

LITHIUM PROTECTS THE JUVENILE BRAIN FROM IONIZING RADIATION

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ABSTRACT

Radiotherapy used in the treatment of brain tumours in children results in a range of cognitive dysfunctions that impact the quality of life in the surviving population. In past decades, great strides were made in understanding the cellular and molecular aetiology of these deficits. Postnatal hippocampal neurogenesis is highly vulnerable to irradiation, especially in the juvenile brain, and dysfunction in this structure is recognised as a prominent feature of the radiation-induced neurocognitive sequelae. With these insights, new therapies for cognitive decline after radiotherapy are emerging. Lithium, a long-known mood stabiliser, has been shown to have neuroprotective and neurogenic effects in several disease models, including irradiation, by positively harnessing neural stem/progenitor cell (NSPC) proliferation in neurogenic regions of the brain, such as the hippocampus. Despite several studies focussing on the effects of lithium, little is known about its effects in the developing brain. This is a valid concern when considering lithium as a potential treatment for childhood cognitive and degenerative disorders. In **paper I**, we addressed the radiation-induced electrophysiological changes in the dentate gyrus, which manifested as an increase in synaptic efficacy as well as a shift from long-term potentiation to long-term depression at medial perforant path granule cell synapses. These findings provided evidence that the higher radiation sensitivity of the juvenile brain compared with the adult brain was attributable to the overt disruption of plasticity mechanisms, which likely correlates with the cognitive impairments observed after radiotherapy. Unfortunately, lithium was ineffective in rescuing this particular impaired synaptic plasticity. In **paper II**, we examined the effects of lithium on growth dynamics and cell cycle arrest in irradiated NSPCs. Lithium rescued proliferation in NSPCs, reduced DNA damage, and prevented the propagation of genotoxicity. In **paper III**, we determined the distribution of lithium in the brains of young mice using time-of-flight secondary ion mass spectrometry. This technique demonstrated that lithium regionalised in brain structures with high cell density, such as neurogenic areas, and this spatial distribution was associated with changes in lipids, such as vitamin E, a potent antioxidant. To exclude the potential of lithium protecting tumour cells, in **paper IV**, we examined whether delaying lithium treatment resulted in the same degree of protection as that previously observed using pre-treatment or early treatment. This study determined a safe treatment regimen for use in future clinical practice and showed that even long after radiotherapy, lithium restored neurogenesis and preserved lineage commitment, as long as periods of treatment discontinuation were allowed. Overall, this work demonstrates that the imminent use of lithium is warranted in treating the radiation-induced cognitive impairments that severely impact the quality of life in children who receive radiotherapy and survive cancer.

Keywords: young, lithium, delayed, irradiation, neurogenesis, DNA damage

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Avhandlingen baseras på följande arbeten:

- I. **Irradiation of the Juvenile Brain Provokes a Shift from Long-Term Potentiation to Long-Term Depression.** Giulia Zanni, Kai Zhou, Ilse Riebe, Cuicui Xie, Changlian Zhu, Eric Hanse and Klas Blomgren. *Developmental Neuroscience*, DOI: 10.1159/000430435 (2015)
- II. **Lithium Increases Proliferation of Hippocampal Neural Stem/Progenitor Cells and Rescues Irradiation-Induced Cell Cycle Arrest *in vitro*.** Giulia Zanni *, Elena Di Martino *, Anna Omelyanenko, Michael Andäng, Ulla Delle, Kecke Elmroth and Klas Blomgren. *Oncotarget*, DOI: 10.18632/oncotarget.5191 (2015)
- III. **Spatial Lithium Dynamics in the Juvenile Brain Elucidated using High Resolution Ion Imaging.** Giulia Zanni, Wojciech Michno, Elena Di Martino, Anna Tjärnlund-Wolf, Klas Blomgren & Jörg Hanrieder. *In manuscript*
- IV. **Delayed Lithium Treatment after Irradiation of the Juvenile Brain Positively Modulates Neurogenesis.** Vinograd Naidoo *, Giulia Zanni *, Gabriel Levy, Elena Di Martino, Klas Blomgren. *In manuscript*

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