Repurposing of the anti-asthmatic drug Montelukast for the treatment of Parkinson's disease

Katharina Strempfl[1,2,3], Michael S. Unger[2,3], Ludwig Aigner[2,3], Jörg Neddens[1], Stefanie Flunkert[1], Birgit Hutter-Paier[1]

[1]QPS Austria GmbH, Neuropharmacology, Grambach, Austria; [2]Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg, Austria; [3]Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University, Salzburg, Austria

BACKGROUND

Neuroinflammation caused by dysregulated leukotriene (LT) signaling may contribute to the pathogenesis of neurodegenerative diseases including Parkinson's disease (PD). Montelukast (MTK) is an anti-inflammatory drug originally approved for the treatment of asthma. This study aims to evaluate the potential of MTK as a treatment for PD using the Line 61 α-synuclein transgenic mouse model.

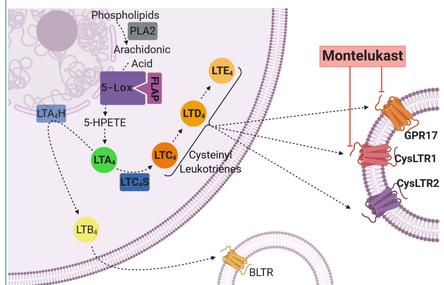

Figure 1: Leukotriene synthesis and signaling pathway. LTs derive from arachidonic acid in a synthesis pathway involving the key enzyme 5-Lox and its activator protein FLAP and evoke inflammatory responses by binding to specific LT receptors on target cells. MTK acts as a cysteinyl receptor antagonist and can inhibit the actions of cysteinyl LTs by blocking CysLTR1 and GPR17.
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Abbreviations: 5-HPETE: 5-Hydroperoxyeicosatetraenoic acid, 5-Lox: 5-Lipoxygenase, BLTR: Leukotriene B_4 receptor, CysLTR: Cysteinyl leukotriene receptor, FLAP: 5-Lipoxygenase activating protein, GPR: G-protein-coupled receptor, LT: Leukotriene, LTA_4H: Leukotriene A_4 Hydrolase, LTC_4S: Leukotriene C_4 Synthase, PLA2: Phospholipase A2

METHODS

Starting at an age of 2 weeks, 40 male transgenic (Tg) Line 61 mice and 40 male non-transgenic (nTg) littermates were treated daily orally with either MTK or vehicle for a total of 10 weeks. Behavioral tests were conducted at different time points of the treatment period to assess effects of MTK on motor function, activity and anxiety.

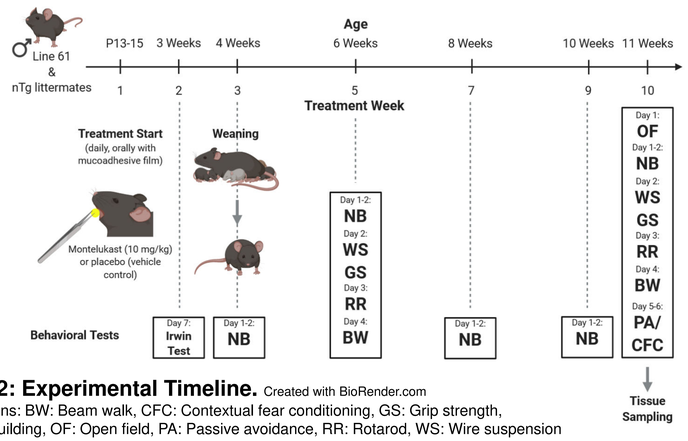

Figure 2: Experimental Timeline. Created with BioRender.com
Abbreviations: BW: Beam walk, CFC: Contextual fear conditioning, GS: Grip strength, NB: Nest building, OF: Open field, PA: Passive avoidance, RR: Rotarod, WS: Wire suspension

RESULTS

- **Improved motor coordination and balance:** MTK treatment significantly improved the performance of transgenic mice in the **beam walk test** as compared to vehicle-treated transgenic mice
- A significant reduction in the latency to start to traverse the beams from treatment week 5 to 10 suggests an effect of MTK on motivation

