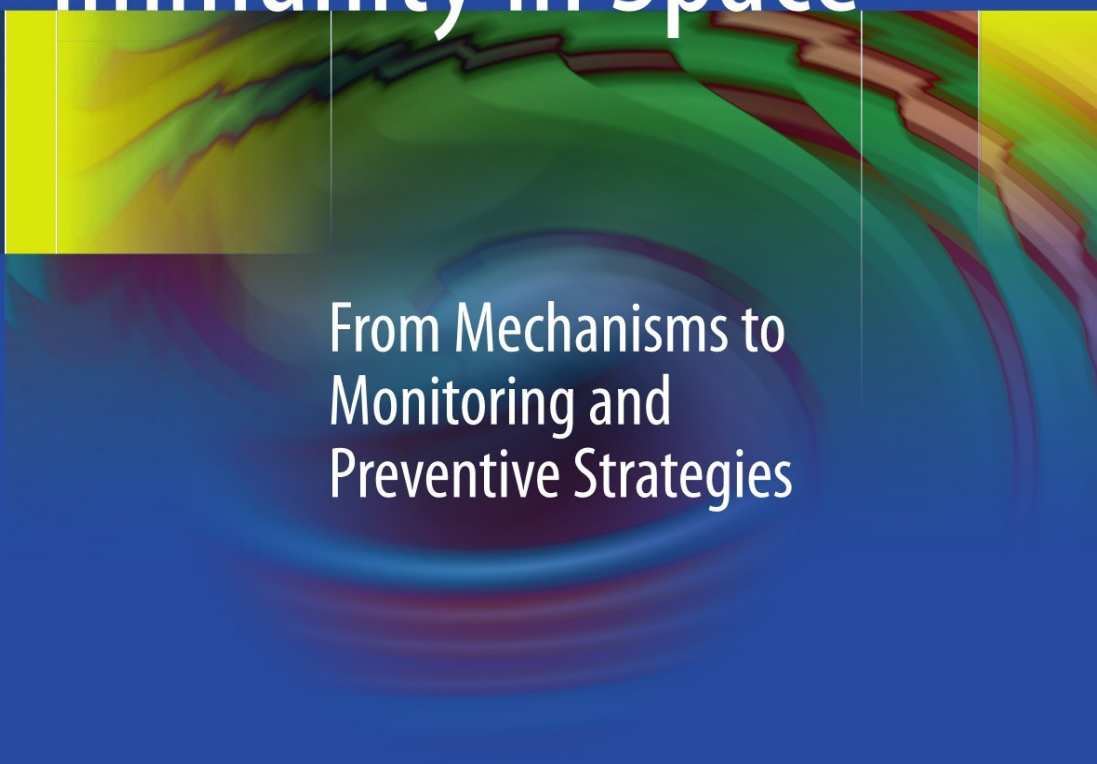
Alexander Choukèr *Editor*

Stress Challenges and Immunity in Space

From Mechanisms to Monitoring and Preventive Strategies



Springer

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ISBN 978-3-642-22271-9 e-ISBN 978-3-642-22272-6
DOI 10.1007/978-3-642-22272-6
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011941401

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

To my wife Martina
To my children Marie-Thérèse, Maxime, Émile and Alphonse

Alexander Choukèr

Preface

"Stress Challenges and Immunity in Space" although seemingly specific in its title is broad in nature. The field of stress research is inherently multidisciplinary and complex as stress can arise from an almost limitless combination of situations and factors, and has the potential to influence all organ systems, either directly or indirectly. As a result, in approaching immune system changes during spaceflight, a highly unusual condition of life with a vast array of stressors and interactions, an integrative and holistic pathway is needed. Yet biological research in space is inherently limited in scope and detail. And therefore the question arises as to how to obtain sufficient detail and understanding to ensure the safety of our astronauts/cosmonauts.

This book is an attempt to approach this issue. It begins with a brief introduction to stress, describes the general interactions between stress, the central nervous system, and immunity; summarizes the current state of research with regard to immunity during spaceflight; and finally concludes with the latest technology and approaches to stress and immune monitoring, therapeutics, and future research platforms. The aim is not only to provide the current state of the art but also to serve as an impetus and drive for new research, which will eventually help mitigate the risks of voyage far beyond Earth. Furthermore, knowledge gained will help humans adapt to many extreme conditions of life, such as the critically ill, shift-workers, miners, Antarctic expedition crews, submariners, and more.

