## Contents

*List of Contributors*  xiii  
*Preface* xvii  

### Part I  Fundamental Concepts  1

1  *Cytosolic and Transcriptional Cycles Underlying Circadian Oscillations*  3  
*R. Michael Hastings and John S. O'Neill*

1.1  Introduction  3

1.2  Assembling the transcriptional feedback loop  5  
1.2.1  Discovering clock genes and their actions in lower species  5
1.2.2  Discovering clock genes and their actions in mammals  6
1.2.3  Imaging the transcriptional clock in real time: a multitude of cellular oscillators appears  6
1.2.4  Elaborating the core transcriptional clockwork  8

1.3  Keeping the transcriptional clockworks in tune  9  
1.3.1  Entrainment of the SCN transcriptional clockwork  9
1.3.2  Entrainment of transcriptional clocks in peripheral tissues  10
1.3.3  Local tissue clocks direct local transcriptional and posttranscriptional programs  11

1.4  Building posttranslational mechanisms into the circadian pacemaker  13  
1.4.1  Posttranslational control of the clock: localization and stability of clock proteins  13
1.4.2  Metabolic regulation of the transcriptional clockwork  13
1.4.3  Cause versus effect in circadian transcriptional regulation  14

1.5  Is the transcriptional clock paramount?  15  
1.5.1  Cytosolic rhythms and the SCN pacemaker  15
1.5.2  Totally transcription-free pacemaking  16
1.5.3  A general model for mammalian cellular circadian timekeeping  17

1.6  Conclusion: cytoscillators, clocks and therapies  18

*References*  18

2  *Molecular Determinants of Human Circadian Clocks*  25  
*R. Steven A. Brown*

2.1  Molecular elements of human clocks: a brief review  25
2.2  Peripheral and central clocks  26
2.3  Signaling to peripheral circadian clocks  28
2.4  Human peripheral and central clocks  29
2.5  Human genetics  29
2.6  Technologies for measurement of human circadian clocks  30
2.7  Cellular methods  30
2.8  Omics-based methods to analyze human clocks  32
2.9  Summary and outlook  33

*References*  33

3  *The Suprachiasmatic Nucleus (SCN): Critical Points*  37  
*R. Christopher S. Colwell, Paul Witkovsky, and Rae Silver*

3.1  SCN is site of master circadian pacemaker in mammals  37
3.2  SCN receives photic information through a specialized light detection pathway  39

*References*  39
3.3 SCN neurons are endogenous single cell oscillators that generate rhythms in neural activity 40
3.4 The SCN has circuit level organization that is just beginning to be unraveled 42
3.5 Coupling with the SCN circuit is mediated by a set of peptides with VIP on top of the hierarchy 44
3.6 SCN outputs 44
3.6.1 SCN neurons are directly neurosecretory cells 45
3.6.2 Body temperature rhythms as an output 47
3.6.3 SCN regulates the autonomic nervous system 47
3.6.4 Melatonin is a key hormone under circadian regulation 47
3.6.5 HPA axis is another important endocrine network regulated by the circadian system 49
3.6.6 The SCN regulates the arousal of the central nervous system 49
3.6.7 The SCN circuit controls the temporal patterning behaviors (activity, sleep, feeding) with widespread implications for our bodily function 50
3.7 SCN in aging and disease 50
References 51

4 Sleep and Circadian Rhythms: Reciprocal Partners in the Regulation of Physiology and Behavior 57
Ralph Mistlberger
4.1 Introduction 57
4.2 What is sleep 59
4.3 Circadian regulation of sleep 60
4.3.1 Behavioral studies: human sleep 60
4.3.2 Behavioral studies: rodent models 63
4.3.3 Neural mechanisms 64
4.3.4 Molecular mechanisms, local oscillators and local sleep 66
4.4 Reciprocity: sleep–wake feedback to the circadian clock 69
4.4.1 Feedback from waking states 69
4.4.2 Feedback from sleep states 71
4.5 Conclusions: Circadian clocks and sleep are intertwined processes 73
References 73

5 Circadian Regulation of Arousal and its Role in Fatigue 81
David R. Bonsall and Mary E. Harrington
5.1 Defining arousal 81
5.2 Brain structures important for arousal 83
5.3 Neurochemicals signaling the states of arousal 84
5.4 Circadian regulation of the arousal system 86
5.5 Influence of input pathways on circadian regulation of arousal 88
5.6 Sustained states of fatigue: a disorder of the arousal network? 88
5.7 Conclusions 90
References 91

