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Research Report

Lithium modulates cortical excitability *in vitro*

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ABSTRACT

The sometimes devastating mood swings of bipolar disorder are prevented by treatment with selected antiepileptic drugs, or with lithium. Abnormal membrane ion channel expression and excitability in brain neurons likely underlie bipolar disorder, but explaining therapeutic effects in these terms has faced an unresolved paradox: the antiepileptic drugs effective in bipolar disorder reduce Na^+ entry through voltage-gated channels, but lithium freely enters neurons through them. Here we show that lithium increases the excitability of output neurons in brain slices of the mouse olfactory bulb, an archetypical cortical structure. Treatment *in vitro* with lithium (1 to 10 mM) depolarizes mitral cells, blocks action potential hyperpolarization, and modulates their responses to synaptic input. We suggest that Na^+ entry through voltage-gated channels normally directly activates K^+ channels regulating neuron excitability, but that at therapeutic concentrations, lithium entry and accumulation reduces this K^+ channel activation. The antiepileptic drugs effective in bipolar disorder and lithium may thus share a membrane target consisting of functionally coupled Na^+ and K^+ channels that together control brain neuron excitability.

1. Introduction

Li^+ is the primary treatment for bipolar disorder, but after more than 50 years since its first reported use (Cade, 1949), its mechanism of action remains enigmatic. Reported actions of Li^+ include effects on monoamine metabolites, neurotransmitter receptors, intracellular second messengers (the phosphotidylinositol cycle in particular), immediate early genes and response elements, membrane ion pumps, neuroprotection and neurogenesis, but which of these, if any, might be the primary therapeutic action of Li^+ remains unclear (reviewed in Atack et al., 1995; Belmaker, 2004; Gurvich and Klein, 2002; Askland, 2006).

Bipolar disorder is a heritable, chronic, periodic disturbance of function in an electrically excitable tissue, and as such it has the characteristics of an ion channel disease (Gargus, 2006; Askland, 2006; Askland and Parsons, 2006). Extensive genetic association studies (Askland and Parsons, 2006; Askland, 2006; The Welcome Trust Case Control Consortium, 2007; Askland et al., 2009) conclude that bipolar disorder may result from altered expression of membrane ion channels in brain neurons. Antiepileptic drugs acting on ion channels are commonly used to treat bipolar disorder (Gargus, 2006, Rogawski and Loscher, 2004b), for which they are the only established alternative to Li^+. The primary shared mode of action of the antiepileptic drugs is to block voltage-gated Na^+ channels (Rogawski and Loscher, 2004a; Errington et al., 2005; Askland, 2006), but Li^+ readily passes through these same channels (reviewed in Hille, 2001). Thus although Li^+ and antiepileptic drugs each stabilize mood, it has not been

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apparent how ion channels controlling membrane excitability could be their common target of action.

Neuronal membrane potential is controlled mainly by relative membrane permeabilities to Na^+ and K^+ ions. Overlapping ranges of voltage-sensitivity allow voltage-gated Na^+ and K^+ channels to functionally interact, and in addition, Na^+ entry directly activates K^+ channels, generating a Na^+-activated K^+ current (IK_{Na}) (Bhattachargee and Kaczmarek, 2005). Li^+ entry readily substitutes for Na^+ in generating inward current, but reduces outward current, affecting the resting membrane potentials or action potentials in many types of brain neuron (Mayer et al., 1984; Schwindt et al., 1989; Safronov and Vogel, 1996; Bischoff et al., 1998; Colino et al., 1998, Franceschetti et al., 2003; Liu and Leung, 2004). If clinically relevant extracellular concentrations of Li^+ (~1 mM) result in sufficient Li^+ entry to block outward current, IK_{Na} in particular, this could contribute to the effectiveness of Li^+ in bipolar disorder. We therefore investigated electrophysiological effects of Li^+ on a representative cortical principal neuron. We chose mitral cells of the olfactory bulb of the brain, as these neurons are the principal output neuron within an archetypical cortical modular circuit (Chen and Shepherd, 2005), with well-characterized membrane properties and responses to synaptic inputs *in vitro* (Carlson et al., 2000; Heyward et al., 2001; Aungst et al., 2003). Similar to many other types of central neuron, they generate voltage-gated Na^+ current at resting potentials (Heyward et al., 2001; Balu and Strowbridge, 2007) providing a route of Li^+ entry independent of action potentials, and in particular, they abundantly express IK_{Na} channels (Egan et al., 1992; Bhattacharjee et al., 2002, 2005; Budelli et al., 2009), a potential target of Li^+ treatment.