The participation of authors and expert scientists spanning a number of fields both from spaceflight and non-spaceflight research is a step toward an integrative and holistic approach, from basic science to applied science to technology. However, integrative and holistic implies that the current knowledge and views as presented are far from complete or comprehensive and by default are open to future discoveries and interpretations.

There, therefore, will be *space* to continue this approach. This book will hopefully serve as a starting point for a more integrative approach to research in the field of stress and immunity.

Munich, Germany — Alexander Choukèr

Acknowledgments

The support of many colleagues, partners, and international collaborators is much acknowledged, as without their support this book project would have not been completed. All contributing authors to this book deserve my highest appreciation for their work and for the extremely positive and kind collaboration during the preparative and review periods. The continuous input from all members of the ESA Topical Team "Stress and Immunity," their constructive criticism, and advice have been major sources of inspiration and the cornerstone for the realization of this book.

Special thanks go to Prof. Dr. Sarah Baatout and to Prof. Dr. Manfred Thiel for helping to generate the necessary momentum during the kick-off phase; and to Dr. Ines Kaufmann, Dr. Alex P. Salam, Sandra Matzel, Dr. Andrew Dobney, Marion Hörl, and to Dr. Chris Choukèr who were extremely supportive in the finalization period. This project would also not have been possible without the generous institutional support from the Department of Anaesthesiology at the Ludwig-Maximilians-Universität, and I want to especially thank the director Prof. Dr. Bernhard Zwissler for providing full encouragement and support at all times during this process.

My appreciation also goes to the scientists, doctors, and operators working in space, in space analogues, and extreme environments, as well as in clinical studies, and to the space agencies and funding institutions, who altogether have provided the intellectual input, experimental performance, and the financial means to realize the achievements presented in this volume. This acknowledgment extends to all participating volunteers and patients, as well as to the staff and students working in all the laboratories who provide critical and highly important contributions toward the further evolution of the field of stress and immune research in space, and on Earth.

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Part I

Prelude

Space Travel: A Personal View from Above

1

Thomas Reiter

Spaceflight has become an indispensable part of our daily life – it significantly contributes to the development of new technologies and applications. Furthermore, it helps to expand our knowledge about our own planet and our environment beyond the boundaries of our atmosphere. This applies especially to human space flight, for example on board the ISS, where research is performed in a wide spectrum of scientific disciplines.

Human space flight is also the source of great fascination. This constant, everyday curiosity drives us to continually expand our boundaries, to find answers to ever new questions. Curiosity is a deeply human quality, which has always played a central role in our development. Space is an excellent environment for research, which paves the way for solutions of earthly problems. Even in the medical field, for example in the understanding of stress and immune interactions, research in the space-environment provides unique possibilities.

The progression and further evolution of our technical and scientific knowledge isthe merit of generations of engineers and researchers, who have been working in the area of spaceflight and who will continue to push the limits of technology and science. In the next few decades, humans could be returning to the moon or travel to more distant destinations. More advanced spaceships will be needed, and a wide range of medical issues have to be solved. Specifically the impact of the space environment on the human body needs to be fully understood.

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A. Choukèr (ed.), *Stress Challenges and Immunity in Space*,
DOI 10.1007/978-3-642-22272-6_1,

Spaceflight is an interdisciplinary regime with a direct impact on science, technology and industrial capabilities. However, we should not loose sight of the human – the cultural – aspect of spaceflight. During training astronauts get prepared for every situation, for every off-nominal situation. Still, there is no preparation for this overwhelming view out of the window. This view gives a totally different perspective on our planet ‘from outside’. The sojourn in space is a totally new experience, no matter what you might have done before. After returning to earth, one wants to share this fantastic experience, the different views and insights with others. The various colours of our planet, cloud formations, the different colours of our atmosphere – a multitude of impressions that an astronaut registers, has to assimilate, and can never forget.

