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Efficacy of olanzapine and haloperidol in an animal model of mania

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Abstract

Purpose: Intracerebroventricular (ICV) administration of ouabain, a potent sodium pump inhibitor, has been used to model mania. Antipsychotic agents have demonstrated efficacy in the management of acute mania. This study was undertaken to determine the prophylactic efficacy of olanzapine and haloperidol in the ouabain mania model.
Methods: Male Sprague–Dawley rats (4–8/group) were treated with two haloperidol decanoate intramuscular shots one week apart (21 mg/kg) or twice daily olanzapine intraperitoneal injections at low dose (1 mg/kg/day) or high dose (6 mg/kg/day) for 7 days prior to ICV administration of ouabain. Open field locomotion was quantified at baseline and after ouabain administration.
Results: Ouabain caused a significant increase in open field locomotion (253.7±SEM 55.12 vs control 53.1±12.13 squares traversed in 30 min in the olanzapine experiments, $P<0.05$; and 236.5±41.42 vs 129.3±38.23, $P<0.05$ in the haloperidol experiments). Olanzapine alone at low dose (102.2±37.7) or high dose (151.2±49.2) did not alter open field activity. Low dose olanzapine (176.6±73.27) but not high dose (307.5±167.32) caused a modest reduction of the ouabain effect. Haloperidol alone significantly reduced motoric activity compared to control (55.6±18.0, $P<0.05$), and prevented ouabain-induced hyperactivity (60.3±33.1, $P<0.05$).
Conclusion: Haloperidol, but not olanzapine, demonstrated efficacy in this mania model, but methodological details may have reduced the effect of olanzapine.
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Keywords: Bipolar disorder; Haloperidol; Hyperlocomotion; Na,K-ATPase; Olanzapine; Ouabain; Sodium pump

Olanzapine, a new psychotropic with antipsychotic activity has shown efficacy in placebo-controlled, blinded trials in reducing acute manic symptoms (Tohen et al., 1999, 2000) and has recently been approved for that indication by the United States Food and Drug Administration. In long-term randomized comparison trials, olanzapine appears to be equivalent to divalproex and superior to lithium in maintaining euthymia (Tohen et al., 2003, 2005). In placebo-controlled relapse prevention studies olanzapine is superior to placebo in bipolar relapse prevention (unpublished cited in Muzina and Calabrese, 2005). Haloperidol is an older antipsychotic agent that remains in wide clinical use. In recent studies, this agent has also demonstrated acute anti-manic efficacy (McElroy et al., 1996; Tohen et al., 2001; Sachs et al., 2002). Prophylactic utility of this agent in long-term studies has not been adequately examined.

Intracerebroventricularly (ICV) administered ouabain can induce hyperlocomotion in rats (El-Mallakh et al., 1995; Decker et al., 2000) which persists for several days (Ruktanonchai et al., 1998) and can be fully prevented by prior lithium administration (Cooper et al., 1996; El-Mallakh et al., 2003). Ouabain is a specific and potent inhibitor of the sodium and potassium-activated adenosine triphosphatase (Na,K-ATPase or Na pump). Its administration inhibits brain Na,K-ATPase activity (Ruktanonchai et al., 1998) and is believed to model the Na pump reduction seen in peripheral red cells of manic subjects (Looney and El-Mallakh, 1997) and cerebral grey of post mortem bipolar patients (Rose et al., 1998).

Abbreviations: aCSF, artificial cerebrospinal fluid; ICV, intracerebroventricular; IM, Intramuscular; Na,K-ATPase or Na pump, sodium and potassium-activated adenosine triphosphatase; NMDA, *N*-methyl-D-aspartate; SEM, standard error of mean.

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The goal of this investigation is to examine the utility of the ouabain animal model of mania in foretelling the possible prophylactic effect of typical and newer neuroleptic medications in human bipolar disorder. The hypothesis is that the results in the model will be similar to those seen in humans and the tested antipsychotic agents would prevent ouabain-induced hyperactivity. The results suggest that while olanzapine had a small effect in reducing ouabain-induced hyperlocomotion, it does so at a fraction of the effect seen with lithium. Haloperidol appears to be more effective, but this may be due to its hypokinetic (parkinsonian) effect.

1. Methods

The study was reviewed and approved by the Institutional Animal Welfare Committee.

The current study followed previously described techniques (El-Mallakh et al., 1995; Decker et al., 2000). Male Sprague–Dawley rats (250–300 g, $n=4–8$ per group with a greater number of animals used to compensate for greater baseline variability) were housed individually, on bedding, with free access to food and water in a 12:12 h::dark:light environment. All experiments were started after the rats acclimated in the animal facility for one week after shipping.