We report that Li^+ treatment *in vitro* blocks outward membrane current in mitral cells of the mouse brain. Treatment *in vitro* with Li^+ depolarized mitral cell resting membrane potentials, altered the frequency and shape of action potentials, and modulated sensitivity to depolarizing synaptic inputs. Our results suggest that at clinically relevant extracellular concentrations, sufficient Li^+ enters through Na^+ channels to suppress an outward membrane current, directly influencing membrane excitability. Ion channels regulating brain neuron membrane excitability could therefore be a common target of drugs effective in the treatment of bipolar disorder.

2. Results

We first used conventional whole-cell recording to test for an acute effect of extracellular Li^+ (10 mM) on mitral cell membrane potential and spontaneous action potential generation. Results from a typical cell during exposure to 10 mM Li^+ and wash out are shown in Fig. 1. Responses to Li^+ had a rapid onset as Li^+ solution washed into the bath (2–3 min), and were fully developed after about 5 min. As 10 mM Li^+ washed

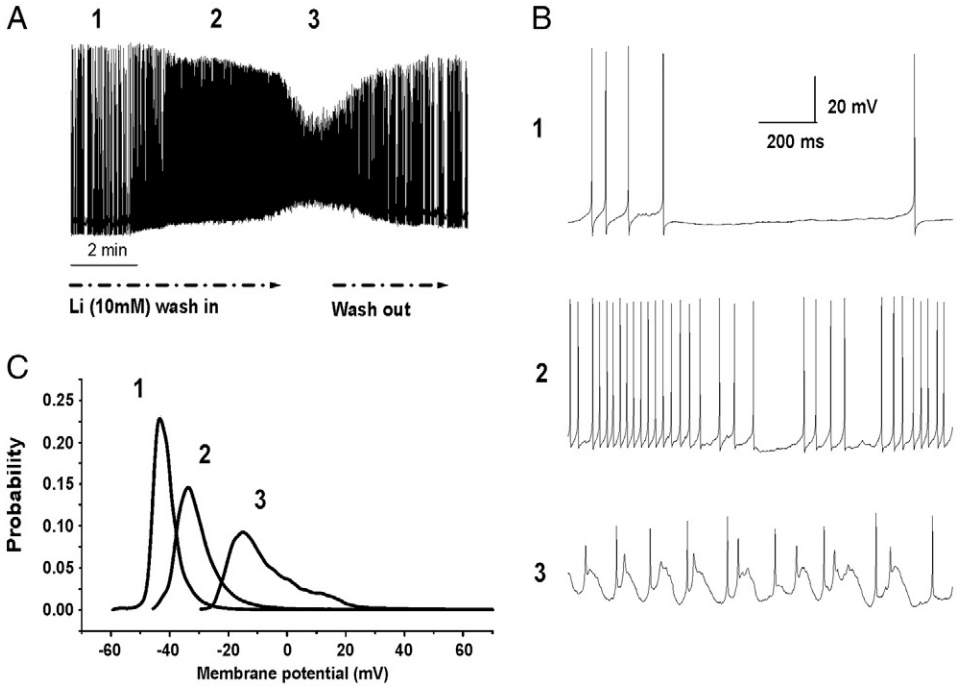

Fig. 1 – Mitral cell response to extracellular Li^+ (10 mM). A. Membrane potential recording obtained during wash in and wash out of Li^+ solution from the recording bath. 1, 2, and 3, above the trace indicate where the numbered expanded traces in panel B were extracted. B. Expanded traces extracted from the record of panel A, at the times indicated by corresponding numbers (1, 2, and 3) in panel A. C. Membrane potential distributions obtained from numbered traces 1, 2, and 3 of panel B. The distributions shift rightwards, indicating depolarization, and broaden, as more voltage points are recorded (i.e. the neuron spends relatively more time) at depolarized voltages. The broad tail of the distribution for trace 3 corresponds to the broad afterdepolarizations seen in that trace. Action potential peaks are not shown, and fall far to the right of the voltage axis.