A summary of the Proceedings of the Fourteenth International Symposium on the Neurobiology and Neuroendocrinology of Aging, Bregenz, Austria July 15-20, 2018

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Abstract A summary of the Fourteenth International Symposium on the Neurobiology and Neuroendocrinology of Aging that was held July 15-20, 2018 in Bregenz, Austria, is presented. Seventeen of the speakers that presented at the conference submitted papers relevant to the topic of their presentation as well as overviews of their respective fields and are included in this special issue. The abstracts from each poster presentation as well as the speaker abstracts are also included at the end of the preface to the special issue.

Keywords Aging · proceedings · neurobiology · neuroendocrinology

Highlights

- Seventeen presentations from the conference are highlighted
- Thirty-two poster and twenty-three speaker abstracts follow the summary
 - Next symposium will take place in July 2021 in Bregenz, Austria

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This special issue of Geroscience consists of the Proceedings of the Fourteenth International Symposium on the Neurobiology and Neuroendocrinology of Aging (<http://www.neurobiology-and-neuroendocrinology-of-aging.org/>) held in Bregenz, Vorarlberg, Austria at the Gasthof Hotel Lamm, July 15-20, 2018. The previous 13 Symposia in this series have been held biennially at the same site since 1992 and published as full proceedings (Journal of Reproduction and Fertility Suppl. 46, 1993; Experimental Gerontology, 30 (3/4) 1995; 32 (4/5) 1997; 33 (7/8) 1998; 35 (9/10) 2000; 38 (1-2) 2003; 39 (11-12) 2004; 42 (1-2) 2007; 44 (1-3) 2009; 46 (2-3) 2011; 48 (7) 2013; 68 2015; and 94 2017). The purpose of the Symposia is to integrate recent information derived from the study of neurobiology, neuroendocrinology, genetics, animal models and degenerative CNS diseases with the fundamental issue of the nature of the aging process. The Fifteenth Symposium is scheduled for 2021.

Twenty-three individuals presented talks at the Symposium along with seven short talks delivered by junior investigators that were chosen from the abstracts. Seventeen of their manuscripts are collected here, in alphabetical order by the presenter (Table 1- List of papers in special issue). A brief introduction to each of the presentations appears below followed by a list of contributors and funding support for this conference. In addition, the special issue contains abstracts of the 23 speakers and the 32 poster presentations from the meeting.

Dylan Souder and Rozalyn Anderson present information regarding a relatively new player in aging studies, glycogen synthase kinase 3 (GSK3). The authors

Table 1 Papers in Special Issue on Neurobiology & Neuroendocrinology of Aging

Authors, Year	Title	Volume, Pages
Attaallah A et al., 2019	A pro longevity role for cellular senescence.	Geroscience 42(3):867-879
Austad SN. 2019	Sex differences in health and aging: A dialog between the brain and gonad?	Geroscience 41(3):267-273
Braun DJ et al., 2019	Genetic knockout of myosin light chain kinase (MLCK210) prevents cerebral microhemorrhages and attenuates neuroinflammation in a mouse model of vascular cognitive impairment and dementia.	Geroscience 41(5):671-679
Darcy J, Tseng Y-H. 2019	ComBATING aging – does increased brown adipose tissue activity confer longevity?	Geroscience 41(3):285-296
Engler-Chiurazzi EB et al., 2020	Role of B cells and the aging brain in stroke recovery and treatment.	Geroscience (in press)
Fulop GA et al., 2018	Nrf2 deficiency in age mice exacerbates cellular senescence promoting cerebrovascular inflammation.	Geroscience 40(5-6):513-521
Geltinger F et al., 2020	The transfer of specific mitochondrial lipids and proteins to lipid droplets contributes to proteostasis upon stress and aging in the eukaryotic model system <i>Saccharomyces cerevisiae</i> .	Geroscience 42(1):19-38
Gonzalo S, Coll-Bonfill N. 2019	Genomic instability and innate immune responses to self-DNA in progeria.	Geroscience 41(3):255-266
Hoffman JM et al., 2020	Tryptophan metabolism is differently regulated between large and small dogs.	Geroscience 42(3):881-896
Komninou D et al., 2020	Methionine restriction delays ageing-related urogenital disease in male Fischer 344 rats.	Geroscience 42(1):287-297
Kunath S, Moosmann B. 2020	What is the rate-limiting step towards aging? Chemical reaction kinetics might reconcile contradictory observations in experimental aging research.	Geroscience 42(3):857-866
Lenzhofer N et al., 2020	N-3 polyunsaturated fatty acids as modulators of thermogenesis in Ames dwarf mice.	Geroscience 42(3):897-907
Liendl L et al., 2020	Raman fingerprints as promising markers of cellular senescence and aging.	Geroscience 42(2):377-387
Popa-Wagner A et al., 2019	Genetic conversion of proliferative astroglia into neurons after cerebral ischemia: A new therapeutic tool for the aged brain?	Geroscience 41(4):363-368
Santin-Marquez R et al., 2019	Sulforaphane – a role in aging and neurodegeneration.	Geroscience 41(5):655-670
Schafer MJ, LaBrasseur NK. 2019	The influence of GDF11 on brain fate and function.	Geroscience 41(1):1-11
Souder DC, Anderson RM. 2019	An expanding GSK3 network: Implications for aging research.	Geroscience 41(4):369-382

