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LITHIUM AUGMENTATION OF THE EFFECTS OF DESIPRAMINE IN A MOUSE MODEL OF TREATMENT-RESISTANT DEPRESSION: A ROLE FOR HIPPOCAMPAL CELL PROLIFERATION

O. F. O'LEARY,[a]* S. ZANDY,[a] T. G. DINAN[b,c] AND J. F. CRYAN[a,b]*

[a] *Department of Anatomy and Neuroscience, University College Cork, Ireland*

[b] *Alimentary Pharmabiotic Centre, University College Cork, Ireland*

[c] *Department of Psychiatry, University College Cork, Ireland*

Abstract—Approximately 50% of patients with a major depressive episode fail to achieve remission with first-line antidepressant treatments. Second-line treatment strategies for such patients include lithium augmentation of antidepressants, particularly with tricyclic antidepressants. The neurobiological mechanisms underlying the therapeutic effects of lithium augmentation are not yet fully understood. Unravelling these mechanisms could aid the development of more effective antidepressant drugs. In the present study, we investigated whether chronic treatment with a combination of lithium and the tricyclic antidepressant, desipramine, could produce antidepressant-like behaviour in a mouse strain (BALB/cOLaHsd) that exhibited reduced sensitivity to the behavioural effects of chronic desipramine treatment in the novelty-induced hypophagia test. Since chronic treatment with antidepressant drugs increases the proliferation of newly-born cells in the hippocampus, and hippocampal cell proliferation is required for the behavioural effects of at least some antidepressants in neohypophagia tests, the present study also investigated whether lithium plus desipramine increased cell proliferation in the hippocampus. Chronic treatment with lithium plus desipramine but neither drug alone, induced antidepressant-like behaviour and increased hippocampal cell proliferation, thus suggesting that increased hippocampal cell proliferation may be a mechanism underlying lithium augmentation of antidepressants. Moreover, since BALB/cOLaHsd mice respond to lithium plus desipramine but not to either drug alone, they may become useful in the development of a mouse model of treatment-refractory depression for which there is an unmet need.

Key words: treatment-resistant depression, lithium, antidepressant, augmentation, hippocampal neurogenesis, behaviour.

INTRODUCTION

Approximately 50% of patients with a major depressive episode fail to achieve remission with first-line antidepressant treatment (Trivedi et al., 2006). Second-line treatment strategies for such patients include: dose optimisation; switching to another antidepressant; or augmentation with an antipsychotic drug, lithium or thyroid hormone (Carvalho et al., 2007). Most of the supporting evidence for the clinical efficacy of augmentation strategies comes from lithium studies (Bauer et al., 2010). The neurobiological mechanisms underlying the therapeutic effects of lithium augmentation are not yet fully understood although there is evidence that serotonin may play a role (Haddjeri et al., 2000; Wegener et al., 2003). Unravelling the precise mechanisms underlying the efficacy of lithium augmentation could prove fruitful for the development of new more effective antidepressant drugs thus also avoiding complications associated with polypharmacy.

Animal models are powerful tools for investigating such mechanisms but yet, few studies have investigated whether lithium augments the behavioural effects of antidepressants in animal models (Nixon et al., 1994; Redrobe et al., 1998). To the best of our knowledge, animal studies investigating the behavioural effects of chronic lithium augmentation of chronic antidepressant treatment have not yet been conducted. Therefore, we investigated whether chronic treatment with a combination of lithium and the tricyclic antidepressant, desipramine, could produce antidepressant-like behaviour in a mouse strain (BALB/cOLaHsd) that exhibits reduced sensitivity to the behavioural effects of chronic desipramine treatment in the novelty-induced hypophagia test (NIH). The NIH test is a behavioural test of anxiety that is sensitive to chronic but not acute antidepressant treatment and thus is used to assess behavioural changes following chronic antidepressant treatment (Dulawa and Hen, 2005). Since the behavioural effects of chronic antidepressant treatment in hyponeophgia tests can be dependent upon hippocampal cell proliferation in some mouse strains (Santarelli et al., 2003; Wang et al., 2008; David et al., 2009; Petrik et al., 2012), and chronic antidepressant

*Corresponding authors. Address: Department of Anatomy and Neuroscience, University College Cork, Ireland. Tel: +353-21-420-5480; fax: +353-21-427-3518 (O. F. O'Leary), tel: +353-21-420-5426; fax: +353-21-427-3518 (J. F. Cryan).
E-mail addresses: o.oleary@ucc.ie (O. F. O'Leary), j.cryan@ucc.ie (J. F. Cryan).

