Austin Child & Adolescent Psychiatry

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Mini Review

Fundamental Clock of Biological Aging: Convergence of Molecular, Neurodegenerative, Cognitive, and Psychiatric Pathways

Dyakin VV[1]* and Dyakina-Fagnano NV[2]

[1]The Nathan S Kline Institute for Psychiatric Research (NKI), Head of Virtu-al Reality Perception Lab (VRPL), USA

[2]Adolescent and Young Adult Psychiatry, USA

***Corresponding author:** Victor Vasilyevich Dyakin, The Nathan S. Kline Institute for Psychiatric Research (NKI), Head of Virtu-al Reality Perception Lab (VRPL), 140 Old Orangeburg Road, Bldg. 35, Rom 201-C, Orangeburg, NY-10962-1167, USA

Received: April 16, 2021; **Accepted:** May 06, 2021; **Published:** May 13, 2021

Abstract

The individualized process of human aging occurs in the intersection of biological, cognitive, and psychological domains. Advances in the field of biochirality reveal new crucial determinants of aging at the molecular, cellular, and organism levels. All biologic macromolecules, including DNA, proteins, and lipids, exhibit a prevalence of chirality. Chirality and stereoselectivity are recognized as the fundamental properties of all life-supporting biomolecular systems. However, all homochiral molecules are vulnerable to multiple types of spontaneous aberrant modifications, including racemization. Indeed, several biomolecular structures, including amyloids, are known as the by-products of the major evolutionary pathway. Accumulation and aggregation of misfolded proteins are commonly recognized biomarkers of biological aging, neurodegenerative, immune, and psychiatric disorders.

Aging, accompanied by the decline in health, independence, perceptual, cognitive, and decision-making abilities, is closely associated with the negative impacts of most typical psychological stress. Both aging and psychological stress aversively affect the immune, hormonal, and neuro-transmitting systems. In our view, at the protein level, the primary determinants contributing to the crosstalk of genetic, epigenetic, and psychological pathways of aging are the spontaneous post-translational modifications.

Keywords: Spontaneous; Non-enzymatic; Post translational modifications; Racemization; Biological clock; Natural selection; Psychological aging

Abbreviations

AAs: Amino Acids; A-β: Amyloid-Beta; DNA: Deoxyribonucleic Acid; NS: Natural Selection; PTM: Post-Translational Modification

Introduction

Self-perception is contributed by the sense of embodiment [1] and conscious control of your own thoughts [2]. No doubt, the biological processes, running at the molecular and cellular levels, that underlie the humans' perception of self-understanding, are influenced by the state of mind and psychological state of the subject [3]. Experimental evidence suggest that both aging and psychological stress affect the immune, hormonal, and neuro-transmitting systems [4-6]. However, the studies of bidirectional links between psychological and biological determinants of aging should be reconsidered in view of new results.

Contemporary concepts of prevalent biochirality and virtual reality brings new dimensions to the exploring mutual influence of biological and cognitive domains of self [1-3,7-9] and new meaning to Schopenhauer's view on the world as the manifestation of "Will and Representations."

Molecular Determinant of Neurodegenerative, Cognitive, And Psychiatric Pathways

The human's mental state's development, integrity, and decline are mediated by the multifactorial interplay of genetic and environmental factors at the molecular domains (Figure 1,2a).

Several types of biologic macromolecules, including DNA, proteins, and lipids, exhibit two interactive (co-existing) characters. First- prevalent chirality [10] and, second, vulnerability to multiple types of aberrant modifications [11]. Prevalent molecular chirality results from natural selection (NS), providing the functionality of DNA, proteins, and lipids along with perceptual and cognitive abilities to live organisms. However, several biomolecular structures, including amyloids, are known as the by-products of the main evolutionary pathway. Aberrant malfunctional structures containing D-amino acids (D-AAs) are the main contributors to the dis-regulation of neuronal signaling, biological aging, and various disease conditions [12].

Aging, as manifested in the neurodegenerative and psychiatric disorders, is associated with the progressive decline of functions at the molecular, cellular, organ, and organism levels [13-16].

At the molecular level, aging is associated with the impact of physical, environmental, and psychological stressors [7-24]. Acute and chronic psychological stressors are characterized as complicated constructs capable to induce the changes at ANA and protein levels [25,26]. In particular, the neuropathology of schizophrenia is characterized by the convergence of morphological, cellular, and molecular correlates [27-30]. The most common pathways of

Citation: Dyakin VV and Dyakina-Fagnano NV. Fundamental Clock of Biological Aging: Convergence of Molecular, Neurodegenerative, Cognitive, and Psychiatric Pathways. Austin Child Adolesc Psychiatry. 2021; 5(1): 1015.