Part II Circadian Regulation of Major Physiological Systems 95

6 Physiology of the Adrenal and Liver Circadian Clocks 97
Alexei Leliavski and Henrik Oster
6.1 Introduction 97
6.2 Circadian control of adrenal function 98
6.2.1 Glucocorticoids (GCs) 99
6.2.2 Mineralocorticoids (MCS) 99
6.2.3 Catecholamines (CAs) 99
6.2.4 Adrenal clocks 100
6.2.5 Local control of MC rhythms 100
6.2.6 Local control of GC rhythms 101
6.3 Circadian control of liver function 101
6.3.1 Glucose metabolism 102
6.3.2 Lipid metabolism 103
6.3.3 Detoxification 103
6.3.4 Hepatocyte clocks 104
6.3.5 Local control of energy metabolism 104
6.3.6 Local control of biotransformation 104
6.4 Conclusion 105
References 105
7 Nutrition and Diet as Potent Regulators of the Liver Clock 107
Yu Tahara and Shigenobu Shibata

7.1 Introduction 107
7.2 Food is a “zeitgeber”: The FEO in the brain 107
  7.2.1 Food entrainment and food anticipatory activity 107
  7.2.2 Role of the SCN on the FEO 108
  7.2.3 FEO formation and characteristics in the brain 108
7.3 The FEO in peripheral tissues 109
  7.3.1 Discovery of the FEO in peripheral tissues 109
  7.3.2 Effect of meal frequency and pattern on the FEO 110
  7.3.3 Role of clock genes in FAA and FEO in the brain and FEO in peripheral tissues 110
7.4 What should we eat? What types of food can stimulate the peripheral clock? 110
  7.4.1 Role of nutrients in the FEO 110
  7.4.2 Foods beyond nutrients 111
  7.4.3 Signal transduction in peripheral FEO 111
7.5 When should we eat? Application to human life science 112
7.6 Circadian rhythm and obesity and diabetes 113
  7.6.1 Feeding frequency and patterns affect obesity and diabetes 113
  7.6.2 Effect of rotation work and shift work on obesity, diabetes, and cancer 114
  7.6.3 Effect of calorie restriction on circadian rhythm and life span 114
  7.6.4 Role of circadian rhythm in pharmacological and nutritional actions 115

References 116

8 The Cardiovascular Clock 119
R. Daniel Rudic

8.1 Introduction 119
8.2 The vascular clock 119
8.3 Circadian clock regulation of the endothelial cell layer of blood vessels 120
8.4 The circadian clock in vascular disease 121
8.5 The circadian clock and vascular cell signaling 122
8.6 The circadian rhythm in blood pressure, nighttime hypertension, and cardiovascular disease in humans 123
8.7 Diabetes, obesity, and blood pressure 125
8.8 AT influences the circadian rhythm in experimental hypertension 126
8.9 The circadian clock and fluid balance 127
8.10 The circadian clock and peripheral vascular resistance 127
8.11 Conclusion 130

References 130

9 Hypertension Caused by Disruption of the Circadian System: Blood Pressure Regulation at Multiple Levels 135
Hitoshi Okamura, Miho Yasuda, Jean-Michel Fustin, and Masao Doi

9.1 Introduction 135
9.2 Effects of deleting Cry genes 135
9.3 Reduced α-adrenoceptor responsiveness in peripheral vessels and primary aldosteronism of Cry-null mice 138
9.4 Rapid blood pressure control system: enhanced baroreflex in Cry-null mice 139
9.5 Conclusion 141

References 141

10 Chronobiology of Micturition 143
Akihiro Kanematsu and Hiromitsu Negoro

10.1 Introduction 143
10.2 Human studies 144
  10.2.1 Children and nocturnal enuresis 144
  10.2.2 Aging and nocturia 144
  10.2.3 Nocturnal polyuria 144
  10.2.4 Daily change in bladder capacity 145
  10.2.5 Central control of the kidneys and the bladder 145
10.3 Animal models 146
  10.3.1 Rats 146
  10.3.2 Mice 146

References 146
10.4 The circadian clock and micturition 147
10.5 The clock in the bladder 148
  10.5.1 The bladder has rhythm: demonstration of the circadian clock in the bladder 148
  10.5.2 Connexin43 (Cx43) is a clock-controlled gene in the bladder 149
10.6 Future directions 150
  10.6.1 Basic research 150
  10.6.2 Clinical research 151
References 151

11 Disruption of Circadian Rhythms and Development of Type 2 Diabetes Mellitus: Contributions to Insulin Resistance and Beta-cell Failure 155
Aleksey V. Matveyenko

11.1 Introduction 155
11.2 Mechanisms underlying pathophysiology of Type 2 diabetes mellitus: interaction between insulin resistance and beta-cell failure 156
  11.2.1 Circadian disruption and predisposition to Type 2 diabetes mellitus: accumulating evidence from epidemiological, clinical and animal studies 159
11.3 Mechanisms underlying the association between circadian disruption and T2DM; potential role of obesity and insulin resistance 160
11.4 Mechanisms underlying the association between circadian disruption and T2DM; potential role of impaired beta-cell secretory function and mass 162
11.5 Conclusion 165
References 166