provide an overview of aspects of GSK3 that pertain to aging and then specifically cover evidence for a direct role of this molecule in several age-related diseases (diabetes, Alzheimer's Disease, cancer) that differ in etiology and pathology. Investigations of the role of GSK3 in normative aging is presented and taken together, the data suggest that GSK3 may drive some age-related processes demonstrating potential as a target for intervention.

In his keynote address, Steven Austad describes sex differences in health and aging. In terms of lifespan, women live longer than men in most cases but in animals, one sex appears to dominate in some conditions while the other lives longer under different conditions. These conditional sex differences are discussed in detail as gonadal activity and neuroendocrine signaling may be mechanistically linked to longevity. Brain-gonad communication is at the center of this discussion with lesser known and studied endocrine hormones such as activin and inhibin receiving special attention.

David Braun, Linda van Eldik and collaborators provide a report on molecules involved in the integrity of the blood brain barrier specifically, a form of myosin light chain kinase (MLCK210). Several neurological insults as

well as chronic pathologies associated with aging exhibit dysfunctional barriers. MLCK210 has been described as a major regulator of barrier integrity but less is known about its potential as a target for neurological disorders. A genetic knockout of MLCK210 appears to protect against chronic hyperhomocysteinemia-induced cerebral microhemorrhages and neuroinflammation suggesting promising therapeutic avenues for this molecule.

Elizabeth Engler-Chiurazzi reviews aspects of the immune system as they relate to stroke pathology and recovery. Communication between the nervous and immune systems has been shown to be bidirectional and complex. Age-related brain injury represents an area that therapeutic targeting of the immune system could be applied. The B cell component in particular, could be targeted to impact inflammatory processes, cell migration signals and alter protective and restorative features that in turn, affect the brain's response to stroke and other age-related neuro-disorders. Aspects of B cells and their interaction with brain cells and function are discussed.

Susana Gonzalo-Hervas discusses genomic instability and innate immune responses to self-DNA in progeria, specifically Hutchinson-Gilford Progeria Syndrome

(HGPS). Lamins are key structural nuclear proteins that contribute to genome integrity. Although over 400 different mutations in the LMNA gene (encoding A-type lamins) are associated with many distinct degenerative disorders, the molecular mechanisms are not well understood. An overview of pathways and mechanisms is presented with details on progerin and HGPS. Replication stress is implicated as a major cause of genomic instability in laminopathies that contributes to immune responses to self-DNA that in turn, accelerate the aging process.

Aurel Popa-Wagner, Andrei Gresita and colleagues present potential, novel methodologies to intervene following ischemic stroke in aged individuals. Neurons are often lost in the infarct core while other cells such as astrocytes become reactive and proliferate after a stroke resulting in an imbalance in cell types in the area of the lesion. Post-stroke, gliotic scars also develop. New technology has emerged and indicates the possibility of genetically reprogramming non-neuronal cells to become neurons thus circumventing cell transplantation therapies.

Jessica Hoffman discusses the utility of companion dogs as models for aging studies with particular attention to results of metabolomic profiling highlighting tryptophan metabolism. Companion dogs share similar environments and disease profiles to humans and are subject to comparable health care. These investigators examined the metabolome of a large number of dogs in three US cities. The strongest signal in the profile was related to location and not breed, age or sex. Once location was accounted for, tryptophan metabolism was strongly linked to body weight providing potential mechanisms underlying size and longevity in a model system that is closely related environmentally to humans.

Mina Konigsberg, Niki Chondrogianni and co-workers describe work focused on sulforaphane, an isothiocyanate found in cruciferous vegetables that has antioxidant and anti-inflammatory activities. The mechanisms underlying many of the beneficial properties of sulforaphane involve induction of the Nrf2 pathway and inhibition of NF κ B. A review of the molecular and physical characteristics, mechanisms of action and downstream effects are presented in the context of prevention of neurodegeneration and slowing aging related processes.