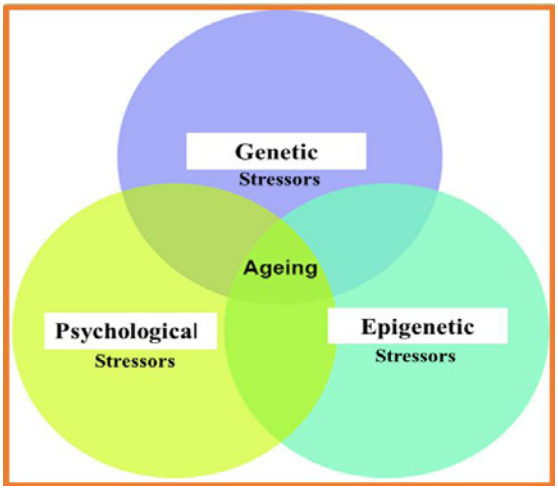

Figure 1: Major determinant of biological aging.

schizophrenia and neurodegeneration include abnormalities in glutamatergic neurotransmission, altered synaptic plasticity, and elevated brain level of Amyloid-beta (A-b) [31,32]. During the last decade, the reciprocal influences of biology, psychology, behavioral, and social factors on health and illness gain significant attention. But the effect of psychological stressors on spontaneous biological events only in the embryonic state [29,30,33]. It is known that people exposed to major psychological stressors in early life, exhibit an elevated rates mortality from chronic diseases of aging [34]. The impact of psychological stressors on spontaneous, age-associated Post-Translational Modifications (PTMs) of protein remains unexplained. In our view, the critical mechanism underlying the link between PSs and lifespan is spontaneous PTMs.

Organism Level

At the organism level, the age-related decline in cognitive function includes compromised memory, language, critical thinking, and decision-making. Impaired cognition affects the psychological-behavioral functions, including social communicants and self-perception, leading to psychological stress associated with a range of psychopathologies. Psychological stress, in turn, is a significant determinant of cognitive decline. Age-associated deterioration of cognition and psychological functions correlates with neuronal degeneration, misfolding, disfunction, and aggregation of synapse-associated proteins and peptides, including NMDA receptors, A-β, TAU, neuroligins, neurexins, and many others [33]. An emerging concept proposes that molecular and sub-cellular structures "sense, integrate, and transduce psychosocial and behavioral factors", suggesting the **reciprocal causation** between molecular, cognitive and psychological factors [34-41].

The psychological perspective of aging, seeing through molecular and cell biology prism, helps to understand the complex interrelationships among protein folding, cell signaling, brain structure, cognition, and behavior for both healthy and pathological trajectories [42,43].

Universal Biological Clocks of Aging

The perceptual and cognitive representations of the external world are associated with internal events at the different levels of biological organization.

At the cellular level, cognitive representations are reflected in neuronal representations [44] that are linked to many biomolecular events.

At the molecular level, the fundamental age-related biological clocks are associated with the alterations in the DNA [44-46] lipids [47], proteins [14,15], and interaction between them [46,48]. All molecular clocks contain chronological and biological information related to genetic and epigenetic impacts [49].

At the protein level, the age-related changes are documented in protein transcription, translation, and PTMs. At the same time, neuronal representations are linked to the dynamic system of enzymatic PTMs. It is well-documented that the dysregulation of PTMs leads to a range of neurological alterations (including intellectual disability, learning and memory impairments, autistic-like features, and seizures) [15,16,50] and aging [51]. Aberrant PTMs can potentially be used as the biological indicators of acute psychological and cognitive states. At PTMs domains, the significant age induced changes are observed in the enzymatic PTMs. Most dramatic age-related changes occur in the level of protein phosphorylation (Figure 2b) [14].

However, the role of spontaneous forms of PTMs remains mostly un-explored [13-16,52]. Notable that enzyme family serine-threonine protein kinases, known as major modulators of cellular transformations, target the most racemization-prone Amino Acids (AAs) residues [15,53]. Therefore, non-enzymatic racemization of serine and threonine are making the cell functions and survival vulnerable to spontaneous time dependent PTMs.

Many agreed that interaction between mental representations and PTMs of proteins are reciprocal. However, the answer to how and to what degree mental determinants of cognitive and psychological states can impact the system of PTMs requires additional experimental efforts.

Conclusion

It is not an accidental combination of events that (a) functions of

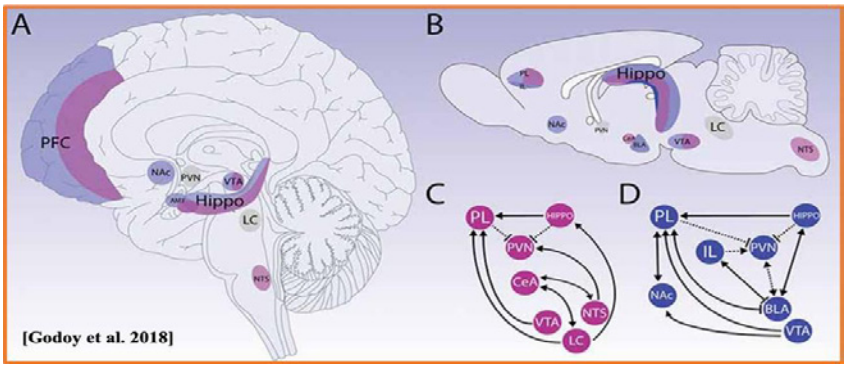

Figure 2a: Neuroanatomy of stress.
Schematic representation of primarily neuroanatomical substrates responsible for physical (pink) and psychological (blue) stressors processing. Upper panels show that neural processing for different types of stressors detection and appraisal of the situation engage several structures, which may overlap at some instances on human and rodent brain (A,B, respectively). Bottom panels represent how physical and psychogenic stressors require engagement of different networks (C, D, respectively). Adapted from [Godoy et al. 2018].

