Strempfl *et al.: Intrinsic Activity*, 2019; **7**(Suppl.1):A3.46
doi:10.25006/IA.7.S1-A3.46
published online: 11 September 2019

INTRINSIC ACTIVITY

Joint Meeting of the Austrian Neuroscience Association (16th ANA Meeting) and the Austrian Pharmacological Society (25th Scientific Symposium of APHAR)

Innsbruck, 25–27 September 2019

MEETING ABSTRACT

A3.46

Relevance of the leukotriene signaling pathway in transgenic mouse models for α-synucleinopathies

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Background: The abnormal extra- and intracellular accumulation of α-synuclein protein (α-syn) in neurons is considered to be the major hallmark of neurodegenerative disorders collectively referred to as α-synucleinopathies. These include, among others, Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although several missense mutations in the α-syn gene (*SNCA*) encoding for α-syn have been linked to familial PD, the majority of PD cases occur sporadically with non-mutated α-syn forms. The molecular mechanisms involved in α-syn aggregation are yet not fully understood, thus treatment options are limited and only aiming to reduce associated symptoms like tremor, rigidity and bradykinesia. Neuroinflammatory processes in the brain evoking neurodegenerative conditions gain increased attention and are mediated by so-called lipid mediators of inflammation, namely leukotrienes. Leukotrienes arise from arachidonic acid and their production is initiated by the rate limiting enzyme 5-lipoxygenase (5-LOX).

Methods: With this work, we investigate the involvement of the leukotriene pathway, specifically 5-LOX expression, in relation to the α-syn aggregation in two well-established transgenic mouse models of α-synucleinopathies that overexpress wild-type human α-syn (D-line and Line 61). While in the D-line α-syn expression is restricted to several brain regions under control of the human platelet-derived growth factor-β (PDGF-β), α-syn expression is more widespread throughout the brain in Line 61 mice where α-syn is controlled by the murine Thy-1 promoter.

Results: Free-floating immunohistochemical stainings of brain sections of mice at pre-symptomatic, symptomatic and late-symptomatic stages of disease progression (D-line: 3, 6 and 9 months; Line 61: 1.5, 3 and 6 months) revealed hotspots of intra- and extracellular α-syn accumulation in the hippocampus, cortex, olfactory bulb and pons. Additionally, α-syn was highly expressed in the cerebellum of Line 61. Focusing on these areas, we investigated the protein expression of 5-LOX and the 5-lipoxygenase-activating protein (FLAP), via immunohistochemical staining. Quantitative analysis of leukotriene synthesis related gene expression (Alox5, Alox5ap, LTC4S) will be performed using qPCR.

Discussion: The aim of this study is to investigate possible alterations in leukotriene signaling, *i.e.* 5-LOX and FLAP expression, at different time points of disease progression. This analysis might uncover a new mechanism underlying the α-syn accumulation and may highlight the leukotriene signaling pathway as an ideal drug target for the treatment of PD, DLB and related neurodegenerative diseases.

Acknowledgements: This work was supported by the FFG (project 867741) and the FWF (project P 31362-B34).

Keywords: α-synucleinopathies – neurodegeneration – leukotrienes – 5-lipoxygenase

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