Abbreviations: BDNF, brain-derived neurotrophic factor; GCL, granule cell layer; GSK3, glycogen synthase kinase 3; NGS, normal goat serum; NIH, novelty-induced hypophagia; qRT-PCR, Quantitative Real Time-PCR; SGZ, subgranular zone; VEGF, vascular endothelial growth factor.

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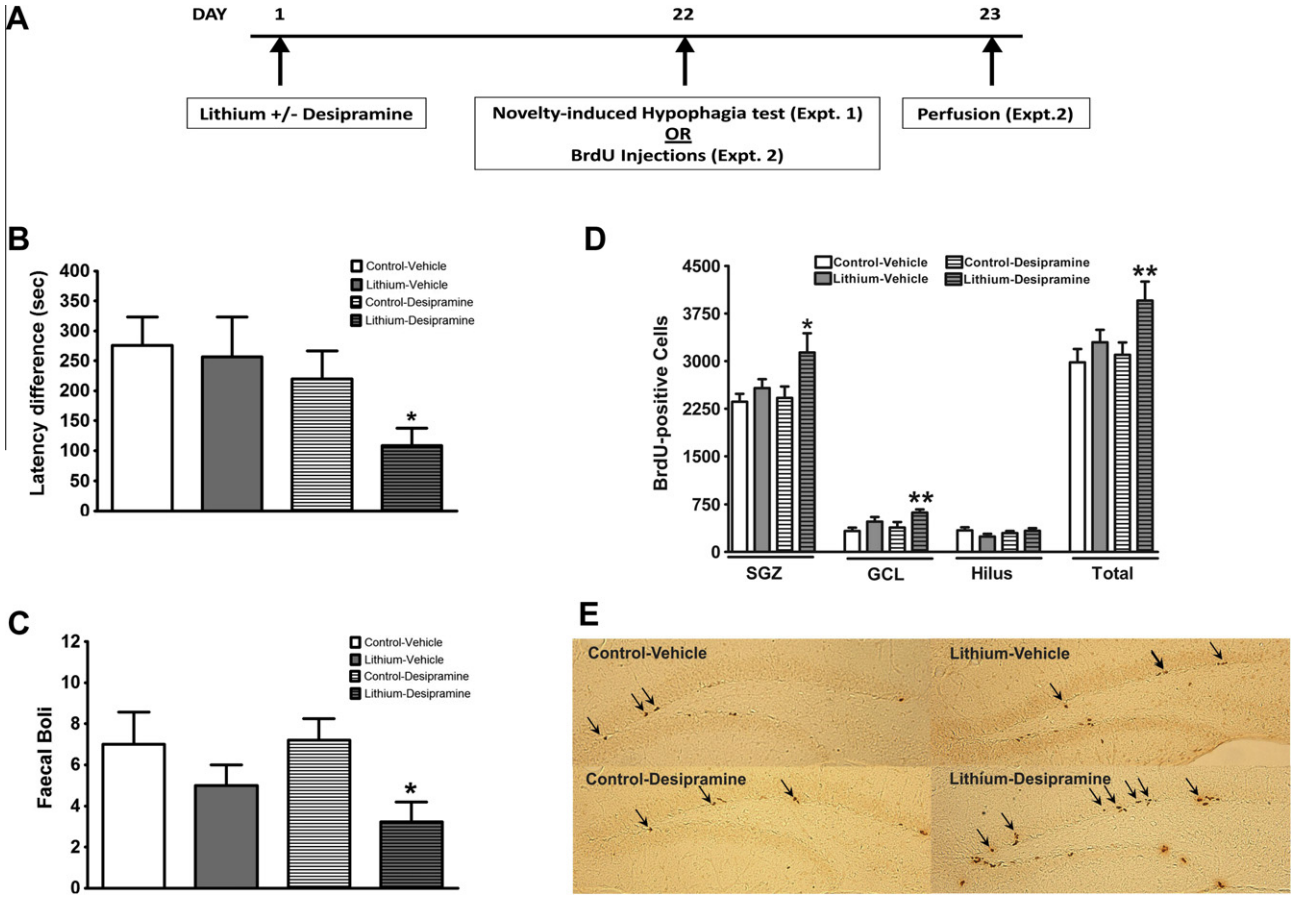