Space Travel: An Integrative View from the Scientists of the Topical Team "Stress and Immunity"

2

Sarah Baatout, Alexander Choukèr, Ines Kaufmann, Nicola Montano, Siegfried Praun, Dominique de Quervain, Benno Roozendaal, Gustav Schelling, and Manfred Thiel

For centuries, mankind has struggled to understand the profound complexity governing the principles of life and the universe. This quest has taken him on scientific journeys far and wide: from the exquisitely simple atomic structure of our DNA to the hellish and chaotic depths of our sun, the energy source for all life on Earth, and

The European Space Agency has supported the teaming up of international experts in "Topical Teams". Topical Teams are open structures lead by European researchers which should address a scientific field in which gravity and access to space or planetary bodies constitute important cornerstones. The founding members of the Topical Team "Stress and Immunity", as listed in alphabetical order as authors of this perlude, were significantly involved in the realization of this book, contributed to it and authored this chapter as a group.
This prelude was supported also by Alex P. Salam.

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A. Choukèr (ed.), *Stress Challenges and Immunity in Space*,
DOI 10.1007/978-3-642-22272-6_2, © Springer-Verlag Berlin Heidelberg 2012

beyond. Scientific, artistic, and social discoveries are what drive us as humans, and what distinguish us from all other species with which we share this planet. One of the fundamental questions that still troubles us is how life began on this planet and whether it exists elsewhere in the universe. This deep desire to understand and search for life has taken humans on exploratory journeys to the extremes of our planet: from the depths of our oceans to the heights of our mountains, and from the cold of Antarctica to the darkness of space. Fifty years ago, Yuri Gagarin marked a defining moment in the history of human exploration when he became the first human to escape the clutches of Earth's gravitational pull. Yet in 1960, before he launched into space, it was not even clear if humans could survive in a zero-gravity environment. At no stage in our evolution had we been prepared for such an environmental stress. From the moment life began in the "pre-biotic soup," some 3 billion years ago, all life on earth, Eukaryotes, Prokaryotes, and Archaea alike, have been shaped by the universal force of gravity. Within the space of a few minutes however, the most complex of these organisms, a human, Yuri Gagarin, seemingly "skipped" this evolutionary force and successfully coped with the absence of gravity. Since his historic 108-min voyage, others have survived for months not only in weightlessness, but also in extreme isolation and confinement, darkness, and danger. However, adapting to such hostile and unnatural conditions is not without any repercussions and is accompanied by adverse physiological and psychological effects, which, over the last decades, have been shown to disrupt almost all organ systems. Whilst our presence has extended beyond low Earth orbit to the moon, manned exploration beyond Earth's vicinity into the depths of our solar system requires a much more detailed understanding of the adaptation of human beings to extreme environments. Major questions remain: What are the principal and most important environmental and social threats to physical and mental health of crews during long-duration space flight missions, and how can we prevent and mitigate the adverse effects from adaptation to these threats?

It was Hans Selye who first used the term "stress" in the 1930s to describe how a biological system might adjust to the challenges and demands associated with major environmental changes (Selye 1936). He realized that when a complex organism is challenged by noxious conditions, the resulting symptoms are independent of the quality of the conditions, i.e., the qualitative end-result of different stressor types is the same. Rather, it is the quantitative effects that vary however. He also recognized that stressful conditions directly affect neural pathways, such as the autonomic nervous system, but also indirectly affect other organ systems, e.g., the immune system. The steps involved in the adaptation process to chronic stress are gradual and the biological system either builds up resistance to the stress and maintains a healthy physiological and psychological equilibrium, or succumbs to the stress, resulting in disequilibrium.

Stress research has expanded tremendously since then and Selye probably never imagined that it would transcend Earth's boundaries. Space flight is associated with a very distinct and unique combination of stressors: zero-gravity, radiation, altered microbial flora, isolation, confinement, altered day/night cycles and closed loop environments. Such stressors will be experienced in the extreme during inter-planetary travel. These combined and multi-factorial challenges affect many organ functions,

including immunity, and overall health. Moreover, in the case of the immune system for example, changes can influence other physiological systems, and even feedback with neural pathways in a bidirectional manner (Tracey 2009).

