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RECEIVED 11 July 2023  
ACCEPTED 14 August 2023  
PUBLISHED 28 August 2023

CITATION  
Lissek T (2023) Aging, adaptation  
and maladaptation.  
*Front. Aging* 4:1256844.  
doi: 10.3389/fnagi.2023.1256844

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# Aging, adaptation and maladaptation

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Aging is accompanied by a dysregulation of adaptive processes. On the one hand, physiological adaptation mechanisms such as learning and memory, immune system plasticity and exercise-dependent muscle remodeling are blunted. On the other hand, several maladaptive processes increase with age including cancer, pathological cardiovascular remodeling and metabolic dysregulation. With increasing age the quotient of beneficial adaptation (Ab) to harmful adaptation (Ah), Ab/Ah, decreases. The adaptation-maladaptation framework of aging entails that there are age-related pathological phenotypes that are the result of activation of physiological adaptation mechanisms (e.g., maladaptation as a result of misdirection of adaptive cascades and molecular damage incurred by adaptation processes) and their occurrence over time might, to some degree, be inevitable. Aging might hence result from the organism's inability to solve the adaptation-maladaptation dilemma. The present work explores the concept of counteracting aging through adaptation and proposes that interventions such as exercise, environmental enrichment and dietary restriction work in counteracting aging because they increase the ratio Ab/Ah by both raising Ab (e.g., by inducing metaplasticity in cells, meaning they raise the adaptability of cells to future stimuli) and decreasing Ah (e.g., through desensitizing certain potentially harmful adaptive mechanisms). Molecules whose aging-related expression changes can explain aspects of dysfunctional adaptation such as CREB and certain immediate early genes are examined and it is delineated how a better understanding of the dynamical organization of adaptation cascades could elucidate the seemingly complex role of adaptation in driving aging as well as protecting against it.

## KEYWORDS

aging, age, adaptation, maladaptation, plasticity, longevity, transcription

## Introduction

One of the major symptoms of aging in animals is a decreased body-wide ability for adaptation, which expresses itself as impaired neural plasticity (Becker and Barnes, 2006), decreased adaptive immune function (Weng, 2006) and blunted muscle anabolism (Breen and Phillips, 2011) among others. As adaptation is a fundamental property of organism function, its reduction leads to profound physiological impairments and in older humans is expressed, among other things, in reduced cognitive flexibility (Hedden and Gabrieli, 2004), decreased mobility (Rantakokko et al., 2015) and increased susceptibility to infectious diseases (Gavazzi and Krause, 2002). At the same time, during aging many maladaptive processes increase including dysfunctional remodeling of metabolism in diabetes (Sinclair et al., 2019), autoimmunity (Goronzy and Weyand, 2012), changes in the cardiovascular system such as atherosclerosis (Heath et al., 2017) as well as oncogenesis (White et al., 2014).

The present work explores how dysregulated adaptation is a central feature in animal aging and provides a framework to integrate various findings on the biology of aging at

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