

Contents

Preface	XV
List of Contributors	XIX

Part I Systems

1	On the Role of Stress in Evolution	3
	<i>Lilach Hadany</i>	
1.1	Introduction	3
1.2	Stress Through the Gene's Eye: the Evolution of Stress-Induced Genetic Mixing	3
1.2.1	Stress-Induced Recombination	4
1.2.1.1	Classic Models of the Evolution of Recombination	4
1.2.1.2	The Evolution of Stress-Induced Recombination	4
1.2.1.3	Evidence for Stress-Induced Recombination	6
1.2.2	Stress and Sex	6
1.2.3	Stress and Outcrossing	7
1.2.4	Stress and Dispersal	8
1.3	The Effect of Stress-Induced Variation on the Evolvability of Complex Traits	9
1.4	Stress-Induced Variation and Pathogen Evolution	10
1.5	Stress-Induced Mortality	10
	Summary	12
	References	13
2	Catecholamines and Stress	19
	<i>Esther L. Sabban</i>	
2.1	Rapid Stress-Triggered Changes in Catecholamines	19
2.2	Catecholamines and Stress-Related Disorders	20
2.2.1	Cardiovascular Disease	20
2.2.2	Post-Traumatic Stress Disorder	21
2.2.3	Depression	21
2.2.4	Immune Disorders	21

2.2.5	Pain	22
2.3	Stress-Triggered Regulation of Catecholamine Biosynthetic Enzymes in Different Locations	22
2.3.1	Pathway of Catecholamine Biosynthesis	22
2.3.2	Adrenomedullary Hormonal System	23
2.3.3	Sympathetic Nervous System	27
2.3.4	Noradrenergic Systems in the Brain	28
	Summary	30
	References	30
3	Stress and the Cholinergic System	37
	<i>Mariella De Biasi</i>	
3.1	Acetylcholine and Stress	37
3.1.1	Cholinergic Innervation of the Brain	38
3.1.2	Brain Cholinergic Receptors	38
3.1.3	AChR Distribution in the CNS	39
3.1.4	The Septohippocampal Pathway and Stress	40
3.1.5	Stress-Induced Molecular Adaptations in the Cholinergic System	41
3.1.5.1	The Nicotinic Cholinergic System and Stress	41
3.2	Contribution of Genetically Engineered Mouse Models to the Understanding of the Role of Cholinergic Receptors in Stress	42
	Summary	43
	References	44

Part II Cells and Circuits

4	Effects of Stress on the Function of Hippocampal Cells	55
	<i>Marian Joëls and Henk Karst</i>	
4.1	Introduction	55
4.2	Non-Genomic Effects of Corticosterone	57
4.3	Genomic Effects of Corticosterone	58
4.3.1	Ion Currents	59
4.3.2	Amino Acid Responses	61
4.3.3	Aminergic Responses	62
4.3.4	Implications for Hippocampal Function	64
	Summary	66
	References	66
5	Stress and Adult Neurogenesis in the Mammalian Central Nervous System	71
	<i>Elizabeth D. Kirby and Daniela Kaufer</i>	
5.1	Introduction	71
5.2	Adult Neurogenesis: a Brief Primer	71
5.3	Measuring Neurogenesis: How to Find New Neurons	72

5.3.1	Using DNA Replication to Detect New Cells	72
5.3.2	Endogenous Markers of Cell Cycle	73
5.3.3	Retroviral Labeling of New Cells	73
5.3.4	Determining Cell Fate	73
5.4	Stress-Induced Alteration in Cell Proliferation	74
5.4.1	Acute Stress	74
5.4.2	Chronic Stress	78
5.4.3	Cell Cycle Arrest Versus Progenitor Death	78
5.5	Stress-Induced Alteration of New Cell Survival	79
5.6	Stress-Induced Alteration of Cell Fate Choice	79
5.7	Mechanism of Stress-Induced Changes in Adult Neurogenesis	81
5.7.1	Direct Effects of Glucocorticoids on Adult Neurogenesis	82
5.7.2	Indirect Effects of Glucocorticoids on Adult Neurogenesis	82
5.7.2.1	Excitatory Amino Acids	82
5.7.2.2	Serotonin	83
5.7.2.3	Growth Factors	83
5.7.3	Intracellular Mechanisms of Glucocorticoids Effects	84
5.7.4	An Overall Picture of Mechanism: Putting the Pieces Together	84
5.7.5	Function of Regulation of Adult Neurogenesis by Stress and Glucocorticoids	84
	Summary	85
	References	86

6 Individual Differences in Reactivity to Social Stress in the Laboratory and Its Mediation by Common Genetic Polymorphisms 93

Idan Shalev, Elad Lerer, Salomon Israel, Florina Uzefovsky, Inga Gritsenko, David Mankuta, Marsha Kaitz, and Richard P. Ebstein