Although astronauts are exceptionally well selected, trained, and healthy individuals, some are now known to be particularly prone to health alterations during the course of space flight. When challenged by complex stressful conditions, e.g., space flight, individuals react differently and adjustment to the conditions can fail. The "milieu intérieur" (*Claude Bernard, 1813–1878*) is no longer able to maintain "coordinated physiological processes which maintain most of the steady states in the organism," as they "are so complex and so peculiar to living beings – involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working cooperatively" (Cannon 1932). This concept of "homeostasis" is extended further by the notion of homeodynamics, i.e., "the stability of the internal milieu toward perturbation" (Lloyd et al. 2001).

Although studying specific cellular models and simple biological organisms under conditions of simulated weightlessness, increased radiation, or isolation and confinement can help unravel the neurophysiological consequences of standardized emotional and physiological strains, no organ, especially in the case of humans, can be considered as a stand-alone entity. For this reason, new integrative and holistic approaches to the understanding of stress responses and individual predispositions and reactions to stress have started to evolve. With the help of research on the International Space Station and in analogous conditions and environments – e.g., group isolation and confinement in chamber studies (e.g., MARS500) or field operational conditions (e.g., Antarctica or sub-aquatic habitats) – the impact of distinct emotional and physical stressors, or a combination thereof, can be investigated. This will eventually help with the understanding of the incremental effects of stress on organ allostasis, from an allostatic load to overload with subsequent exhaustion and failure to re-establish an appropriate equilibrium.

Because allostasis is a continuous and evolving process, efficient and simple tools to monitor physiological and behavioral adaptation processes and consequences during long-duration deep space missions are needed to enable early detection of disease and early implementation of appropriate countermeasures. Given that the reaction to stress can vary between individuals, how can we design strategies to meet the astronauts' individual needs under evolving and unpredictable conditions? This may prove very difficult and will require new technologies and devices. Should we select astronauts based on the presence of genetic characteristics that confer resistance to stress? The new technological tools of molecular biology, such as micro-arrays, will help to understand the genetic and epigenetic (e.g., DNA-methylation, post-transcriptional regulation) reasons for (mal) adaption, and therapeutic consequences. If genetic testing were to provide the potential to select and de-select candidates, this would have important ethical, social, and psychological implications. However, because "reading genes" is not equivalent to "understanding genes" and because human complexity goes beyond genetic heritage, identification of genetic polymorphisms that appear to correlate with a higher predisposition to physiological and behavioral stresses should not disqualify a potential space flight

candidate. Although polymorphisms in genes, for example, genes regulating sleep (Goel et al. 2009), or traumatic memory encoding, or DNA repair, may possibly lead to increased risk, individuals may have unidentified genetic resistance to other space-related stress factors, as well as behavioral resistance that may mitigate genetic risk. "The right stuff" seems very likely to be a very complex mix of gene–environment interactions. Given the ethical implications, the use of genetic analysis is *not* to define candidates who are suitable or not suitable for space flight, *but* rather to identify possible risks in order to personalize the frequency and mode of physiological and psychological assessments and countermeasures in space, and during rehabilitation upon return to Earth.

There is much left to qualify and quantify but with time we will refine the physiological, psychological, and pharmaceutical factors and interventions that will allow humans to travel inter-planetary distances. Along the way, these developments will not only benefit our space agencies but also wider society. Stress has the ability to alter the function of virtually every single organ system and cell type in the human body. The study of healthy humans experiencing high levels of stress in confinement and isolation, and in other space analogous environments, allows us to draw clear causal links between stress and physiological disequilibrium and disease. Understanding the interaction between stress and the human body and mind will lead to better healthcare not only for astronauts, but also for the vast majority of us who will never escape gravity's pull. Every single person on this planet experiences stress and no one is completely immune to its effects.

Acknowledgment The authors acknowledge the funding of this Topical Team by the European Space Agency (ESA) and express their thanks to Dr. Oliver Anger (ESA) for his support. The funding of the authors by national space agencies or other national or international funding institutions is acknowledged and specified in more detail in the authors' individual chapters

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The topics addressed in this prelude will be presented also in the parts II to VI of this volume. In addition, the following sources have been used to compile this prelude:

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Part II

"Stress and Immunity" - Research: A Link Between Space and Earth

What Is Stress?