Animals generally arrived to the animal facility on days −10 to −7. Two doses of olanzapine were chosen: 1 and 6 mg/kg/day. Since the half-life of olanzapine in rats is approximately 3 h (compared with 27 h in humans), the lower dose used is some five times higher than clinical doses (Potts, 2000). Nonetheless, at the time of testing, 12 to 16 h after the last IP injection, the animals would be expected to have equivalent plasma levels to human patients (Potts, 2000; Callaghan et al., 1999) without a sedative effect. Olanzapine was administered IP in two daily doses for 7 days. Five microliters of ouabain 10^{-5} M diluted in artificial cerebrospinal fluid (aCSF) (Changaris et al., 1988) or aCSF alone, were injected through the cannulae immediately prior to activity testing on day 14. Haloperidol was administered at 21 mg/kg/injection because this dose is associated with neurochemical brain changes in rats (Li et al., 1993).

Surgery was performed on day zero. Open field testing was performed on days 0, 7, and 14. Intraperitoneal (IP) olanzapine injections were started on day 7, after completion of baseline behavioral testing, and continued until day 13. The last olanzapine dose was 12–16 h prior to final open field testing on day 14. Intramuscular (IM) haloperidol decanoate injections were performed on days 0 and 6.

As previously described (Changaris et al., 1988; El-Mallakh et al., 1995), ICV cannulae were surgically implanted into the left lateral cerebral ventricle following total anesthesia (IM ketamine 90.0 mg/kg and acepromazine 0.91 mg/kg). Cannulae were advanced to a depth of 3.5 mm through a number 60 hole drilled 2.5 mm lateral and 1 mm caudal to the bregma while the animal was fixed in a stereotactic setup.

Behavioral testing was carried out in an open field arena (16 contiguous squares of 21.5×21.5 cm for a total area of 86×86 cm). The data were expressed as the number of squares traversed in 30 min. Data were analyzed by ANOVA with post hoc Fisher PLSD.

2. Results

ICV ouabain induces significant open field hyperlocomotion (Figs. 1 and 2). Olanzapine alone at either low dose or high dose, did not significantly alter open field activity (Fig. 1). Low dose olanzapine nonsignificantly reduced ouabain-induced hypeactivity. Locomotion in olanzapine preadministered rats were not significantly different from either control animals or ouabain-treated animals (Fig. 1). High dose olanzapine did not alter ouabain-induced hyperlocomotion (Fig. 1).

Haloperidol alone significantly reduced activity in aCSF-administered rats (Fig. 2). This hypolocomotor effect is believed to be equivalent parkinsonism in humans. Haloperidol also significantly reduced the ouabain-induced hyperlocomotion, but this may have been due to the parkinsonian effect (Fig. 2). Haloperidol alone was not significantly different from haloperidol plus ouabain.

3. Discussion

Olanzapine appears to have a mild effect in reducing ouabain-induced hyperactivity in rats at doses comparable to those consumed by human patients (Potts, 2000; Callaghan et al., 1999). However, this is only 45% of the effect observed for lithium in this model (El-Mallakh et al., 2003). Higher doses of olanzapine are wholly ineffective (Fig. 1). A similar biphasic response has been observed in olanzapine's ability to facilitate *N*-methyl-D-aspartate (NMDA)-induced inward current in hippocampal slices (Wang et al., 2000). Haloperidol appeared very effective in normalizing the hyperlocomotion induced by ouabain (Fig. 2) However, this effect may be due to the bradykinetic (parkinsonian) effect of haloperidol administered alone (Fig. 2).

Determining the appropriate dose of a neuroleptic in an animal model is a difficult enterprise (Kapur et al., 2003). Several

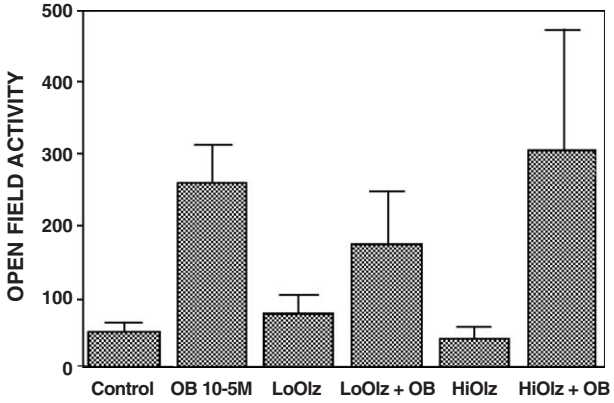

Fig. 1. The effect of olanzapine on ouabain-induced open field hyperlocomotion as measured by number of squares traveled in 30 min in the open field arena. Neither low dose (1 mg/kg/day) nor high dose (6 mg/kg/day) olanzapine alone alters open field activity. Low dose olanzapine nonsignificantly reduces ouabain-induced hyperactivity (not significantly different from either control or ouabain) but high dose olanzapine is totally ineffective. (Means±SEM bars, $n=5–8$ rats/group). OB 10-5M=ouabain 10^{-5} M; LoOlz=low dose olanzapine, 1 mg/kg/day; LoOlz+OB=low dose olanzapine, 1 mg/kg/day plus ouabain 10^{-5} M; HiOlz=high dose olanzapine, 6 mg/kg/day; HiOlz+OB=high dose olanzapine, 6 mg/kg/day plus ouabain 10^{-5} M.

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