6.1	Stressors and HPA Axis Regulation: Naturalistic Studies	93
6.2	Trier Social Stress Test	94
6.3	Genes and Regulation of the HPA Axis	95
6.4	Jerusalem Studies	97
6.4.1	Experimental Design	97
6.4.2	Genes Associated with TSST Response	98
6.5	Growth Factors	98
6.5.1	BDNF Gene	98
6.6	Neuropeptides	103
6.6.1	Arginine Vasopressin 1a Receptor (AVPR1a)	103
6.7	Serotonin Transmission	104
6.7.1	Serotonin Transporter (SLC6A4)	104
6.7.2	Monoamine Oxidase A (MAOA)	104
6.8	Sex Steroids	105
6.8.1	Estrogen Receptor Alpha (ESR1)	105
6.8.2	Genes Not Associated with TSST Response	106
	Summary	107
	References	108

Part III Cognition and Behavior

- 7 Corticosteroid Hormones in Stress and Anxiety – Role of Receptor Variants and Environmental Inputs 119**
Roel H. DeRijk, Efthimia Kitraki, and E. Ronald de Kloet
- 7.1 Introduction 119
- 7.2 Corticosteroid Hormones, Fear and the Stress Response 121
- 7.2.1 Neuroanatomical Basis 121
- 7.2.2 Role of Corticosteroids and Other Stress Mediators 122
- 7.2.3 Cognitive and Emotional Aspects of Stress 124
- 7.3 Gene Variants and Early Life Experiences 125
- 7.4 MR and GR Gene Structure 126
- 7.5 Genetic Variants of the MR and GR Genes 127
- 7.5.1 MR Gene 129
- 7.5.2 GR Gene 129
- 7.6 HPA Axis Regulation 131
- 7.6.1 Basal Cortisol Levels 131
- 7.6.2 Feedback Sensitivity 131
- 7.6.3 Psychosocial Challenges 132
- 7.7 Epigenetic Modifications Affecting GR and MR Actions 133
- 7.8 Stress-Related Psychopathology 135
- 7.8.1 Corticosteroid-Controlled Pathways as Targets for New Therapeutic Interventions 135
- 7.9 Early Experience and Psychopathology 136
- 7.10 Genetic Variants and Psychopathology 137
- 7.11 Concluding Remarks 140
- Summary 141
- References 142
- 8 Corticotropin-Releasing Factor (CRF) and CRF-Related Peptides – a Linkage Between Stress and Anxiety 151**
Thomas Blank and Joachim Spiess
- 8.1 The CRF Family, Its Receptors and Ligands 151
- 8.2 The Role of CRF and CRF-Related Peptides in Neuroendocrine Aspects of Stress 153
- 8.3 The Role of CRF and CRF-Related Peptides in Behavioral Aspects of Stress 154
- 8.4 The Role of CRF and CRF-Related Peptides in Anxiety 156
- 8.5 Crosstalk Between the CRF and Serotonin Systems 158
- 8.6 Future Directions 159
- Summary 159
- References 160

9	Stress, Emotion and Memory: the Good, the Bad and the Intriguing	167
	<i>Marie-France Marin, Tania Elaine Schramek, Françoise S. Maheu, and Sonia J. Lupien</i>	
9.1	Introduction	167
9.2	The Relativity of Stress	168
9.3	Important Characteristics of Stress Hormones	169
9.3.1	Stress Hormone Receptors	169
9.3.2	The Impact of Stress Hormones on Cognition	170
9.4	Effects of GCs on Learning and Memory	171
9.4.1	Direct Effects of GCs	172
9.4.2	Modulatory Effects of GCs	173
9.4.3	Chronic Effects of GCs on Cognition and Brain Integrity	174
9.5	Stress, Emotion and Memory	176
9.5.1	Central Focus Phenomenon	176
9.5.2	Retention Intervals and Emotional Memory	177
9.5.3	Stress Hormones and Emotional Memory	178
9.5.4	Stress Hormone Effects of the Encoding and Consolidation of Emotional Material	178
9.5.5	Stress Hormone Effects of the Retrieval of Emotional Material	179
9.6	Contextual Effects	180
9.7	New Directions	181
9.8	Conclusion	182
	Summary	183
	References	183
10	Contribution of Early Life Stress to Anxiety Disorder	189
	<i>Marta Weinstock</i>	
10.1	Introduction	189
10.2	Organization of the Stress Response	190
10.2.1	Glucocorticoid Receptors	190
10.2.2	CRH and Its Receptors	191
10.2.3	Role of the Amygdala and CRH in Mediating Anxiogenic Behavior	192
10.3	Alterations in Circulating Hormonal Levels Induced by Chronic Gestational Stress	192
10.3.1	Experimental Animals	192
10.3.2	Human Subjects	193
10.4	Alterations in the Regulation of the HPA Axis as a Result of Prenatal Stress	194
10.4.1	Experimental Animals	194
10.4.1.1	Effects on Basal HPA Axis Activity	194
10.4.1.2	Effect of Prenatal Stress on the Response to Stress of the HPA Axis	194

