

Modulating the inflammation after spinal cord injury: a double-edged sword



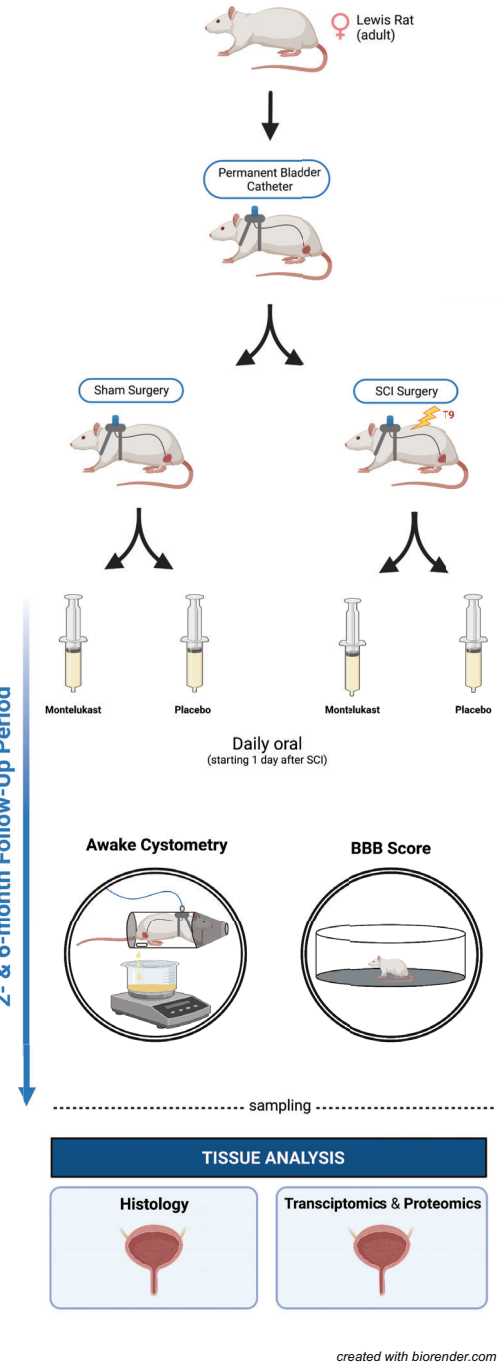
Michael Kleindorfer^{1,2}, Sophina Bauer^{1,2}, Karin Roeder^{1,2}, Evelyn Beyrer^{1,2}, David Hercher³, Patrick Heimel³, Katia Monastyrskaia⁴, Akshay Akshay⁴, Lukas Lusuard², Ludwig Aigner¹ and Elena E. Keller^{1,2}

¹ Institute of Molecular Regenerative Medicine, Spinal Cord Injury and Tissue Regeneration Center Salzburg, Paracelsus Medical University, Salzburg, Austria; ² University Clinics of Urology and Andrology, Salzburg General Hospital, Salzburg, Austria; ³ Ludwig Boltzmann Institute for Traumatology, Vienna, Austria; ⁴ Department for BioMedical Research, Functional Urology research laboratory, University of Bern, Bern, Switzerland

Introduction

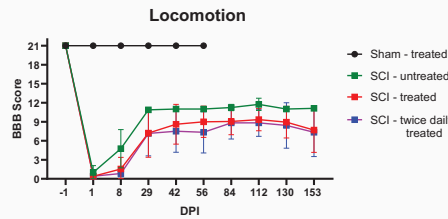
Overshooting neuroinflammation after spinal cord injury (SCI), termed secondary injury, is believed to be a major contributor to the overall damage and responsible for the chronicity of multiple symptoms. Modulation of this process might hold the potential to prevent extensive damage and create a more beneficial surrounding for regeneration. One attractive target are leukotrienes¹, small fatty acids with pro-inflammatory properties. They are among the most abundant substances at the injury site and in peripheral tissues. With early treatment of Montelukast, a licensed leukotriene receptor antagonist, we aim to limit their effects and improve functionality after injury. We focused especially on the bladder, as it is prone to developing pathophysiological dysfunctions², but it is crucial for the patients' quality of life (QoL)³.

Methods



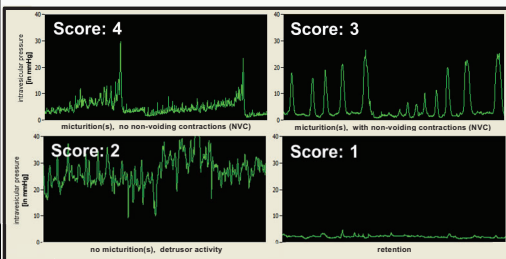
Results

1 Anti-inflammatory treatment affects locomotion



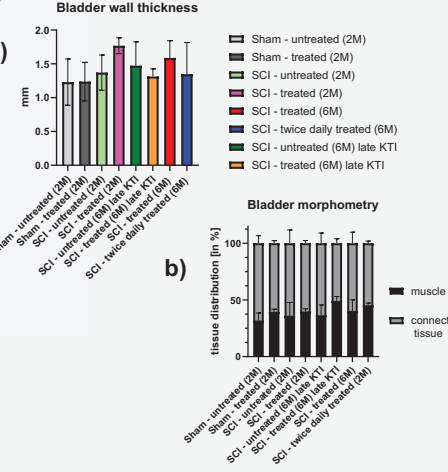
After complete functional loss, shortly after injury, BBB locomotor score (mean of both hind limbs) indicated better functional recovery for the untreated animals over the entire follow-up period of 153 days post injury (DPI). Values displayed as mean ± standard deviation.