3

Bruce S. McEwen and Ilia N. Karatsoreos

> 'I am stressed out' is non-accusatory, apolitical and detached. It is a good way to keep the peace and, at the same time, a low-cost way to complain.
>
> – America's Latest Export: A Stressed-Out World
> By Richard A. Shweder
> Published: January 26, 1997

3.1 Introduction

Stress is a word that is used throughout the world, and it has many meanings. There is "good stress" and "bad stress." Some would prefer to use "stress" to refer only to the experience and consequences of a situation when one is unable to cope physically or psychologically with the challenge (Cohen et al. 2007; Lazarus and Folkman 1984). Physiologically, cortisol and adrenalin are stress hormones and the fight or flight response is usually the focus of discussions of stress. But that is only part of the story. There are multiple biological mediators besides the adrenal stress hormones that are responsible for adaptation in situations that evoke the fight or flight response (McEwen and Stellar 1993; Sterling and Eyer 1988) and help us stay alive, but these same mediators also contribute to pathophysiology when overused and dysregulated, resulting in allostatic load and overload (McEwen 1998; McEwen and Wingfield 2003).

The brain is the central organ of stress and adaptation because it determines not only what is threatening, or at least different and potentially threatening, in a new

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A. Choukèr (ed.), *Stress Challenges and Immunity in Space*,
DOI 10.1007/978-3-642-22272-6_3, © Springer-Verlag Berlin Heidelberg 2012

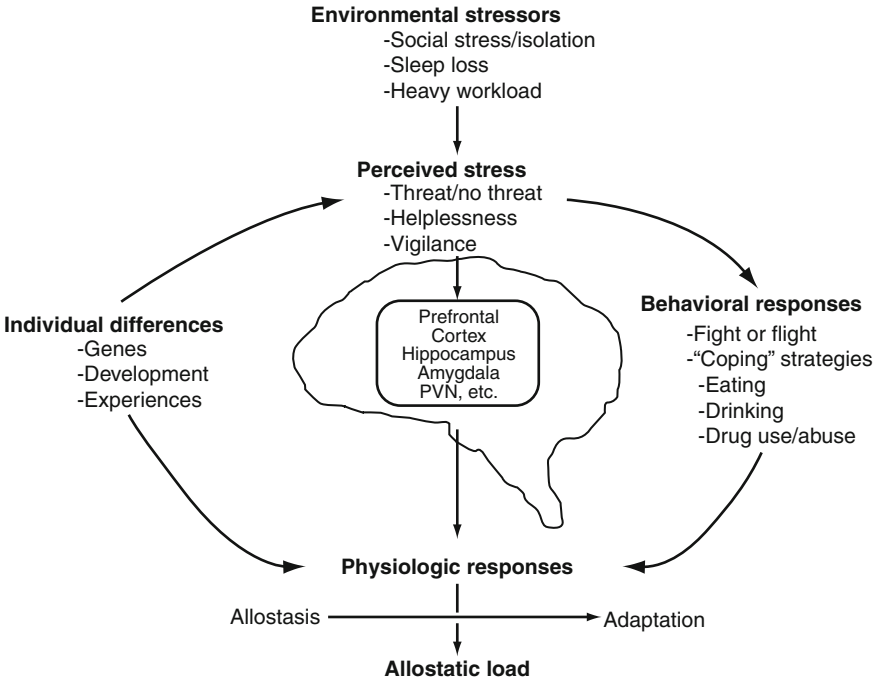

Fig. 3.1 The brain is the central organ of stress and adaptation and plays a major role in determining whether there is successful adaptation as well as cumulative wear and tear on the body and brain, i.e., allostatic load and overload. *PVN* paraventricular nucleus in the hypothalamus

situation, but also determines the physiological and behavioral responses (Fig. 3.1). Alterations in brain structure and function by experiences throughout life determine how each individual will respond to new events. But there are also important contributions from genes; individual life-style habits reflecting items, such as sleep quality and quantity; diet, exercise and substance abuse; adverse early life experiences that set life-long patterns of behavior and physiological reactivity; and exposure to toxic agents in the environment.

One purpose of this chapter is to describe the concepts of allostasis and allostatic load and overload as a way of making the discussion of the physiology and psychobiology of stress more precise and biologically based and related to life style and health-related behaviors, as well as the stressful experiences themselves. The other purpose of this chapter is to highlight ways in which the brain and its architecture play a key role in how individuals respond to new challenges. The relevance of the adaptation to stressors will be discussed in relation to the challenges of space flight and adaptation to microgravity providing further basis for understanding how the brain, immune system and health can be affected under such conditions.