Fig. 1. A combination of lithium plus desipramine but neither drug alone increases antidepressant-like behaviour and hippocampal cell proliferation in the BALB/cOLaHsd mouse strain. (A) Experimental design: two separate cohorts of mice were used for the behavioural (n = 9–10 per treatment group) and hippocampal cell proliferation experiments (n = 6 per treatment group). (B) In the novelty-induced hypohagia (NIH) test, a combination of lithium plus desipramine but neither drug alone decreased the latency (latency in novel cage minus latency in home cage) to drink the milk, thus indicating an antidepressant effect. (C) A combination of lithium plus desipramine but neither drug alone decreased defecation in the novel cage, thus indicating a reduction in an autonomic stress response. (D and E) A combination of lithium plus desipramine but neither drug alone increased cell proliferation in the dentate gyrus of the hippocampus with this effect occurring specifically in the subgranular zone (SGZ) and granule cell layer (GCL) but not in the hilus. Arrows indicate examples of cells or clusters of cells that are BrdU-positive. *Significantly different to the control diet-vehicle group according to Fisher's PLSD $^{*}p < 0.05$, $^{**}p < 0.01$.

treatment can increase hippocampal cell proliferation and neurogenesis in depressed humans (Boldrini et al., 2009; Lucassen et al., 2010), we also examined the effects of combination treatment on hippocampal cell proliferation in these mice.

EXPERIMENTAL PROCEDURES

Subjects

Nine-week-old male BALB/cOLaHsd mice (Harlan, UK) were housed under controlled conditions (temperature 20–21 °C, 55–60% humidity) on a 12 h light/dark cycle and provided with chow and water *ad libitum*. Mice were acclimated to housing conditions for one week prior to experimental treatment. Experiments were conducted in accordance with the European Directive 86/609/EEC and the Recommendation 2007/526/65/EC, and were approved by the Animal Experimentation Ethics Committee of the University College Cork. All efforts were made to minimise the number of animals used and their suffering.

Experimental design and drug treatment

Three separate cohorts of male 9-week-old BALB/cOLaHsd mice were fed a lithium-supplemented diet (0.2% LiCl; Teklad, Harlan) or control diet as previously described (O'Leary et al., 2010) and received daily injections of either desipramine (10 mg/kg (calculated as base weight), 10 ml/kg, i.p.) or saline for 21 days (Fig. 1A). Similar doses of desipramine have previously been reported to have antidepressant-like behavioural effects and increase hippocampal cell proliferation in the mouse brain (Crowley et al., 2004; Gur et al., 2007; O'Leary et al., 2007). The dose of lithium was chosen based on previous reports that similar treatment regimens achieved serum lithium levels of 0.75–0.97 mM in mice (Chen et al., 2000; Riadh et al., 2011) which is within the therapeutic concentration range (0.6–1.2 mM) in humans. Mice were also given free access to a second drinking bottle containing 0.89% NaCl to prevent lithium-induced ion imbalance (Gould et al., 2008).

One day following the last drug treatment, the behaviour of one cohort of mice was examined using the novelty-induced hypophagia test (Expt. 1; Fig. 1A), another cohort of mice were injected with BrdU (75 mg/kg, i.p) every 2 h over an 8-h period to label newly-born cells as previously described (Wu and Castren, 2009; O'Leary et al., 2012) (Expt. 2; Fig. 1A), and a