Göteborg, 2020

ON AGING, BEHAVIOR AND THE ROLE OF PA28αβ IN PROTEIN HOMEOSTASIS

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal Arvid Carlsson, Medicinaregatan 3, fredagen den 15 maj 2020, klockan 13.00 på länk: https://play.gu.se/media/0_x1bohu2q

av Julia Adelöf

Fakultetsopponent:
Kai Kaarniranta, Professor
University of Eastern Finland, Finland

Avhandlingen baseras på följande delarbeten

I. Adelöf, J., Andersson, M., Porritt, M., Petersen, A., Zetterberg, M., Wiseman, J., Hernebring, M. *PA28αβ overexpression enhances learning and memory of female mice without inducing 20S proteasome activity.* BMC Neuroscience 2018; 19: 70–85.

II. Adelöf, J., Ross, J.M., Lazic, S.E., Zetterberg, M., Wiseman, J., Hernebring, M. *Conclusions from a behavioral aging study on male and female F2 hybrid mice on age-related behavior, buoyancy in water-based tests, and an ethical method to assess lifespan.* Aging (Albany, NY) 2019; 11: 7150-7168.

III. Hernebring, M., Adelöf, J., Wiseman, J., Petersen, A., Zetterberg, M. *H2O2-induced cataract as a model of age-related cataract: lessons learned from overexpressing the proteasome activator PA28αβ in mouse eye lens.*

IV. Adelöf, J., Wiseman, J., Zetterberg, M., Hernebring, M. *PA28α overexpressing female mice maintain exploratory behavior and capacity to prevent protein aggregation in hippocampus as they age*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2020

ON AGING, BEHAVIOR AND THE ROLE OF PA28αβ IN PROTEIN HOMEOSTASIS

Julia Adelöf

Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

As life expectancy increases, understanding challenges related to the processes of aging are more relevant than ever. Common age-related diseases progress as consequences of accumulative protein damage and protein aggregates. PA28αβ has previously demonstrated protective effects against proteinopathy and is involved in removal of protein damage early in mammalian embryonic development. In this thesis project, female and male mice overexpressing PA28αβ have been followed and analyzed throughout their lifespan to investigate the molecular function of PA28αβ and what physiological and behavioral effects its overexpression induces.

Herein, the finding of a chaperone-like function of PA28αβ is demonstrated by enhanced aggregation prevention in hippocampal extracts from mice overexpressing PA28αβ. This function correlates to enhanced cognitive capacities represented as improved learning and memory in young adults and as exploratory activity in aging mice, the latter a strong behavioral marker of aging. Thus, we have found a previously unprecedented role of PA28αβ in neuronal protein homeostasis, which improves cognitive behavior in mice, but with altered behavioral outcomes in young and old mice.

The neuronal role of PA28αβ and its cognitive effects combined with PA28αβ's molecular mechanism of preventing protein aggregation, highlight a therapeutical potential of PA28αβ in combating proteinopathies, especially neurogenerative diseases.

Keywords: Aggregation prevention, Aging, Animal ethics, Cataract, Exploratory behavior, F2 hybrid mice, Healthy aging, Learning and memory, PA28αβ, Proteasome capacity, Sex comparisons, Water-based behavioral tests

ISBN: 978-91-7833-808-5 (TRYCK) http://hdl.handle.net/2077/63276
ISBN: 978-91-7833-809-2 (PDF)