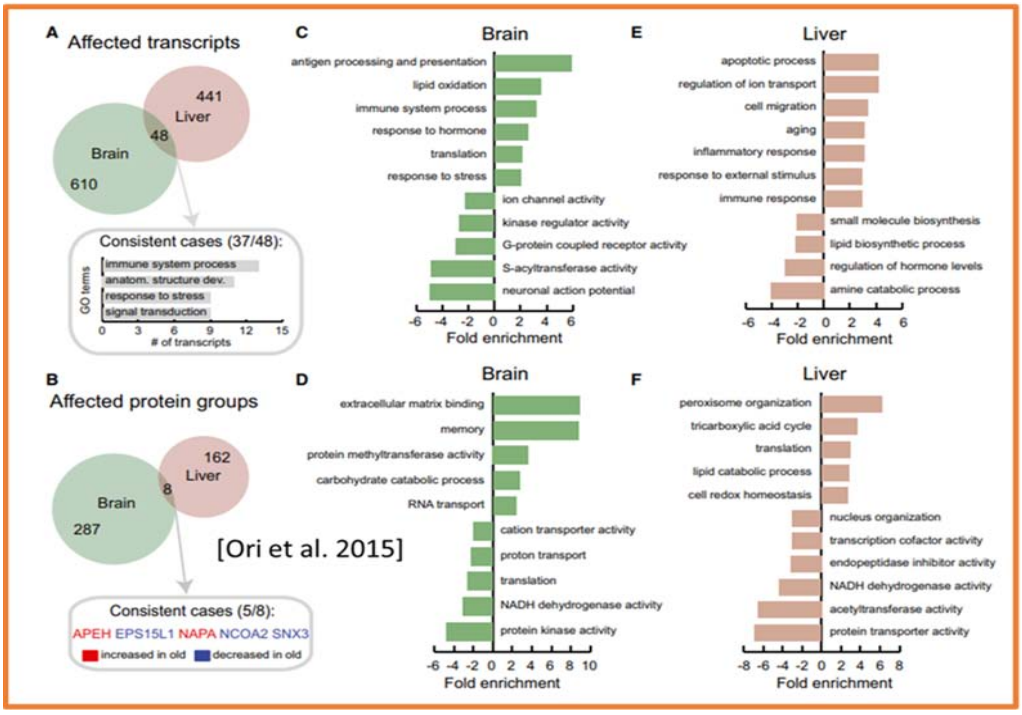

Figure 2: Common and organ-specific alterations of the proteome in old rats.
(A and B) We identified only 48 transcripts affected at the level of translation output (A) and eight proteins affected at the level of protein abundance (B) that were altered in both brain and liver. The most represented gene ontology (GO) terms among consistently affected transcripts are shown in (A) while the five consistently affected proteins are indicated in (B). (C-F) Functional enrichment was performed on the list of quantified transcripts and proteins that were ranked according to the level of differential expression (fold change) using (Eden et al., 2009). Displayed GO terms are representative cases selected from among those significantly enriched (cut-off for transcripts: q value < 0.05, minimum number of transcript > 4, fold enrichment ≥2; for proteins the same criteria were applied with the exception of q value < 0.2). The fold enrichments are plotted using positive values for terms enriched in transcripts/proteins that are increased in old animals or using negative values for terms enriched in transcripts/proteins that are decreased in old animals. Adopted from [14].

the CNS are based in the molecular chirality [13,14], (b) numerous psychiatric drugs are chiral compounds [54-56], and (c) psychiatric disorders are strongly associated with the bilateral asymmetry of the brain [57]. But the link between seemingly unrelated events constitutes the challenging barrier for neuroscience and psychology. Psychological stressors, linked with the genetic and epigenetic modifications, are known as the influential causal events changing the physiology of many organs (including brain and gut [58]) and systems (including an immune system [59] and hormonal [5]) of the human body.

Aging, accompanied by the decline in health, independence, perceptual, cognitive, and decision-making abilities, is closely associated with the negative impacts of typical psychological stress [60,61]. Indeed, both psychological stress and aging show cumulative impact on most physiological systems [62-66] involving biological events at the molecular [67] and cellular [68] levels.

Epigenetic alterations are triggering by stressful or beneficial environmental input [69]. The excessive and chronic stresses are associated with the accelerated molecular and cellular aging. Time-dependent accumulation of changes is a major molecular determinant of organism aging.

The chain of interlinked molecular, cellular, systemic and organism level of biological events allow to consider, the non-enzymatic racemization, time dependent and irreversible PTMs as the fundamental determinant of biological age. An organism's aging and its counterpart spontaneous molecular events are inevitable processes. However, the body of evidence suggests that epigenetic aging could be if not preventable that treatable [70-73].

Acknowledgment

I gratefully thank Abel Lajtha for productive discussions and corrections.

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