2 Double-treatment worsens bladder functionality



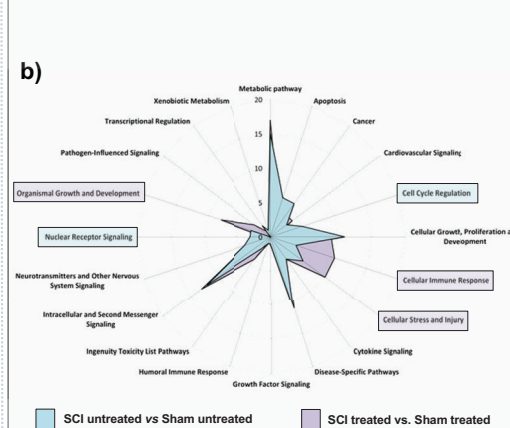
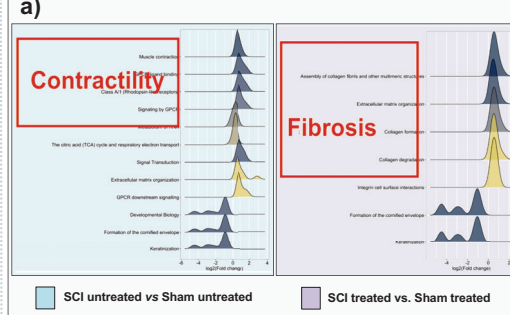
Pattern analysis of the weekly awake urodynamic recordings from single- or double-treated animals over 24 weeks post-injury (WPI) revealed differences in bladder function. After the initial drop in function for all SCI rats, the single-treated group showed better bladder function, characterized by more controlled micritions and fewer non-voiding contractions (NVC). Values are displayed as mean ± standard deviation.

3 Montelukast affects bladder wall thickness



a) Animals treated with Montelukast showed a slight increase in bladder wall thickness two months (2M) post SCI. After six months (6M), no obvious difference was observed, also not in the group with late catheter implantation (KTI). b) There was no striking change in the distribution of muscle and connective tissue in the bladder. Values displayed as mean ± standard deviation.

4 Increased bladder fibrosis and inflammatory changes in treated animals



a) Both groups (correlated to their respective shams) showed evidence of cell proliferation, increase in contractility and inflammation at two month post SCI in transcriptomic GSEA analysis. However, changes were significantly stronger (higher fold change) in the treated group. b) Radar graph of proteomic analysis displaying the main biological processes. Inflammatory and fibrotic changes, as well as injury associated response to stress, were significantly more advanced in the treated group at 2 months post SCI.

Summary

- Montelukast caused lower locomotion score
 - Montelukast negatively affected bladder function
 - Montelukast increased inflammatory and fibrotic changes in the bladder
- Our results point towards reduced bladder function, attenuated immune response and organ fibrosis if treated with Montelukast.

To our knowledge, this is the first time that a long-term anti-inflammatory treatment has been applied in a contusion spinal cord injury model of such severity in rats, with such a plethora of functional, structural and molecular data

Outlook

Due to the still ongoing immunohistochemical analysis of the spinal cord, a clearer picture of the inflammatory mechanisms and regenerative processes that differ between treated and untreated animals, can be drawn at a later time point.

References
 [1] Marchal-Sajó J, Alvarado B, Bockstein E, Holzhammer M, Garmann-Roth J, Pitschauer N, Leister I, Huber-Pajer B, Stempf K, Unger MS, Christy M, Felder T, Johnson M, Adams J, Maslach E, Aigner L. The Leukotriene Receptor Antagonist Montelukast Reduces Alpha-Synuclein Load and Restores Memory in an Animal Model of Dementia with Lewy Bodies. *Neurotherapeutics*. 2020; doi: 10.1007/s13311-020-00836-3.
 [2] Schneider MP, Hughes FM Jr, Engmann AK, Purves JT, Kasper H, Teasdale M, Sprull LS, Gula M, Schwab ME, Kessler TM. A novel urodynamic model for lower urinary tract assessment in awake rats. *BJU Int*. 2015; doi: 10.1111/bju.13038. PMID: 25597776.
 [3] Weik B. Quality of Life in Neurology Patients. *Eur Urol Focus*. 2020; doi: 10.1016/j.euf.2019.09.001.

