rat forced swim test similar to the positive reference desipramine suggesting antidepressant-like properties of the compound. Although lamotrigine showed a trend to decreasing immobility, the effect did not reach significance. The anti-depressant-like activity of JZP-4 in the rat forced swim test was not a result of a negative property of the compound as seen in the locomotor activity tests. The greater potency of JZP-4 in the mania and depression models could well be related to its higher potency at the sodium channels or the additional action of JZP-4 on calcium channels.

- Both JZP-4 and lamotrigine showed anxiolytic-like activities as seen in the increased number of punished crossings in the four plate test in mice. In addition JZP-4 was active in the elevated plus maze. At 15 mg/kg, mice treated with JZP-4 spent more time in the open arms compared to vehicle. Lamotrigine showed a non-significant trend to also increasing the % time mice spent in the open arms.

- These data suggest that JZP-4 may have the pharmacological attributes of an effective mood stabilizer both for suppressing the switching from mania to depression in bipolar disorder and

- JZP-4 showed anti-manic activities in the amphetamine/CDP-induced hyperactivity model in mice.

Figure 1: Chemical Structures of Lamotrigine and JZP-4

Figure 2: JZP-4 exhibits antidepress-like properties in rats

Figure 3: Neither JZP-4 nor lamotrigine showed locomotor-stimulant properties in rats

Figure 4: JZP-4 and lamotrigine increased the number of punished crossings in mice

Figure 5: JZP-4 increased the percentage of the time spent in the open arms of the Elevated Plus Maze

Figure 6: JZP-4 did not cause sedation in the Elevated Plus Maze

Figure 7: JZP-4 showed anti-manic effects in the amphetamine/CDP-induced hyperactivity model in mice

References