Box 3.1: Levels of Stressful Experiences: Their Causes, Consequences and Why We Experience Them!

Positive Stress
- A personal challenge that has a satisfying outcome
- Result: Sense of mastery and control
- HEALTHY BRAIN ARCHITECTURE
- Good self-esteem, judgment and impulse control

Tolerable Stress
- Adverse life events buffered by supportive relationships
- Result: Coping and recovery
- HEALTHY BRAIN ARCHITECTURE
- Good self-esteem, judgment, and impulse control

Toxic Stress
- Unbuffered adverse events of greater duration and magnitude
- Result: Poor coping and compromised recovery
- Result: Increased life-long risk for physical and mental disorders
- COMPROMISED BRAIN ARCHITECTURE
- Dysregulated physiological systems

3.2 Types of Stress

This chapter will use the following classifications of types of stress: good stress, tolerable stress, and toxic stress (Box 3.1)*.

Good stress is a term used in popular language to refer to the experience of rising to a challenge, taking a risk and feeling rewarded by an often positive outcome. A related term is "eustress." Good self-esteem and good impulse control and decision-making capability, all functions of a healthy architecture of the brain, are important here. Even adverse outcomes can be "growth experiences" for individuals with such positive, adaptive characteristics.

"Tolerable stress" refers to those situations where bad things happen, but the individual with healthy brain architecture is able to cope, often with the aid of family, friends, and other individuals who provide support. Here, "distress" refers to the uncomfortable feeling related to the nature of the stressor and the degree to which the individual feels a lack of ability to influence or control the stressor (Lazarus and Folkman 1984).

Finally, "toxic stress" refers to the situation in which bad things happen to an individual who has limited support and who may also have brain architecture that reflects effects of adverse early life events that have impaired the development of good impulse control and judgment, and adequate self-esteem. Here, the degree

* See http://developingchild.harvard.edu/index.php/activities/council/ for the document 'The Science of Early Childhood Development: Closing the Gap Between What We Know and What We Do' as well as many other useful papers on the topic of brain development and stress

and/or duration of "distress" may be greater. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, and this will result in a higher degree of allostatic overload, as will be explained later in this chapter.

3.3 The Concepts of Allostasis and Allostatic Load and Overload

The body responds to many experiences by releasing chemical mediators – for example, catecholamines that increase heart rate and blood pressure. These mediators promote adaptation to simple acts like getting out of bed in the morning or climbing a flight of stairs or more complex acts, like giving a lecture or a musical performance. However, chronically increased heart rate and blood pressure can cause pathophysiological changes. For example, in the cardiovascular system, these changes can result, over time, in pathophysiological conditions like atherosclerosis, that can result in stroke and myocardial infarctions (Cohen et al. 2007).

Because these mediators are involved, paradoxically, in both protection and damage, and also because the word "stress" has ambiguities and connotations that interfere with its precise use, the term "allostasis" was introduced (Sterling and Eyer 1988) to refer to the active process by which the body responds to daily events and maintains homeostasis (allostasis literally means "achieving stability through change"). See Box 3.2 "Definitions." Because chronically increased allostasis can lead to pathophysiology, we introduced the terms "allostatic load or overload" (see distinction in Box 3.2 "Definitions" and below) to refer to the wear and tear that results from either too much stress or from inefficient management of allostasis, such as not turning off the response when it is no longer needed (McEwen 1998; McEwen and Stellar 1993; McEwen and Wingfield 2003).

Other forms of allostatic load/overload involve not shutting off the response efficiently, or not turning on an adequate response in the first place (McEwen 1998). Having many stressful events and many stress responses also contributes to "wear and tear" on the body and brain (McEwen 1998). Likewise, not habituating to the recurrence of the same stressor and thus dampening the allostatic response can also lead to overexposure of the brain and body to the mediators of allostasis (McEwen 1998).

Box 3.2: Definitions

Homeostasis is the stability of physiological systems that maintain life, used here to apply strictly to a limited number of systems such as pH, body temperature, glucose levels, and oxygen tension that are truly essential for life and are therefore maintained within a range optimal for each life history stage.

