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A summary of the Proceedings of the Tenth International Symposium on the Neurobiology and Neuroendocrinology of Aging Bregenz, Austria, July 25–30, 2010

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This special issue of *Experimental Gerontology* consists of the Proceedings of the Tenth 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 25–30, 2010. The previous nine 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 and 44 (1–3) 2009. 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 Eleventh Symposium is planned for 2012.

Twenty-two individuals presented talks at the Symposium; twenty of those manuscripts are collected here, in alphabetical order by the presenter. A brief introduction to each of the presentations appears below.

Greti Aguilera presents information on the major neuroendocrine system that mediates stress adaptation and its potential role in the aging process. The activation and termination of the hypothalamic pituitary adrenal axis is key to appropriate responses to stress. With aging, there is evidence of increased corticotropin releasing hormone levels centrally and increased glucocorticoid activity. These increases, in turn, cause damage and contribute to pathologies associated with advancing age such as neurodegeneration, anxiety, depression and immune and metabolic disorders. Transient activation of this axis is necessary for survival but prompt termination of the stress response is essential to prevent the negative effects of excessive CRH and glucocorticoids.

Ignacio Torres Aleman discusses the role of insulin-like growth factor 1 (IGF1) in mammalian brain aging. There are many reports showing that IGF1 is detrimental for long life. However, in the brain, conflicting data exists showing that IGF1 is a potent neuroprotective factor, a deterrent of brain aging in some cases while in others, it may contribute to the neurodegeneration underlying Alzheimer's disease. A partial explanation

for this disparity is that different experimental approaches have led to these results. The approach-dependent effects of IGF1 highlight the fundamental gap in our understanding of the relationship between peripheral and central IGF1 function and aging-related processes.

Craig Atwood examines the Reproductive-Cell Cycle Theory of Aging that posits that reproductive hormones (human chorionic gonadotropin, luteinizing hormone, follicle-stimulating hormone) act in an antagonistic pleiotropic manner to control aging via cell-cycle signaling. These hormones promote growth and development early in life but in late life, they become dysregulated and promote senescence. This theory explains multiple aspects of aging, age-related processes and age-related disease in sexually reproductive organisms.

Andrzej Bartke presented the keynote address at this Symposium and in this review, discusses the potential mechanisms linking growth hormone, IGF1 and insulin to delayed aging and extended longevity. Spontaneous and experimentally-induced mutations in these endocrine pathways leads to shifts in stress resistance, mTOR signaling, insulin sensitivity and metabolism resulting in healthspan and survival benefits to the organism. Careful examination of whether the conclusions drawn from the studies on GH-related mutants can be extrapolated to normal animals and to humans are presented.

Christian Benedict describes studies linking circulating insulin to memory function in animals and humans. In patients with Alzheimer's disease, central nervous system insulin signaling is reduced and associated with cognitive decline. A therapeutic strategy to overcome CNS insulin deficiency or resistance is intranasal delivery of this hormone to the system. The beneficial effects of direct delivery of insulin to the brain via an intranasal route include improved memory function in healthy humans as well as in patients with cognitive impairment such as in Alzheimer's disease. Insulin also acts as a neuroprotective agent thus intranasal insulin administration appears to be a promising approach in the treatment and prevention of CNS insulin deficiency and resistance.

Rochelle Buffenstein details the extraordinary physiology of the naked mole-rat and the potential mechanisms that likely contribute to the 30-year lifespan of this rodent. Naked mole-rats are mouse-sized subterranean animals that have evolved a number of anti-aging strategies resulting in delayed aging, sustained reproductive capacity and marked cancer resistance. These animals are eusocial, living in colonies with restricted breeding (one queen and a few males). They also exhibit extreme tolerance to hypoxia and acid insensitivity due to the lack of the neuropeptides Substance P and calcitonin gene-related peptide. Their unique neurobiology, endocrinology and social structure are discussed in the context of human biogerontology.

