Lithium chloride triggers primary cilia elongation and inhibits hedgehog signalling in articular chondrocytes

CL Thompson[1], *CA Poole*[2], *MM Knight*[1]
[1] The Bioengineering Institute Queen Mary University of London, London, E1 4NS, United Kingdom;
[2] Dunedin School of Medicine University of Otago, Dunedin, New Zealand

Introduction

In osteoarthritis (OA), the hedgehog signalling pathway is activated and promotes chondrocyte hypertrophy and matrix catabolism through the upregulation of ADAMTS-5 and MMP-13. Inhibiting this pathway reduces cartilage degradation in surgical models of OA. Hedgehog signalling requires the primary cilium, a microtubule-based organelle present on the majority of chondrocytes. The trafficking of hedgehog signalling proteins through the ciliary compartment is essential for pathway regulation. Recent studies indicate that lithium chloride (LiCl) is chondroprotective largely due to its anti-inflammatory properties. LiCl modulates cilia structure in numerous cell types. We hypothesise that LiCl may also affect cilia-mediated signalling pathways in chondrocytes, like hedgehog, through the regulation of ciliary structure.

Materials and Methods

Articular chondrocytes were treated with 0-50mM LiCl for up to 24hrs. Immunocytochemistry and confocal imaging were used to measure primary cilia length and prevalence. Activation of the hedgehog signalling pathway in response to recombinant Indian hedgehog (r-Ihh) was quantified using real-time PCR for GLI1 and PTCH1.

Results

LiCl induced dose dependent primary cilia elongation such that mean cilia length was increased by 95% in response to 50mM LiCl. Cilia elongation was rapid, with the majority of growth occurring within the first hour resulting in an increased proportion of cilia with bulbous tips. Following r-Ihh treatment, the expression of GLI1 and PTCH1 was significantly increased by 5.22 and 4.23-fold respectively indicative of pathway activation. Co-treatment with LiCl inhibited this response in a dose dependent manner such that 50mM LiCl completely abolished pathway activation.

Discussion

These data show that LiCl stimulates rapid, dose dependent cilia elongation in primary articular chondrocytes and inhibits hedgehog signalling. Recent studies show that the modulation of ciliary structure can affect the organisation of proteins at the distal tip of the ciliary compartment resulting and disrupts ligand-mediated hedgehog signalling. We therefore propose that pathway inhibition may be linked to the effects of LiCl on cilia structure, future studies will investigate this by examining the effects of LiCl on the localisation of Kif7 and IFT81 at the ciliary tip. This study highlights the potential for targeting the ciliary structure as a novel therapeutic approach to modulate hedgehog signalling and matrix catabolism in OA.