THE EFFECT OF CHRONIC LITHIUM AND LITHIUM WITHDRAWAL ON VENTRAL TEGMENTAL AREA DOPAMINERGIC FUNCTION

L.J. Ferrie, C.M. Martin, A.H. Young, S.E. Gartside and R. McQuade (A.K. Daly)  
Psychobiology Research Group. School of Neurology, Neurobiology and Psychiatry,  
University of Newcastle upon Tyne, NE 2 4HH, UK.

The mesocorticolimbic dopamine (DA) system arises in the ventral tegmental area (VTA). Evidence suggests that dysfunction of this system maybe associated with bipolar disorder (Wise, 1982). Lithium is effective in the prophylactic treatment of bipolar disorder however on withdrawal of lithium therapy patients are at increased risk of mania (Goodwin, 1994). It has been proposed that modulation of the mesocorticolimbic DA system underlies both the therapeutic action of lithium and the withdrawal induced mania (Berggren, 1985). Here we have used in vitro extracellular electrophysiology to examine the effects of chronic lithium treatment and withdrawal from chronic lithium treatment on VTA DAergic neuronal function in the rat.

Male lister hooded rats (140-180 g) were given control or lithium (0.17% LiCl) containing diet for 28 days, or lithium diet for 25 days followed by control diet for 3 days. On day 28 rats were sacrificed and brain slices (350 µm) containing the VTA were collected. Slices were perfused with oxygenated artificial cerebrospinal fluid at 36°C, and spontaneously active putative DAergic neurones recorded in the VTA. Initial studies were carried out on naïve animals to characterise VTA neuronal responses to DA (30-300 µM) and NMDA (3 -10 µM). Drugs were applied via the perfusion. A single average value for each animal was calculated from the 2-4 neurones recorded.

Neurones included in the analysis had triphasic action potentials of long duration (> 2 ms) and fired in a slow and regular pattern (coefficient of variation of interspike interval <15%), typical of DA neurones. In neurones from naïve animals, two minute application of DA caused a concentration-dependent inhibition which was attenuated by the D2 antagonist, haloperidol (response to 300 µM DA in the presence and absence of 50 µM haloperidol: 35 ± 13.3% and 97 ± 7.9% inhibition of firing respectively). NMDA caused a concentration dependent excitation which was blocked by the NMDA receptor antagonist AP-5 (response to 10 µM NMDA in the presence and absence of 50 µM AP-5: 105.5 ± 7.3% and 256.5 ± 85.4% increase in firing rate respectively). A total of 84 neurones from 12 control, 8 lithium and 8 lithium withdrawn animals was recorded. There was no significant difference in mean basal firing rate between the three groups (1.27 ± 0.11 Hz in control, 0.99 ± 0.12 Hz in lithium treated and 1.17 ± 0.11 Hz in lithium withdrawn animals). DA (30-300 µM) caused a concentration-dependent inhibition in firing activity; this did not differ between treatment groups (two-way ANOVA p > 0.05). NMDA (3 -10 µM) caused a concentration dependent increase in firing activity, this did not differ between treatments (two-way ANOVA p > 0.05).

Results from this study confirm that DA-induced inhibitions and NMDA-induced excitations in VTA DAergic neurones are mediated by D2 like receptors and NMDA receptors respectively. Lithium treatment and lithium withdrawal did not appear to affect either basal firing of VTA DAergic neurones or their responses to DA and NMDA. However, these results do not preclude the possibility that, in vivo, lithium treatment may alter VTA function by modulation of afferents projection.