- 10.4.2 Human Subjects 195
 - 10.4.2.1 Effects of Prenatal Stress on Basal HPA Axis Activity 195
 - 10.4.2.2 Effect of Prenatal Stress on the Response to Stress of the HPA Axis 196
- 10.5 Alterations in the Regulation of the HPA Axis as a Result of Postnatal Stress 196
 - 10.5.1 Experimental Animals 196
 - 10.5.2 Human Subjects 197
- 10.6 Association Between Prenatal Stress and Anxiety Disorder 197
 - 10.6.1 Experimental Animals 197
 - 10.6.2 Human Subjects 199
- 10.7 Association Between Early Life Stress and Anxiety Disorder 200
 - 10.7.1 Experimental Animals 200
 - 10.7.2 Human Subjects 202
 - Summary 202
 - References 203

Part IV Immune Responses

- 11 Stress Effects on Immunity in Vertebrates and Invertebrates 209**
Michael Shapira
 - 11.1 Introduction 209
 - 11.2 The Neuroendocrine Stress Response in Vertebrates and Invertebrates 210
 - 11.2.1 Stress Responses and Hormones in Invertebrates 211
 - 11.3 The Immune System in Vertebrates and Invertebrates 212
 - 11.3.1 Effects of Acute Stress on Immunity 216
 - 11.3.1.1 Vertebrates 216
 - 11.3.1.2 Invertebrates 218
 - 11.3.2 Effects of Chronic Stress 219
 - 11.3.2.1 Vertebrates 219
 - 11.3.2.2 Invertebrates 220
 - Summary and Future Prospects 221
 - References 222
- 12 Immunity to Self Maintains Resistance to Mental Stress: Boosting Immunity as a Complement to Psychological Therapy 229**
Gil M. Lewitus, Osnat Schwartz-Stav, and Michal Schwartz
 - 12.1 Introduction 229
 - 12.2 Stress and the Blood–Brain Barrier 230
 - 12.3 Lymphocyte Surveillance of the CNS 230
 - 12.4 Stress-Induced Lymphocyte Mobilization 231
 - 12.5 Stress Hormones and Lymphocyte Trafficking 232
 - 12.6 The Physiological Relevance of Lymphocytes in the Brain 233

12.7	Protective Autoimmunity	233
12.8	Behavioral Immunization	235
12.9	Immune Memory to Self Antigens Underlies Resilience to Mental Stress	235
	Summary	237
	References	238
13	Brain Interleukin-1 (IL-1) Mediates Stress-Induced Alterations in HPA Activation, Memory Functioning and Neural Plasticity	243
	<i>Inbal Goshen and Raz Yirmiya</i>	
13.1	Introduction	243
13.2	The Bi-Directional Interaction Between IL-1 and the HPA Axis	243
13.3	Stress-Induced HPA Axis Activation is Regulated by Brain IL-1	246
13.3.1	IL-1 Mediates Immunological Stress-Induced HPA Axis Activation	246
13.3.2	Brain IL-1 Mediates Psychological Stress-Induced HPA Axis Activation	246
13.4	Stress-Induced Alterations in Memory and Neural Plasticity are Regulated by Brain IL-1	249
13.4.1	Brain IL-1 Underlies Stress-Induced Memory Impairment by Modulating Glucocorticoids Secretion	250
13.4.2	Stress-Induced IL-1 Reduces Hippocampal Neurogenesis: Implications for Memory Impairments	253
	Summary	254
	References	255
Part V	Post-Traumatic Stress Disorder	
14	Post-Traumatic Stress Disorder in Animal Models	263
	<i>Hagit Cohen, Nitzan Kozlovsky, Gal Richter-Levin, and Joseph Zohar</i>	
14.1	Introduction	263
14.2	Animal Models of PTSD	265
14.2.1	Trauma/Stress-Based Models	265
14.2.2	Mechanism-Based Models	266
14.2.2.1	Enhanced Fear Conditioning	267
14.2.2.2	Impaired Extinction	267
14.2.3	Individual Differences in Response to an Exposure to a Traumatic Experience	268
14.2.4	Behavioral Assessments	268
14.2.5	Classification According to Cut-Off Behavioral Criteria	269
14.3	Selected CBC-Based Studies	271
14.3.1	Behavioral Response Patterns Versus Time	271
14.3.2	Physiological Correlates	272
14.3.3	Strain/Genetic Studies	272

