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Research Report

Lithium prevents parkinsonian behavioral and striatal phenotypes in an aged parkin mutant transgenic mouse model

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ABSTRACT

Lithium has long been used as a treatment for the psychiatric disease bipolar disorder. However, previous studies suggest that lithium provides neuroprotective effects in neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease. The exact mechanism by which lithium exerts these effects still remains unclear. In the present study, we evaluated the effects of low-dose lithium treatment in an aged mouse model expressing a parkin mutation within dopaminergic neurons. We found that low-dose lithium treatment prevented motor impairment as demonstrated by the open field test, pole test, and rearing behavior. Furthermore, lithium prevented dopaminergic striatal degeneration in parkin animals. We also found that parkin-induced striatal astrogliosis and microglial activation were prevented by lithium treatment. Our results further corroborate the use of this parkin mutant transgenic mouse line as a model for PD for testing novel therapeutics. The findings of the present study also provide further validation that lithium could be re-purposed as a therapy for PD and suggest that anti-inflammatory effects may contribute to its neuroprotective mechanisms.

1. Introduction

Parkinson's disease is a common neurological movement disorder characterized by bradykinesia, muscle rigidity, and resting tremor. The main pathological feature of PD is loss of dopamine nigrostriatal neurons. Although the exact etiology of neurodegeneration in PD is unclear, neuronal cell loss has been linked to protein mutations, oxidative stress, environmental toxins, and neuroinflammation (Reeve et al., 2014). Currently available treatments using dopamine replacement therapy can effectively ameliorate symptoms. However, chronic use of these treatments does not provide neuroprotection and can lead to disabling drug-induced side effects (Smith et al., 2012). Development of novel treatments for PD requires extensive preclinical testing for safety and efficacy prior to making them widely available to the patient population. Therefore, a medication that provides neuroprotection and is already approved for clinical use would be an ideal candidate for PD therapy.

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Lithium is a drug approved for treatment of psychiatric diseases, primarily bipolar disorder. Lithium is able to significantly decrease manic episodes and suicidal tendencies. To date, the mechanism(s) by which lithium elicits antipsychiatric effects is not entirely clear. However, studies indicate that lithium is a multifaceted drug that modulates multiple second messenger signaling systems, gene expression, and neurotransmission (Malhi et al., 2013).

More recently, *in vitro* and *in vivo* studies have demonstrated that lithium has neuroprotective effects in various neurodegenerative diseases. Lithium has been reported to reduce brain pathology and recovery time in experimental intracerebral hemorrhage models (Kang et al., 2012). Lithium treatment also has been demonstrated to inhibit beta-amyloid peptide production in Alzheimer's disease transgenic mice (Su et al., 2004) and to reduce tau hyperphosphorylation (Munoz-Montano et al., 1997). Striatal lesions in the rat, which mimic neurodegeneration associated with Huntington's disease, are found to be attenuated by chronic lithium exposure (Wei et al., 2001). In parkinsonian mice, low-dose lithium prevents both nigrostriatal degeneration and dopamine depletion (Kim et al., 2011; Li et al., 2013; Youdim and Arraf, 2004). *In vitro,* lithium can prevent the neurotoxic effects of MPP^+ and rotenone, two agents linked to PD degeneration (King et al., 2001). These studies provide evidence that lithium could possibly be re-purposed as a treatment for neurodegenerative diseases.

To further validate findings from previous reports in a chronic disease model and to identify neuroprotective mechanisms associated with lithium, we studied the effects of low-dose lithium in an aged transgenic mouse model that expresses a parkin mutation selectively within dopamine neurons (Lu et al., 2009). The results of our study show that low-dose lithium can prevent parkin-induced motor impairment and striatal degeneration. Furthermore, parkin-related glial cell activation is also attenuated with lithium treatment. This suggests that lithium may be a viable option for PD and could act in part via its ability to reduce neuroinflammation.

2. Results

Mice in these studies (parkin mice and wildtype littermate controls) were treated with either normal chow or chow containing 0.125% lithium chloride, constituting ~25% of the lowest normal clinical dose in humans (0.2 mM sera versus 0.8 mM sera equivalents). Lithium feeding was commenced at 13 months of age and continued over a 10 month period. Higher long-term clinical dosages in humans (1.5–2.0 mM sera equivalents) have been linked in some patients to side-effects including acute encephalopathy, nephrogenic diabetes insipidus, and hyperthyroidism (Shen et al., 2007). Based on behavioral and neuropathological analyses, we noted no evidence of CNS effects associated with this lower dosage of the drug; in humans lowering of dosage is reported to result in disappearance of CNS symptoms. Additionally, mice experienced no signs indicating presence of peripheral side effects (weight loss, diarrhea, excess urination, etc).

2.1. *Lithium prevents parkin-induced behavioral impairment*

As previously reported (Lu et al., 2009), mice expressing a truncated parkin mutation associated with reduced protein solubility and function show behavioral dysfunction analogous to parkinsonism by 16 months of age. In the present study, we analyzed the number of floor plane moves, a parameter that was previously reported to be significantly reduced in this model. We found a significant reduction in the number of floor plane moves in animals expressing the parkin mutation when compared to non-transgenic (nTg) littermate controls. This impairment was prevented by low-dose lithium administration over a period of 10 months (Fig. 1A). Results from the pole test show that parkin animals take longer to descend the length of the pole. Lithium was also able to attenuate this behavior (Fig. 1B). We found no major differences in turning down behavior amongst the groups (data not shown). Finally, rearing behavior in parkin animals also decreased, an additional indicator of motor impairment previously demonstrated to be reduced in these animals (Lu et al., 2009). Rearing impairment was also prevented by lithium treatment in this parkin mouse model (Fig. 1C). No significant effects were noted in any of these parameters at earlier time points (i.e. after 3 months of lithium treatment, data not shown). In addition, lithium treatment in the nTg group showed no motor behavioral differences compared to the control group. Taken together, these behavioral results demonstrate that motor dysfunction associated with this particular parkin mutation can be prevented by chronic low-dose lithium treatment.

2.2. *Lithium attenuates parkin-induced striatal degeneration*

We found that expression of mutated parkin in these animals resulted in loss of tyrosine hydroxylase (TH) expression in the striatum (ST), similar to levels previously reported by Lu and colleagues (Fig. 2A and B). Moreover, lithium treatment significantly prevented striatal TH loss in these animals. Lithium in nTg animals also produced a modest increase in TH when compared to the control group. These data suggest that lithium can prevent previously reported parkin-induced dopaminergic striatal degeneration in this model.

2.3. *Lithium prevents parkin-induced neuroinflammation*

Expression of glial fibrillary astrocytic protein (GFAP) has been used extensively to determine the extent of astrogliosis in mouse models of PD e.g. (Mallajosyula et al., 2008). GFAP has previously been demonstrated to be elevated in effected tissues from PD patients and, in earlier *in vitro* studies, lithium was shown to inhibit 6-OHDA-mediated GFAP elevations and subsequent neurodegeneration (Su et al., 2012; Wang et al., 2013). Based on these previous findings, we examined levels of GFAP-positive cells in the striatum of parkin mutants versus controls and if levels were reduced by lithium treatment. Animals expressing the parkin mutation had significantly more $GFAP^+$ cells present in the striatum