Ehud Cohen provides the current knowledge on the neuroprotective mechanisms that are suppressed by insulin/insulin-like growth factor 1 signaling (IIS) and the potential to exploit this system as a therapy to treat neurodegenerative disorders. In humans, neurodegeneration results from the accumulation and deposition of aberrant aggregated proteins. Uniquely, these disorders typically have a late-onset suggesting that aging processes play a major role in the emergence of these diseases. Studies in invertebrates and mice suggest that a reduction in signaling of the IIS pathway not only extends lifespan but importantly, counters the toxic effects of the aberrant proteins and prevents the behavioral impairments, pathological phenotypes and premature death that normally occur in models of Alzheimer's disease.

Monica Driscoll presents studies linking a new pathway, largely independent of the IIS pathway, to healthspan and lifespan in *C. elegans*. Activation of the epidermal growth factor (EGF) receptor is associated with increased lifespan, maintenance of pharyngeal pumping,

extended locomotory function and low lipofuscin and advanced glycation end product accumulation. One negative regulator of EGF signaling, HPA-1, appears to control overall aging of the animal whereas HPA-2, affects locomotory aging primarily. Thus, HPA-2 is an example of a protein that affects healthspan but not lifespan. This is a key finding as this class of genes are likely overlooked in screens using longevity as an endpoint.

Rita Effros reviews the importance of using humans in studies focused on immunosenescence and telomere/telomerase dynamics since other organisms are not subject to specific factors that cause the aging-related restructuring of the human immune system. The aging of the immune system is responsible for the increased severity of infections, reduced vaccine responses and increased cancer incidence in elderly humans. Herpes viruses, usually acquired in early life, persist for decades and can contribute to the generation of senescent dysfunctional T cells as can psychological and oxidative stresses. Strategies to overcome these issues and enhance immune function in older persons are presented.

Thomas Flatt addresses recent work showing that lipophilic hormones play an important role in modulating lifespan and other life history traits in two invertebrate organisms. A significant amount of longevity research has focused on the insulin/IGF-1 pathway but another major component of the endocrine system, the steroid hormones, appear to affect longevity of both *C. elegans* and *D. melanogaster*. The longevity effects of steroid hormones depend on interconnectivity with the gonad. Together, with data in mice showing that ovaries transplanted from young donor mice increases life expectancy of old recipient mice, suggests that gonadal regulation of lifespan might be evolutionarily conserved.

Donald Ingram discusses the concept of calorie restriction mimetics and their potential impact in gerontology. Calorie restriction (CR) is the most robust environmental intervention for altering aging processes and increasing healthspan and lifespan. Long-term calorie restriction in humans is plagued by compliance issues while potential negative consequences over the long-term are unknown. Thus, the search for potential compounds that mimic the positive aspects of CR including metabolic, hormonal and other physiological systems could have significant impact on healthspan in humans. Glycolytic inhibition is one strategy that is under development as this pathway would inhibit energy utilization and mimic multiple CR-like effects in the organism.

Brian Kennedy focuses on recent studies investigating the target of rapamycin (mTOR) and Alzheimer's disease, Parkinson's disease and polyglutamine expansion syndromes such as Huntington's disease. mTOR signaling has been shown to modulate lifespan in organisms ranging from yeast to mice. The mTOR signaling pathway and the utilization of mTOR by neurons regulates brain function including feeding behavior, synaptic plasticity and memory formation. Rapamycin slows new protein translation and induces autophagy. The possibility exists that rapamycin or its analogs could benefit the aging brain and serve as therapeutic agents for treating age-related neurodegenerative diseases.

Bernd Moosmann examines longevity-related structural adaptations in biological macromolecules and how these adaptations provide insight into molecular mechanisms of aging. In screening animal proteomes for signals associated with longevity, cysteine depletion in respiratory complexes was the strongest predictor, on the amino acid level, to co-vary with lifespan. In contrast, methionine accumulation, a feature of mitochondrially-encoded proteins affording antioxidant protection, was not predictive of longevity. These adaptations are discussed in terms of the 'plastination hypothesis of aging'.

