Stress – From Molecules to Behavior

A Comprehensive Analysis of the Neurobiology of Stress Responses

Edited by
Hermona Soreq, Alon Friedman, and Daniela Kaufer

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Contents

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Preface

This book is entitled "Stress: from Molecules to Behavior", which immediately highlights the complexity of the topic and the difficulty of assembling a decent representation of its various features and perspectives. To refine what we tried to cover in this volume, we added a subtitle statement attempting to present a comprehensive analysis of the neurobiology of stress responses, which in retrospect was even more presumptuous. One year later, we obviously realize that we aimed at the impossible; however, thanks to the efforts of those friends and colleagues who agreed to contribute chapters to this volume, we also learned that the assembled collection of chapters does provide a multi-leveled view of stress, substantially adding to our knowledge on this subject, while emphasizing to the readers the immense and intricate scope of the topic of stress.

Trying the impossible, in turn, brings to mind the 17th century poet Margaret Cavendish, who implemented conceptualization of mind through mathematics and is often called "the first poetess of science". One of her famous poems portrays the brain as a circle and states, as a metaphor, that *The Circle of the Brain Cannot be Squared*. Mirrored in poetic language, showing how mathematics in the 17th century influenced people's view of reality, Cavendish also explains in this succinct and powerful poem that man's attempt to take control over irrational nature will never cease; which is compatible with our ambitious effort.

The Circle of the Brain Cannot be Squared

A Circle round divided in four parts
Hath been great Study 'mongst the men of Arts;
Since Archimed's or Euclid's time, each Brain
Hath on a Line been stretched, yet all in Vain;
And every Thought hath been a Figure set,
Doubts Cyphers were, Hopes as Triangles met;
There was Division and Subtraction made,
And Lines drawn out, and Points exactly laid,
But none hath yet by Demonstration found
The way, by which to Square a Circle round:
For while the Brain is round, no Square will be,

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While Thoughts divide, no Figures will agree.
And others did upon the same account,
Doubling the Cube to a great Number mount;
But some the Triangles did cut so small,
Till into equal Atoms they did fall:
For such is Man's curiosity and mind,
To seek for that, which is hardest to find.

The different chapters comprising this book are loosely grouped into more general stress-related topics. We open with the topic of *Systems*, encompassing studies on the role of stress in evolution by Lilach Hadany, on catecholamines and stress by Esther L. Sabban and on stress and the cholinergic system by Mariella De Biasi. These are clearly not the only systems that are relevant yet, when reading these chapters one gets a glimpse of the systems which might contribute to stress reactions and their significance. We then proceed with the topic of *Cells and circuits*, under which we collected diverse subjects such as the effects of stress on the function of hippocampal cells by Marian Joëls and Henk Karst, the "burning" issue of stress and adult neurogenesis in the mammalian central nervous system by Elizabeth D. Kirby and Daniela Kaufer and the state-of-the-art neurogenetic search for individual differences in reactivity to social stress in the laboratory and its mediation by common genetic polymorphisms by Richard P. Ebstein and co-workers.

Next, we moved on to *Cognition and behavior*, a highly complex topic by its own merit in which recent studies show causal links to specific molecules and cognitive functions. Ronald de Kloet and colleagues open this section with a coverage of corticosteroid hormones in stress and anxiety, as it is reflected in the role of particular receptor variants and environmental inputs. Thomas Blank and Joachim Spiess proceed with corticotropin-releasing factor (CRF) and CRF-related peptides, which together present a linkage between stress and anxiety. Sonia J. Lupien and co-authors then deal with the intriguing subject of stress, emotion and memory. Marta Weinstock closes this topic with the recently much-discussed contribution of early life stress to anxiety disorders.

The immune system and inflammatory responses are emerging as central components of stress reactions. In *Immune responses*, these are covered by Michael Shapira, who describes stress effects on immunity in vertebrates and invertebrates; by Michal Schwartz and co-workers, who present the concept of immunity to self as a mechanism to maintain resistance to mental stress and argue that boosting immunity can serve as a complement to psychological therapy; and by Inbal Goshen and Raz Yirmiya, whose chapter on brain interleukin-1 (IL-1) describes this pro-inflammatory cytokine as a mediator of stress-induced alterations in the activation of the hippocampal–pituitary–adrenal (HPA) axis, as well as in memory functioning and neural plasticity.