Sascha Kunath and Bernd Moosmann examine the Free Radical Theory of Aging. Free radicals have been studied for decades in the aging research field with a strong focus on antioxidant enzymes. Free radical reactions can be divided into three kinetically independent events including

initiation, propagation and termination. Those in favor of the theory have focused experiments on radical propagation while those against centered their work on initiation and termination. Manipulation of antioxidative enzymes *in vivo* has not impacted longevity in experimental systems as predicted likely because initiation and termination are not rate-limiting steps of the aging cascade. The authors conclude that radical propagation is rate-limiting for aging and needs further study.

Antonello Lorenzini and colleagues review the key features of cellular senescence and its involvement in tissue development, tumor prevention and aging. Data is presented using cells from long-lived species showing that they respond to a DNA damage challenge with a more vigorous induction of senescence. This information suggests a positive role of this fundamental process during development that contributes to longevity. The role of apoptosis is also analyzed in terms of longevity but a significant positive relationship with longevity was not observed.

Florian Geltinger, Mark Rinnerthaler and collaborators describe the relationship between mitochondria and lipid droplets and the role they play in stress and aging. Lipid droplets have many functions including modulation of protein and lipid homeostasis and interacting with mitochondria to uptake certain proteins and prevent apoptosis. Experiments in yeast confirmed that lipid droplets serve as a major protein sink. They also observed that the lipid composition of the droplets impacts functions and interactions with mitochondria during stress and with aging.

Marissa Schafer covers the influence of growth differentiation factor 11 (GDF11) on brain fate and function. This protein impacts CNS patterning, development and differentiation of new cells and its actions may be dependent upon local production. Peripheral delivery of GDF11 to the aged brain may stimulate neurogenesis, angiogenesis and improve neurological outcomes, contrasting the activities of this protein during development. A greater understanding of GDF11 biology in aging systems will be critical to determine therapeutic value in older organisms.

Lisa Liendl, Markus Schosserer and colleagues present a review discussing the potential of Raman fingerprints as markers of cellular senescence and aging. Senescent cells accumulate with age and exhibit irreversible growth arrest, specific gene expression and secretory patterns. Detection of these cells *in vivo* is difficult but new technology, Raman microspectroscopy, provides a non-invasive,

label-free technique to identify senescent cells and provide a biochemical fingerprint of tissues and cells allowing differentiation between cellular states, and healthy versus pathological tissue. Application of Raman microspectroscopy in aging research is specifically discussed.

Despina Komninou, Raghu Sinha and collaborators present evidence that methionine restriction (MR) delays aging-related urogenital disease in rats. A reduction in dietary methionine levels extends lifespan in many species. In this study, male rats were fed control or methionine restricted (80% reduction) diets throughout life until 30 months of age. Histopathology indicated that 87% of control fed animals exhibited kidney pathology and 62% had chronic progressive nephropathy while no evidence of kidney disease was observed in MR-fed rats. A significant reduction in testicular tumor incidence was also detected in these animals. These results indicate that longevity enhancing diets may protect against age-related disease through altering metabolic pathways.

Justin Darcy and Hua Tseng introduce a novel approach to combat aging using brown adipose tissue as a target. Brown adipose tissue (BAT) acts as a metabolic sink taking up plasma glucose and lipids for oxidation in large quantities to maintain high thermogenic capacity. A renewed interest in BAT as an approach to intervene in obesity and metabolic syndrome has provided insight to aging as the metabolic biomarkers overlap with extended health and lifespan. A review of BAT and the potential of targeting BAT to promote healthy aging is provided.

Gabor Fulop, Zoltan Ungvari and coworkers present information related to senescence and age-related cerebrovascular disease. Senescent cells have been shown to promote inflammation via expression of specific genes and secretion of inflammatory cytokines and chemokines. The investigators provide evidence of up-regulated molecular markers of senescence as well as microglial activation in 24-month-old cerebral arteries of mice. Genetic depletion of Nrf2, a transcriptional regulator further impaired expression of the aging-induced senescence markers promoting hippocampal inflammation. These experiments suggest that dysfunctional Nrf2 and aging promote cellular senescence in cerebral vessels contributing to age-related pathologies.

Nadine Lenzhofer, Teresa Valencak and colleagues provide evidence for polyunsaturated fatty acid modulation of thermogenesis in long living mice. All biological membranes contain a mix of mono- and polyunsaturated fatty

acids that differ in composition depending on the tissue. This lipid composition has been shown to be related to longevity in mammals. Ames dwarf mice exhibit extended health and lifespans, lower n-3 fatty acids and higher n-6 fatty acids when compared to age-matched wild type controls. In this study, isocaloric diets with differing fatty acid compositions were fed to Ames mice for two months resulting in increased body masses, higher subcutaneous body temperatures and changes in phospholipid content of tissues. The results suggest that the diets increased body fat and insulation increasing thermogenesis and subcutaneous temperatures in these mice.

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