Published in final edited form as:

Exp Gerontol. 2015 August ; 68: 1–2. doi:10.1016/j.exger.2015.01.004.

A summary of the Proceedings of the Twelfth International Symposium on the Neurobiology and Neuroendocrinology of Aging, Bregenz, Austria July 27–August 1, 2014

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Abstract

A summary of the Twelfth International Symposium on the Neurobiology and Neuroendocrinology of Aging that was held July 27–August 1, 2014 in Bregenz, Austria, is presented. Fifteen of the speakers that presented at the conference submitted review papers covering the topic of their presentation as well as an overview of their respective fields and are included in this special issue. The abstracts from each poster presentation as well as seven of the speakers' abstracts are also included at the end of the preface to the special issue.

Keywords

Aging; Proceedings; Neurobiology; Neuroendocrinology

This special issue of *Experimental Gerontology* consists of the Proceedings of the Twelfth International Symposium on the Neurobiology and Neuroendocrinology of Aging (<http://www.neurobiology-and-neuroendocrinology-of-aging.org/>) held in Bregenz, Vorarlberg, Austria at the Kloster Mehrerau, July 27–August 1, 2014. The previous 11 Symposia in this series have been held biennially at the same site since 1992 and published as full proceedings (*J. Reprod. Fertil. Suppl.* 46, 1993; *Exp. Gerontol.*, 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 and 48 (7) 2013). The Symposia attempt 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 Thirteenth Symposium is planned for 2016.

Twenty-three individuals presented talks at the Symposium, and fifteen of their manuscripts are collected here, in alphabetical order by the presenter. A brief introduction to each of the presentations appears below followed by a list of contributors and funding support for this

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conference. In addition, the special issue contains abstracts of seven of the speakers and the 28 poster presentations from the meeting.

Julie Andersen presents information on the relationship between cellular senescence and brain aging. In the periphery, it has been shown that senescent cells accumulate with age and secrete a variety of pro-inflammatory cytokines, chemokines, growth factors, and proteases. This secretory phenotype is known as senescence-associated secretory phenotype (SASP). Senescent cells have been found in human brain and markers of senescence increase with aging and neurodegeneration. Neurodegeneration is associated with neuroinflammation and a potential source of pro-inflammatory SASP is from senescent brain cells suggesting that there are novel targets for pharmacological intervention to treat age-related disease.

Andrea Fusco describes studies focused on environmental factors and their impact on epigenetic marker expression. Aging and neurodegenerative disorders, especially Alzheimer's disease (AD), exhibit specific epigenetic modifications. Nutritive components also influence expression of these markers ultimately affecting the epigenome. The relationships between nutrition and epigenetic modification in AD will be presented.

Othman Ghribi discusses pathological similarities of two major neurodegenerative diseases, AD and Parkinson's disease (PD). Each disease has a pathological signature but a subpopulation of AD patients exhibits aggregates of alpha-synuclein while some PD patients have tangles and amyloid plaques. Mechanisms that trigger these pathologies may overlap. Along this line, this laboratory has studied the role of oxysterols in AD and PD. Increased 27-hydroxycholesterol contributes to the pathogenesis of AD and PD and may represent a therapeutic target for both diseases.

James Kirkland details the possibilities of senolytic drug development to treat age-related pathologies and chronic diseases. Several steps are necessary to develop successful pharmaceuticals to clear senescent cells including identification of appropriate animal models of human disease, characterization of beneficial phenotypic effects clearing senescent cells as well as off target effects on non-senescent cells and models to test drug efficacy and untoward side effects. Efforts to determine animal models and clinical paradigms are warranted and underway. Identification of successful senolytic agents to slow or reverse age-related would be a major breakthrough in the field.

Jay Mitchell focuses on a factor, hydrogen sulfide (H₂S), that is garnering renewed attention as a player in a number of biological effects on health. Changes in the endogenous production of H₂S via the transsulfuration pathway have been implicated in the beneficial effects of dietary restriction including stress resistance, metabolic fitness and lifespan. The underlying mechanisms leading to the positive health effects of dietary restriction are unknown. Evidence is presented indicating that diet can impact the regulation of the transsulfuration pathway and H₂S production, and alter metabolism.

Simon Moller describes the complexity of Parkinson's disease and that the incidence is predicted to rise in the coming decades. Most cases of PD are sporadic although many studies have focused on a variety of gene mutations that induce the early-onset and late-onset cases. The interaction of environmental and genetic factors is thought to play a major

role in triggering the disease while age is known to be a risk factor. Key proteins involved in PD and the relationships with aging and age-related risk are presented.

Maria Moreno-Villanueva reviews psychological stress and the potential cellular mechanisms involved in the context of aging. Psychological stress affects several physiological systems including the endocrine, immune and nervous systems. Each of these contributes to the feelings of being overwhelmed, anxious, insecure and depressed, which are potentially exacerbated in elderly patients. Further study of the molecular changes induced by psychological stress may assist in maintenance of healthy aging.

Laura Niedernhofer covers the strengths and weaknesses of the use of mouse strains engineered to age rapidly in the pursuit of a better understanding of mammalian aging. Recapitulating aging and age-related disease is an onerous task. These mouse models differ both genetically and phenotypically, sometimes making direct comparisons to human aging difficult. Examples of these strains include animals with DNA repair and mitochondrial dysfunction. However, identifying common features of aging in each of these aberrant cases may lead to discoveries that are key to understanding the mechanisms involved.