- 14.3.3.1 HPA Axis Response in Lewis and Fischer Rats 273
- 14.3.3.2 Stress-Induced Behavioral Responses in Inbred Mouse Strains 273
- 14.3.4 Molecular Neurobiological Correlates 273
- 14.3.5 Drug Studies 274
- 14.3.5.1 Early Intervention with an SSRI (Sertraline) 275
- 14.3.5.2 Early Intervention with Corticosterone 275
- 14.3.5.3 Early Intervention with Benzodiazepine (Alprazolam) 276
- Summary 276
- References 277

15 The Cholinergic Model for PTSD: from Acute Stress to PTSD, from Neuron to Network and Behavior 283

Alon Friedman and Lev Pavlovsky

- 15.1 From Acute Stress to PTSD 283
- 15.2 Stress and Brain Cholinergic Pathways 283
- 15.3 Anatomical Considerations 284
- 15.4 Neurophysiological Considerations 285
- 15.4.1 The Role of ACh in Behavior, Learning and Memory 288
- 15.5 Stress Induces Cholinergic Dysfunction 288
- 15.5.1 Stress Event Affects Cholinergic Functions 289
- 15.5.2 Cholinergic Dysfunction Persists After Stress 289
- 15.5.3 Cholinergic Dysfunction May Underlie Short- and Long-Term Clinical Symptoms 290
- 15.6 The Cholinergic Basis for PTSD: the Model 290
- Summary 292
- References 292

Part VI Vulnerability to Disease

16 Stress and Neurodegeneration: Adding Insult to Injury? 299

Amit Berson, Mor Hanan, and Hermona Soreq

- 16.1 Abstract 299
- 16.2 Alzheimer's Disease Shares Phenotypic Biomarkers with Stress Reactions 299
- 16.3 Molecular Underpinnings of Stress-Induced Cognitive Impairments 300
- 16.4 Direct Evidence Linking Stress Reactions and AD 303
- 16.5 The Cholinergic System Connects Stress Reactions and AD 304
- 16.6 Chronic Stress Affects Behavior Through Chromatin Remodeling and Alternative Splicing 307
- 16.7 GCs Regulate Neuronal Excitability by Modifying Alternative Splicing 309
- Summary 310
- References 310

- 17 Stress and Neurotransmission: Clinical Evidence and Therapeutic Implications 317**
Hadar Shalev and Jonathan Cohen
- 17.1 Introduction 317
- 17.2 Serotonin 319
- 17.3 Adrenergic Antagonists 321
- 17.4 γ -Aminobutyric Acid 323
- Summary 325
- References 327
- 18 Metabolic Components of Neuroendocrine Allostatic Responses: Implications in Lifestyle-Related Diseases 331**
Ronan M.G. Berg and Bente Klarlund Pedersen
- 18.1 Introduction 331
- 18.2 Neuroendocrine Allostatic Responses and Fat Metabolism 332
- 18.2.1 Background 332
- 18.2.2 Effects of GCs on Fat Metabolism and Distribution 333
- 18.2.3 Effects of Catecholaminergic Signaling on Lipolysis and Dyslipidemia 334
- 18.3 Neuroendocrine Allostatic Responses and Glucose Metabolism 335
- 18.3.1 Background 335
- 18.3.2 The Effects of GCs on Gluconeogenesis and Glycogen Synthesis 335
- 18.3.3 Effects of Catecholaminergic Signaling on Hepatic Glucose Metabolism 337
- 18.3.4 Effects of GCs on Peripheral Insulin Sensitivity 337
- 18.3.5 Effects of Catecholaminergic Signaling on Peripheral Glucose Transport 338
- 18.4 Discussion 339
- Summary 342
- References 342
- 19 Environmental Stress is Not Always Vicious: a Lesson from Heat Acclimation-Mediated Neuroprotection After Traumatic Brain Injury 349**
Michal Horowitz and Esther Shohami
- 19.1 Introduction 349
- 19.2 TBI Damage – Detrimental Signaling and Possible Protective Pathways 349
- 19.2.1 Short Background 349
- 19.2.2 TBI-Induced Tissue and Cellular Stress Response 350
- 19.2.2.1 Glutamate 350
- 19.2.2.2 Reactive Oxygen Species 351
- 19.2.2.3 Neuroinflammation 351
- 19.2.3 Treatments 352

19.3	Preconditioning: Inherent Protective Mechanisms Are Induced by Preceding Sub-Lethal (Multiple) Stressors	352
19.4	Heat Acclimation and Neuroprotection	353
19.4.1	Heat Acclimation	353
19.4.2	Heat Acclimation Affords Neuroprotection After TBI	354
19.4.2.1	Physiological Evidence	354
19.4.3	Underlying Signaling Pathways	356
19.4.3.1	Oxidative Stress	356
19.4.3.2	HIF-1-Erythropoietin Pathway	356
19.4.3.3	Acute Inflammatory Response	357
	Summary	359
	References	359
	Index	365