Allostasis is achieving stability through change, a process that supports homeostasis, i.e., those physiological parameters essential for life defined

above, as environments and/or life history stages change. This means that the "setpoints" and other boundaries of control must also change. There are primary mediators of allostasis such as, but not confined to, hormones of the hypothalamo–pituitary–adrenal (HPA) axis, catecholamines, and cytokines. Allostasis also clarifies an inherent ambiguity in the term "homeostasis" and distinguishes between the systems that are essential for life ("homeostasis") and those that maintain these systems in balance ("allostasis") as environment and life history stage change.

Allostatic state: The allostatic state refers to altered and sustained activity levels of the primary mediators, e.g., glucocorticoids, that integrate physiology and associated behaviors in response to changing environments and challenges such as social interactions, weather, disease, predators, pollution, etc. An allostatic state results in an imbalance of the primary mediators, reflecting excessive production of some and inadequate production of others (Koob and LeMoal 2001). Examples are hypertension, a perturbed cortisol rhythm in major depression or after chronic sleep deprivation, chronic elevation of inflammatory cytokines, and low cortisol that increases risk for autoimmune and inflammatory disorders. Allostatic states can be sustained for limited periods if food intake and/or stored energy such as fat can fuel homeostatic mechanisms. For example, bears and other hibernating animals preparing for the winter become hyperphagic as part of the normal life cycle and at a time (summer and early autumn) when food resources can sustain it.

Allostatic load and allostatic overload: The cumulative result of an allostatic state (e.g., a bear putting on fat for the winter) is allostatic load. It can be considered the result of the daily and seasonal routines; organisms have to obtain food and survive and extra energy needed to migrate, molt, breed, etc. Within limits, these are adaptive responses to seasonal and other demands. However, if one superimposes additional loads of unpredictable events in the environment such as disease, human disturbance, and social interactions, then allostatic load can increase dramatically. Type 1 allostatic overload occurs when energy demands exceed energy income as well as what can be mobilized from stores. Type 2 allostatic overload occurs if energy demands are not exceeded and the organism continues to take in or store as much or even more energy than it needs. This may be a result of stress-related food consumption, choice of a fat-rich diet, or metabolic imbalances (prediabetic state) that favors fat deposition. There are other cumulative changes in other systems, e.g., neuronal remodeling or loss in hippocampus, atherosclerotic plaques, left ventricular hypertrophy of the heart, glycosylated hemoglobin, and other proteins by advanced glycosylation end products as a measure of sustained hyperglycemia. High cholesterol with low HDL may also occur, and chronic pain and fatigue, e.g., in arthritis or psoriasis, may also occur associated with imbalance of immune mediators.

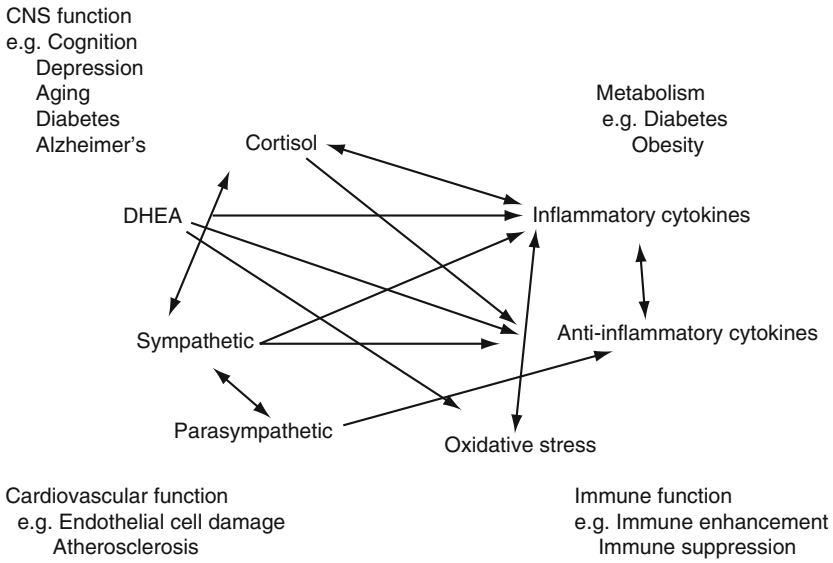

Fig. 3.2 Multiple interacting mediators and nonlinearity of interactions between them. *Arrows* represent direct and indirect regulatory influences of one mediator system upon the other systems. At the corners of the figure are listed some of the body systems that are concurrently affected by these mediators and their dysregulation (Reprinted from McEwen 2006 by permission). *DHEA* dehydroepiandrosterone