12 Circadian Clock Control of the Cell Cycle and Links to Cancer 169
T. Katherine Tamai and David Whitmore

12.1 Introduction 169
12.2 Epidemiology 169
12.3 Does circadian clock disruption have any relevance in a clinical setting? 170
12.4 Circadian clock control of the cell cycle in healthy tissues 171
12.5 How might the cellular circadian clock regulate cell cycle timing? 173
12.6 Clock disruption and cancer 177
12.7 Does alteration in clock gene expression in human tumors correlate with the survival of patients? 178
12.8 Circadian-based chemotherapy (Chronotherapy): timing cancer treatment to improve survival 178
12.9 Conclusion 180
References 180

13 How Shift Work and a Destabilized Circadian System may Increase Risk for Development of Cancer and Type 2 Diabetes 183
An Pan, Elizabeth Devore, and Eva S. Schernhammer

13.1 Introduction 183
13.2 Shift work and cancer 184
  13.2.1 Epidemiologic studies of shift work and breast cancer risk 184
  13.2.2 Epidemiologic studies of shift work and prostate cancer 190
  13.2.3 Epidemiologic studies of shift work and risk of other cancers 193
  13.2.4 Summary of evidence for an association between shift work and cancer 193
  13.2.5 Consideration of obesity in epidemiologic studies of night shift work and cancer risk 194
13.3 Shift work and obesity, metabolic syndrome, and type 2 diabetes 194
  13.3.1 Epidemiological studies of shift work and obesity and metabolic syndrome 194
  13.3.2 Epidemiological studies of shift work and type 2 diabetes 202
  13.3.3 Pathways linking shift work to type 2 diabetes 203
13.4 Conclusions and perspective of future studies 205
References 205

14 Circadian Rhythms in Immune Function 211
Kandis Adams, Oscar Castanon-Cervantes, and Alec J. Davidson

14.1 Introduction 211
14.2 Daily variations in health and disease 212
14.3 Early evidence of circadian regulation on immunity 212
14.4 Clinical relevance of circadian regulation of the immune system 213
14.5 The circadian system communicates time of day information to immune cells and tissues 214
14.6 Immune effector cells under circadian regulation 214
  14.6.1 Natural killer cells 214
  14.6.2 Macrophages 215
  14.6.3 T cells 215
  14.6.4 B cells 215
14.7 Circadian disruption role in immune pathology and disease 216
14.8 The effects of clock gene alterations on immune functions 217
14.9 Conclusions 217
References 218

Part III  Clocks in the Central Nervous System 221

15 Circadian Clock, Reward and Addictive Behavior 223
Urs Albrecht
15.1 Introduction 223
15.2 Evidence for a time of day basis of addictive behavior 223
15.3 Drugs, circadian clock genes and addictive behavior 224
  15.3.1 Cocaine 224
  15.3.2 Methamphetamine 225
  15.3.3 Alcohol 226
  15.3.4 Nicotine 226
  15.3.5 Opioids 227
  15.3.6 Cannabinoids 227
15.4 Links between feeding, addictive behavior and the clock 228
15.5 Treatment of addiction changing the circadian clock 229
References 231

16 How a Disrupted Clock may Cause a Decline in Learning and Memory 235
Christopher S. Colwell
16.1 Introduction 235
16.2 Molecular clockwork expressed in brain regions central to learning and memory including the hippocampus, amygdala, and cortex 236
16.3 The circadian clockwork regulates intracellular signaling pathways known to be important to learning and memory 237
16.4 The circadian system impacts electrical activity and synaptic plasticity 238
16.5 The circadian system regulates neuroendocrine secretions that are well known to alter learning and memory processes 240
16.6 Disruptions of the circadian timing system alter learned behavior 241
16.7 Conclusions 245
References 245

17 Circadian Rhythms in Mood Disorders 249
Colleen A. McClung
17.1 Introduction 249
17.2 Categories of rhythm disruptions 251
  17.2.1 Entrainment 251
  17.2.2 Amplitude 251
  17.2.3 Period 251
  17.2.4 Phase 252
17.3 Seasonal affective disorder 252
17.4 Treatments for mood disorders alter rhythms 253
  17.4.1 Bright light therapy (BLT) 253
  17.4.2 Melatonin 253
  17.4.3 Sleep deprivation therapy (SDT) 254
  17.4.4 Interpersonal and social rhythm therapy (IPSRT) 255
  17.4.5 Antidepressant and mood stabilizing drugs 255
  17.4.6 Future drugs 256
17.5 Human genetic studies 257
17.6 Animal studies 257
  17.6.1 Light–dark manipulations 258
  17.6.2 The SCN and mood 258
  17.6.3 Circadian gene mutations 259
17.7 SCN output-rhythmic hormones and peptides 260
17.8 Regulation of mood-related brain circuits by the SCN and circadian genes 262
17.9 Neuroinflammation 263
17.10 Cell cycle regulation/neurogenesis 264
17.11 Conclusions 265
References 265