Arlan Richardson in his keynote address, discusses the evidence regarding the potential anti-aging effects of rapamycin, a drug that has been shown to increase lifespan and delay age-related phenotypes in mice. The effects of rapamycin treatment on the central nervous system and in particular, Alzheimer's disease, range from prevention and restoration of memory deficits, reductions in beta-amyloid and tau aggregation as well as restoration of cerebral blood flow. These studies and others suggest that rapamycin may be a reasonable pharmaceutical candidate in the treatment of neurodegenerative disease as well as other age-related neurological disorders.

Klaus Richter presents a review focused on aging skin and the processes key to maintaining mitotic activity and appropriate function. The keratinocytes are constantly renewed but the turnover rate declines with aging. The differentiation of these cells is calcium dependent and a disturbance in calcium homeostasis develops as individuals age resulting in dramatic changes in the composition of the cornified envelope. The changes in calcium regulation are not specific to skin aging thus further studies to identify the genes and proteins involved in skin aging may provide mechanistic insight into skin diseases as well.

Christian Sell provides background and supporting evidence regarding the mechanistic target of rapamycin (mTOR) pathway and its potential role in mitochondrial stress and senescence. Elevated mTORC activity has been detected in aged heart and muscle tissues as well as in cellular models of senescence. Mitochondrial dysfunction has been shown to increase in senescent cells. Rapamycin, an mTOR inhibitor, reduces mitochondrial stress and maintains mitochondrial function. A better understanding of the molecular events involved in the activation of mTOR with aging is warranted.

Andreas Simm shows that the accumulation of advanced glycation end products (AGEs) with age in tissues is associated with physiological dysfunction such as high blood pressure and diastolic heart failure. Inflammatory responses are induced when soluble AGEs bind to the receptor for AGEs (RAGE) resulting in tissue injury. However, there is also evidence that

AGEs have protective effects such as inhibition of tumor growth, and reductions in ischemia-reperfusion injury and ROS-induced cellular damage. It appears that AGEs may function as hormetic agents, promoting aging and degenerative disease as well as inducing protective effects.

William Sonntag presents a review centered on the hormones, growth hormone (GH) and insulin-like growth factor 1 (IGF1), and their relationship to cognitive decline in aging. Plasma levels of GH and IGF1 decline with aging in mammals. Aging is associated with physical and mental decline as well as a host of age-related diseases. Impaired growth factor signaling during aging and disease leads to altered neuronal structure and function, specifically cognition. The maintenance of appropriate levels of GH and IGF1 is key in preserving brain function with age.

Jian-Zhi Wang discusses the role of tau hyperphosphorylation in the neurodegeneration found in Alzheimer's disease. They provide evidence that tau hyperphosphorylation makes cells more resistant to apoptosis. A number of molecular mechanisms appear to be involved including activation of Akt, substrate competition, changes in Bcl-2 and Bax, and the unfolded protein response among others. They also show that tau hyperphosphorylation interferes with cholinergic function and proteasome activity. Their work suggests that tau phosphorylation plays dual roles in AD neurodegeneration dependent on whether its presence is acute or chronic.

Barry Zirkin describes Leydig cell production of testosterone and the reduction of serum testosterone with age (hypogonadism). Hypogonadism is associated with fatigue, depression, mood changes, decreased lean body mass, worsening cognition, and decreased libido among others. The decrease in production with age is associated with several cellular changes including reductions in cholesterol transport proteins and downstream steroidogenic enzymes. Exogenous testosterone administration is used to treat hypogonadism but is associated with increased risk of stroke, cardiac events, and prostate cancer and can suppress luteinizing hormone, endogenous testosterone production and spermatogenesis. New approaches to increase plasma testosterone levels directly via the Leydig cell may avoid the negative side effects of current therapies.

The organizers would like to thank Dr. Thomas Johnson for his guidance and assistance in the publication of these proceedings in *Experimental Gerontology*. We also would like to thank Dr. Kurt Borg (Grand Forks, North Dakota, USA) for his assistance with the review and editing of this special issue.

The 2014 Symposium was organized by Drs. Holly Brown-Borg (Grand Forks, North Dakota, USA) and Scientific Secretary Michael Ramek (Graz, Austria).

Members of the 2014 program committee included: Alexander Bürkle (Konstanz, Germany), Aimin Bao (Zhangjiang, China), Günter Lepperdinger (Innsbruck, Austria), Roberto C. Melcangi (Milan, Italy), Marie-Christine Pardon (Nottingham, UK), George Roth (Pylesville, Maryland, USA) and Jay Zimmerman (Jamaica, New York, USA).

We extend our gratitude to the financial supporters of the 2014 Symposium:

National Institute on Aging R13 AG047703 Bethesda, Maryland, USA;

Orentreich Foundation for the Advancement of Science, Cold Spring-on-Hudson,
New York, USA;

Co-morbidity in Relation to AIDS, European Commission Seventh Framework
Programme;

Junifur and Pasquale Foundation, Chatham County, North Carolina, USA;

Land Vorarlberg and Landeshauptstadt, Bregenz, Austria;

Office of the Dean, School of Medicine and Health Sciences, University of North
Dakota, Grand Forks, North Dakota, USA.