3.4 Multiple Interacting Mediators

Protection and damage are the two contrasting sides of the physiology involved in defending the body against the challenges of daily life, whether or not we call them "stressors." Besides adrenalin and noradrenalin, there are many mediators that participate in allostasis, and they are linked together in a network of regulation that is nonlinear, meaning that each mediator has the ability to regulate the activity of the other mediators, sometimes in a biphasic manner (Fig. 3.2). For example, glucocorticoids produced by the adrenal cortex in response to ACTH (adrenocorticotropic hormone) from the pituitary gland are the other major "stress hormone." Yet, pro- and anti-inflammatory cytokines are produced by many cells in the body, and they regulate each other and are, in turn, regulated by glucocorticoids and catecholamines. That is, whereas catecholamines can increase pro-inflammatory cytokine production (Bierhaus et al. 2003), glucocorticoids are known to inhibit this production (Sapolsky et al. 2000). Yet, there are exceptions – e.g., pro-inflammatory effects of glucocorticoids that depend on dose and cell or tissue type (Munhoz et al. 2010). The parasympathetic nervous system also plays an important regulatory role in this nonlinear network of allostasis, since it generally opposes the sympathetic nervous system and, for example, slows the heart, and it also has anti-inflammatory effects (Borovikova et al. 2000; Thayer and Lane 2000).

What this nonlinearity means is that when any one mediator is increased or decreased, there are compensatory changes in the other mediators that depend on time course and level of change of each of the mediators (McEwen 2006). Unfortunately, biomedical technology cannot yet measure all components of this system simultaneously and must rely on measurements of only a few of them in any one study, or their secondary consequences (McEwen and Seeman 1999). Yet the nonlinearity must be kept in mind in interpreting the results. One approach to "tap into" these mediators, and their surrogates, and obtain a broader picture of the network of allostasis is the "allostatic load battery" (McEwen and Seeman 1999; Seeman et al. 2010a, b).

A further, important aspect the mediators of allostasis is the biphasic nature of many of their effects, a concept embodied by the term "hormesis" (Calabrese 2008) and represented very clearly for cortisol (Joels 2006) and for pro- and anti-inflammatory cytokines, e.g., interleukin-6 (Campbell et al. 1993; Moidunny et al. 2010; Patterson 1992).

3.5 Stress in the Natural World

The operation of allostasis in the natural world provides some insight into how animals use this response to their own benefit or for the benefit of the species. As an example of allostasis, in springtime, a sudden snowstorm causes stress to birds and disrupts mating, and stress hormones are pivotal in directing the birds to suspend reproduction, to find a source of food and to relocate to a better mating site or at least to delay reproduction until the weather improves (Wingfield and Romero 2000). As an example of allostatic load, bears preparing to hibernate for the winter eat large quantities of food and put on body fat to act as an energy source during the winter (Nelson 1980). This accumulation of fat is used, then, to survive the winter and provide food for gestation of young. In contrast, the fat accumulation that occurs in bears that are captive in zoos and eating too much, partially out of boredom, while not exercising (McEwen and Wingfield 2003), is an example of "allostatic overload" referring to a more extreme condition that is associated with pathophysiology and is all-too-common in our own species.

Yet, allostatic overload can also have a useful purpose for the preservation of the species, such as in migrating salmon or the marsupial mouse, that die of excessive stress after mating – the stress, and allostatic load, being caused for salmon, in part, by the migration up the rapidly flowing rivers, but also because of physiological changes that represent accelerated aging and include suppression of the immune system (Gotz et al. 2005; Maule et al. 1989). One beneficial result of eliminating the adult salmon is freeing up food and other resources for the next generation. In the case of the marsupial mouse, it is only the males that die after mating, and the hypothesized mechanism is a response to mating that reduces the binding protein, CBG, for glucocorticoids and renders them much more active throughout the body, including likely suppressive actions on the immune defense system (Cockburn and Lee 1988).