18 Sleep and Circadian Rhythm Disruption in Psychosis 271
Stuart N. Peirson and Russell G. Foster
18.1 Introduction 271
18.2 Psychosis 273
18.2.1 The psychosis spectrum 273
18.2.2 The social and economic impact of psychosis 275
18.3 Sleep and circadian rhythm disruption in psychosis 275
18.3.1 Schizophrenia 275
18.3.2 Bipolar disorder 276
18.3.3 Relationship between psychosis and SCRD 277
18.4 Possible mechanisms underlying SCRD in psychosis 277
18.4.1 Common neurotransmitters 279
18.4.2 Synaptic dysfunction 279
18.4.3 Internal desynchrony 279
18.4.4 Stress 280
18.4.5 Synaptic homeostasis 280
18.5 Conclusions 280
References 281

19 Alzheimer’s Disease and the Mistiming of Behavior 283
Roxanne Sterniczuk and Michael Antle
19.1 Introduction 283
19.2 Behavioral changes 283
19.2.1 Sundowning behavior 285
19.3 Physiological changes 285
19.3.1 Sleep architecture 285
19.3.2 Core body temperature 286
19.3.3 Melatonin secretion 286
19.4 Neurological changes 286
19.4.1 The circadian pacemaker 287
19.4.2 Sleep regulatory regions 288
19.5 Modeling AD 289
19.6 Chronobiological treatment of AD symptomology 290
19.6.1 Melatonin 290
19.6.2 Bright light therapy 292
19.6.3 Structured environment and behavioral modification 292
19.7 Conclusion 292
References 293

20 Circadian Dysfunction in Parkinson’s Disease 295
Christopher S. Colwell
20.1 Introduction 295
20.2 Dysfunction in the circadian system may contribute to the nonmotor symptoms of PD 296
20.3 Dopaminergic treatments for the motor symptoms of PD may contribute to circadian disruption 297
20.4 PD models show sleep and possible circadian disruption 298
20.5 Possible underlying mechanisms 300
20.6 Conclusion 301
References 302

21 Circadian Dysfunction in Huntington’s Disease 305
A. Jennifer Morton
21.1 Introduction 305
21.2 Mechanisms underlying sleep and circadian rhythm generation 305
21.3 Circadian disruption in HD 306
21.4 Circadian disruption in animal models of HD 306
21.5 Circadian disruption of peripheral clocks and metabolism in HD 311
21.6 Pharmacological manipulation of circadian disruption in HD mice 311
21.7 Environmental modulation of circadian disruption in HD mice 311
21.8 Clinical changes in sleep in HD 312
21.9 Disturbance in sleep architecture in HD 312
21.10 Pathology underlying changes in sleep and circadian activity in HD 313
21.11 The orexin system in HD 313
21.12 The role of non-SCN oscillators in HD 314
21.13 Consequences of sleep–wake disturbance in HD 314
21.14 Cognitive dysfunction and mood disturbance in HD 315
21.15 Management of circadian disturbance in HD 315
21.16 Conclusion 317
References 318
22 The Aging Clock 321
Stephan Michel, Gene D. Block, and Johanna H. Meijer

22.1 Introduction 321

22.2 The effects of aging on rhythmic behaviors 321
22.2.1 Humans 321
22.2.2 Rodents 322
22.2.3 Drosophila 322

22.3 The effects of aging on components of the circadian system 323
22.3.1 Ocular pacemaker of Aplysia 323
22.3.2 In vivo studies in rodents 323
22.3.3 Rodent in vitro work 325
22.3.4 Clock neuron physiology 326

22.4 Molecular rhythms in steady state 328
22.4.1 Intracellular SCN oscillators 328
22.4.2 Peripheral oscillators 328

22.5 The effects of aging on the resetting behavior of central and peripheral oscillators 329

22.6 The effects of the circadian system on aging and age-related disease:
Circadian misalignment and longevity 330

22.6.1 Drosophila 330
22.6.2 Circadian misalignment and longevity in rodents 330

22.7 Therapeutic possibilities for age-related circadian disorders 331

22.8 Conclusions 332
References 332

23 Can we Fix a Broken Clock? 337
Analyne M. Schroeder and Christopher S. Colwell

23.1 Introduction 337

23.2 Light therapy 339

23.3 Scheduled meals 340

23.4 Scheduled exercise 341

23.5 Scheduled sleep 343

23.6 Pharmacological targeting of the circadian system 343

23.7 Conclusions 345
References 346

Index 351