Last, but not least, we turn to studies of stress-related diseases in animal models and human patients. Hagit Cohen leads this section with a comprehensive coverage of post-traumatic stress disorder (PTSD) in animal models, then Alon

Friedman and Lev Pavlovsky proceed with the cholinergic model for PTSD as it progresses from acute stress and as it extends from a single neuron to functional networks and altered behavior. Stress-related vulnerability to other diseases is also represented, although the presented examples should be viewed as a sample of the very broad and diverse field rather than as in-depth coverage. The link between stress and neurodegeneration is covered by Amit Berson and co-workers, and a glimpse into the relevant clinical evidence and therapeutic implications of the inter-relationship between stress and neurotransmitter systems is provided by Hadar Shalev and Jonathan Cohen. The pertinent topic of the metabolic aspects of neuro-endocrine allostatic responses as it implicates on lifestyle-related diseases is also presented from the clinician's view point by Ronan M.G. Berg and Bente Klarlund Pedersen. The final chapter by Michal Horowitz and Esther Shohami, on environmental stress, bears a positive message by covering the added values of heat acclimation-mediated neuro-protection from traumatic brain injury.

Together, these chapters reflect a dynamic, evolving field of research of tremendous dimensions and spheres and possessing clinical and social implications that are of interest to many. We wish to thank all of the contributors to this volume, accept the blame for any errors or exclusion of important topics and promise our readers that there is much more to stress than is presented in this book.

Beer Sheva, Berkeley, Jerusalem
October 2009

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Part I
Systems

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1
On the Role of Stress in Evolution

Lilach Hadany

1.1
Introduction

Most of the work on stress considers its mechanisms and effects during the lifetime of the stressed individual. In this chapter, we concentrate on the possible effects of stress on genes and populations. In particular, we consider the effects of the information contained in the stress response, especially in chronic stress: namely, that the stressed individual is maladapted to its current environment.

In addition to the physiological responses induced by stress, it can also have genomic responses. One type of response which is of particular interest is an increase in genetic variation, especially the mixing of different genotypes through recombination, sex and outcrossing. Here, we consider the evolution of such a genomic response and its possible implications for the long-term success of the population and for the evolution of complex traits.

When considering the evolution of a genomic response to stress, we can take one of two approaches: we can either consider what would be the "best" response at the level of the population (i.e., the response that would, on average, maximize the average fitness of the population), or consider the fate of a selectively neutral modifier allele [1] inducing the genetic response – would such an allele increase in frequency within the population, due to the forces of natural selection?

1.2
Stress Through the Gene's Eye: the Evolution of Stress-Induced Genetic Mixing

Let us consider the point of view of a gene that regulates genetic mixing – for example, recombining with a different genotype – in response to stress. This gene affects its own probability of moving to a different genetic background in the next generation. When would it be advantageous (at the level of the gene) to move to a different background? The answer depends on the quality of the current genetic background. If the current background is maladapted to the current environment

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(e.g., includes multiple deleterious alleles), there is a much greater advantage in "taking the risk" of moving to a different, unknown, background. But how can the gene "know" the quality of the whole genome? One crucial source of information can be stress responses, which relay information about the well-being of the whole organism down to the molecular level. An individual carrying an unfit genome is more likely to be stressed, and the stress responses it experiences can affect the gene regulating genetic mixing. As a result, an increase in mixing is more likely to occur in the presence of stress.

An increase in genetic mixing can occur through various mechanisms, acting at different levels. Each of these mechanisms carries its own costs and benefits. Below we specifically discuss four of these mechanisms – recombination, sex, outcrossing and dispersal.

1.2.1 Stress-Induced Recombination

1.2.1.1 Classic Models of the Evolution of Recombination

The evolution of recombination has been the subject of scientific debate for over 70 years, see [2–7] for reviews. One major problem is that uniform recombination not only generates new advantageous combinations, but also breaks down existing good ones that were generated by selection [8, 9].

Models concentrating on population-level effects show that recombination might be advantageous only under limited conditions [10, 11]. Specifically, recombination can only be advantageous when associations between different loci in the genome result in decreased variation within the population (a situation termed negative linkage disequilibrium). Such associations can be generated by drift [12], synergistic epistasis [13, 14], or environmental changes [15–17]. In these cases recombination reduces linkage disequilibrium and leads to increased average fitness, resulting in a long-term advantage for the population as a whole.

The same question was also studied using modifier models, concentrating on the short-term dynamics of an allele affecting the rate of recombination. These models found that, in the absence of deleterious mutations or environmental changes, a recombination modifier tends to increase from rarity only if it *reduces* the recombination rate between selected loci [18], a result known as "the reduction principle". However, negative epistasis between deleterious mutations [19, 20], drift [21], or adaptation [22, 23], including inter-species interactions [24, 25], can explain the evolution of recombination modifiers under some circumstances. Nevertheless, none of these models fully accounts for the wide abundance of sex and recombination among higher eukaryotes.

1.2.1.2 The Evolution of Stress-Induced Recombination

When introducing the possibility of stress-induced recombination, radically different results are obtained. Let us first consider the modifier approach: a modifier regulating the level of recombination in a haploid organism according to the state