Marie-Christine Pardon presents information regarding underlying mechanisms that link lifestyle factors to the risk and progression of Alzheimer's disease (AD). Negative lifestyle

factors that induce excessive stress, accelerate the progression of AD. In contrast, positive lifestyle factors such as physical and mental exercise have been shown to slow the progression of AD symptoms and neuropathology and are thought to improve overall brain function. Some of the potential players related to stress responses include the glucocorticoids, corticotropin-releasing hormone (CRH) and synaptic acetylcholine-terase receptors. It is thought that CRH plays a critical, dose-dependent role in AD progression and that the components of the cholinergic stress reaction may yield promising therapeutic agents.

Clemens Steegborn reviews the role of mitochondrial signaling mechanisms and their therapeutic potential as targets in the treatment of metabolic and age-related disease. Mitochondria are central to the regulation of cell survival and cell death and dysfunction of these organelles has been implicated in metabolic and age-related diseases. The signaling systems utilized by the mitochondria to interact with the cell, other organelles and the environment include the NAD⁺-dependent protein deacetylases, p66Shc and components of the cyclic adenosine monophosphate pathways. Many of these systems contain components that could serve as targets aimed at treating aging-related diseases.

Dick Swaab discusses the evidence that ‘wear and tear’ in the brain underlies aging processes in this tissue. It is thought that stimulation of brain function may slow the progression of brain aging and lower the risk of neurodegenerative disease. Several neural pathways and mechanisms likely contribute to the overall age-related decline and dysfunction and include maintenance of cell numbers, the activity levels of neurons and their downstream effectors (i.e. the hypothalamus and arginine vasopressin, CRH), functioning of the hypothalamic–pituitary–adrenal axis, components of the circadian clock and growth factors among others. Each of these may serve as targets for the development of therapeutic strategies aimed at the prevention and treatment of neurodegenerative disease.

Ellie Tzima describes factors within the vascular and cardiovascular systems that are altered in aging and that contribute to the onset and severity of cardiovascular disease. Endothelial dysfunction in aging is characterized by a significant decrease in nitric oxide production and bioavailability. As a consequence of reduced bioavailability, aging vessels exhibit endothelial cell senescence and oxidative stress. Shear stress decreases the sensitivity of endothelial cells by unknown mechano-signaling mechanisms but results in decreased nitric oxide production. A better understanding of these events in the endothelial cell would be beneficial and contribute to the development of cardiovascular treatment strategies.

Alexander Vaiserman considers the natural experiment-based evidence concerning the developmental origins of disease in adult humans. At one time, susceptibility to disease was thought to be primarily determined by the genetic information carried in the DNA sequence. More recent evidence points towards epigenetic mechanisms and their potential role in disease development. The developmental time period appears to be very susceptible to environmental modulation thus, documented natural studies are discussed in detail. Based on these key studies, the early-life environment is probably the most critical component contributing to the etiology of some diseases including cancer, metabolic disorders and cardiovascular disease.

Holly van Remmen details the current understanding of age-related muscle loss and relates this to the impact on quality of life in the elderly. Although several hypotheses have been proposed, the mechanisms underlying age-related muscle atrophy, wasting and weakness are relatively unknown. Degeneration of the neuromuscular junction is a key event and includes areas within the pre-terminal motor axons that exhibit abnormal thinning, distention and sprouting and postsynaptic endplates that are smaller in size, number, length and density.

Recent studies provide direct evidence that the age-associated increase in oxidative stress plays a crucial role in neuromuscular junction degeneration and progression to sarcopenia.

Barbara Viviani examines the role of cytokines in age-related neuronal dysfunction. Cytokines within the central nervous system have been shown to modulate neurological function and thus affect brain behavior. An increase in neuroinflammatory processes have linked to functional changes in both normal and pathological aging. Cytokines specifically interact with neuronal channels and have been shown to regulate neuronal excitability, synaptic plasticity and responses to injury. Therefore, modulation of neuronal function by cytokines may play a key role during aging and in age-related disease.

Also included in this issue are 22 abstracts of posters that were presented at the Symposium.

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