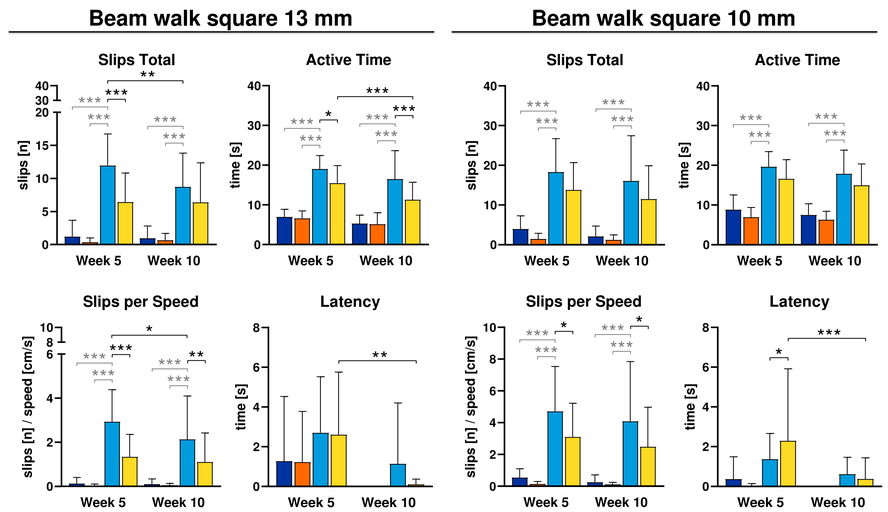

Figure 3: Beam walk test performance of mice in treatment week 5 vs. week 10 on the square 13 mm beam (left) and the square 10 mm beam (right): The graphs show the total number of slips [n], the time mice needed to traverse the beam [s], the number of slips per speed [n/(cm/s)] and the latency before mice started to walk across the beams [s]. Data is displayed as group means (n=18-22) ± SD per week. Two-way ANOVA followed by Bonferroni's multiple comparison test compared to the nTg vehicle-treated group. *p<0.05, **p<0.01, ***p<0.001.

- Trend towards a higher latency to fall from the rotating rod in the **Rotarod test** in MTK-treated transgenic animals as compared to vehicle-treated transgenic animals

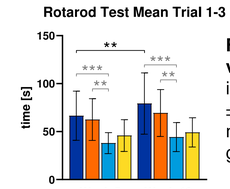

Figure 4: Rota Rod test mean results of treatment week 5 vs. week 10: The graphs show the mean latency to fall [s] of 3 individual trials. Data is presented as group means (n=18-22) ± SD per week. Two-way ANOVA followed by Bonferroni's multiple comparisons test compared to the nTg vehicle-treated group. **p<0.01, ***p<0.001.

- Motor functions were unchanged in MTK-treated mice in additional behavioral tests

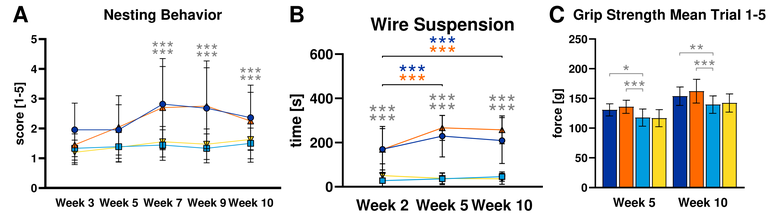

Figure 5: Motor ability tests: Scores obtained in the evaluation of the nesting behavior [1-5] in treatment weeks 3, 5, 7, 9 and 10 (A), the latency to fall off a wired grid [s] in the wire suspension test during treatment weeks 2, 5 and 7 (B) and the mean force [g] of 5 consecutive trials exerted on a grid with the fore paws in the grip strength test of treatment weeks 5 and 10 (C). Data is displayed as group means (n=18-22) ± SD per week. Mixed-effects model with repeated measures (A,B) and two-way ANOVA (C) followed by Bonferroni's *post hoc* test compared to the nTg vehicle-treated group. *p<0.05, **p<0.01, ***p<0.001

- Throughout all groups, no significant differences could be observed in emotional learning behavior, activity and anxiety as assessed by the **open field**, **contextual fear conditioning** and **passive avoidance test**

CONCLUSION AND OUTLOOK

This study investigated the effects of a 10-week daily treatment with the anti-asthmatic drug MTK on the behavior of the Line 61 mouse model for PD. Significant genotype effects were detected in motor functions, but not in emotional learning, activity and anxiety. When comparing Tg MTK-treated and Tg vehicle-treated animals, significant improvements were detected in the beam walk test already after 5 weeks of treatment and a non-significant trend towards an improved performance in the Rotarod test was observed. In contrast, both groups showed similar muscle strength results in the wire suspension and grip strength test. This suggests, that MTK treatment has an early effect on motor coordination and balance rather than on muscle strength itself. **In conclusion, these findings propose MTK as a possible treatment to alleviate motor impairments in PD.**

Future plans: Sampled brain tissue and gastrocnemius muscles will further be analyzed immunohistochemically and biochemically to investigate cellular and molecular changes underlying the effect of MTK treatment on motor coordination and balance.

For more information about the models please visit: www.qpsneuro.com or send us an e-mail: office-austria@qps.com