Contents

List of Contributors  xvii
Foreword  xxiii

Part I  Anatomy and physiology  1

1  Functional anatomy of trigeminovascular pain  3
Karl Messlinger and Mária Dux
1.1  Anatomy of the trigeminovascular system  3
1.1.1  Vascularization and innervation of the dura mater encephali  3
1.1.2  Extracranial extensions of the meningeal innervation  4
1.1.3  Neuropeptides and their receptors in meningeal tissues  5
1.1.4  Transduction channels and receptors in the trigeminovascular system  8
1.2  Trigeminal ganglion  9
1.2.1  Types of trigeminal ganglion cells  9
1.2.2  Neuropeptides and their receptors in the trigeminal ganglion  9
1.2.3  Representation of intracranial structures in the trigeminal ganglion  12
1.3  Trigeminal brainstem nuclear complex  12
1.3.1  Organization of the trigeminal brainstem nuclear complex  12
1.3.2  Nociceptive afferent projections to the spinal trigeminal nucleus  13
1.3.3  Functional representation of meningeal structures in the spinal trigeminal nucleus  14
1.3.4  Efferent projections from the spinal trigeminal nucleus  14
1.3.5  Neuropeptides and their receptors in the trigeminal nucleus  15
1.3.6  Channels and receptors involved in synaptic transmission in the trigeminal nucleus  16
References  17

2  Physiology of the meningeal sensory pathway  31
Andrew M. Strassman and Agustin Melo-Carrillo
2.1  Role of the meningeal sensory pathway in headache  31
2.2  Nociceptive response properties of peripheral and central neurons in the meningeal sensory pathway  32
2.2.1 Primary afferent neurons  32
2.2.2 Central neurons (dorsal horn and thalamus)  35
2.3 Activity of neurons in the meningeal sensory pathway under conditions associated with headache: CSD and nitroglycerin  36
2.4 Role of blood vessels in activation of the meningeal sensory pathway  38
2.5 Unique neuronal properties of the meningeal sensory pathway  39
2.6 Intracranial vs extracranial mechanisms of migraine: new findings  40

References  41

3  Meningeal afferent ion channels and their role in migraine  49
Gregory Dussor
3.1 Meningeal afferents and migraine pain  49
3.2 Transient receptor potential (TRP) channels and headache  49
3.2.1 TRPA1  50
3.2.2 TRPM8  52
3.2.3 TRPV1  52
3.2.4 TRPV4  53
3.3 Acid-sensing ion channels  54
3.4 Glutamate-gated channels  55
3.5 ATP-gated channels  55
3.6 K⁺ channels  56
3.7 Other ion channels that may contribute to dural afferent signaling  57
3.8 Conclusions  57
3.9 Acknowledgements  58
References  58

4  Functional architecture of central pain pathways: focus on the trigeminovascular system  69
Rodrigo Noseda and Luis Villanueva
4.1 Introduction  69
4.2 Ascending trigeminal nociceptive pathways  69
4.2.1 Ascending nociceptive pathways from the superficial laminae of the dorsal horn  70
4.2.1.1 Spino/trigemino-bulbar projections  70
4.2.1.2 Spino/trigemino-hypothalamic projections  73
4.2.1.3 Spino/trigemino-thalamic projections  73
4.2.2 Ascending nociceptive signals from the deep laminae of the dorsal horn  75
4.2.2.1 Spino/trigemino-reticulo-thalamic projections  75
4.3 Trigeminovascular pain is subject to descending control  77
4.3.1 Descending modulation from the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM)  77
4.3.2 Diffuse noxious inhibitory controls (DNIC)  79
4.3.3 Hypothalamic links for the descending control of trigeminovascular pain  80
4.3.4 The cortex as a major source of descending modulation  81
4.4 Conclusions  82
References  83
Part II  Special features of migraine pain  91

5  Visceral pain  93  
  Michael S. Gold and G.F. Gebhart  
5.1 Organization of innervation  93  
5.2 Common features of visceral pain and headache  96  
5.2.1 Referred sensations  96  
5.2.2 Sensitization  98  
5.2.3 Potential sensitizers  100  
5.2.4 Immune system involvement in visceral pain and migraine  100  
5.3 Summary and conclusions  101  
5.4 Acknowledgement  101  
References  102  

6  Meningeal neurogenic inflammation and dural mast cells in migraine pain  107  
  Dan Levy  
6.1 Introduction  107  
6.2 The neurogenic inflammation hypothesis of migraine  108  
6.3 Meningeal neurogenic plasma protein extravasation and migraine  108  
6.4 Meningeal neurogenic vasodilatation and migraine  110  
6.5 Neurogenic mast cell activation in migraine  111  
6.6 Endogenous events that could promote meningeal NI in migraine  113  
6.7 Anti-migraine drugs and meningeal NI  113  
6.8 Is meningeal NI a pro-nociceptive event in migraine?  114  
6.9 Conclusions  115  
References  116  

7  Sensitization and photophobia in migraine  125  
  Aaron Schain and Rami Burstein  
7.1 Introduction  125  
7.2 Experimental activation of trigeminovascular pathways  125  
7.3 Peripheral sensitization  127  
7.4 Central sensitization: medullary dorsal horn  127  
7.5 Central sensitization: thalamus  129  
7.6 Temporal aspects of sensitization and their implications to triptan therapy  129  
7.7 Modulation of central sensitization  131  
7.8 Neural substrate of migraine-type photophobia  133  
References  135  

8  Central circuits promoting chronification of migraine  139  
  Christopher W. Atcherley, Kelsey Nation, Milena De Felice, Jennifer Y. Xie,  
  Michael H. Ossipov, David W. Dodick and Frank Porreca  
8.1 Introduction  139  
8.2 Pharmacotherapy of migraine  140
8.3 Medication overuse headache (MOH) and migraine chronification 141
8.4 Central circuits modulating pain 143
8.5 Evaluation of descending modulation: diffuse noxious inhibitory controls and conditioned pain modulation 145
8.6 Conclusions 148
References 149

9 Triptans to calcitonin gene-related peptide modulators – small molecules to antibodies – the evolution of a new migraine drug class 157
Richard J. Hargreaves

9.1 Introduction 157
9.2 Trigeminovascular system – migraine physiology and pharmacology 157
9.3 Small molecule CGRP receptor antagonists 159
9.4 Current status of small molecule CGRP receptor antagonist programs 161
9.5 Unraveling the site of action of small molecule CGRP receptor antagonists using clinical pharmacology and brain imaging 162
9.6 Biologic approaches to CGRP modulation 163
9.6.1 Early experimental studies with CGRP antibodies 163
9.6.2 CGRP antibody therapeutics 164
9.6.3 Comparing the CGRP modulators clinically 165
9.6.4 Safety and tolerability of the CGRP antibodies 167
9.7 Summary and conclusion 167
References 168

10 Lessons learned from CGRP mutant mice 175
Levi P. Sowers, Annie E. Tye and Andrew F. Russo

10.1 Introduction 175
10.2 Modeling migraine 175
10.3 Calcitonin gene-related peptide (CGRP) in migraine 176
10.4 What has CGRP manipulation in mice taught us about migraine? 177
10.4.1 CGRP ligand mouse models 177
10.4.2 CGRP receptor mutant mouse models: CLR, CTR, and the RAMPs 180
10.4.2.1 Calcitonin receptor-like receptor (CLR) 180
10.4.2.2 Calcitonin receptor (CTR) 180
10.4.2.3 hRAMP1 overexpressing mice 180
10.4.2.4 RAMP1 knockout 182
10.4.2.5 RAMP2 overexpression 182
10.4.2.6 RAMP2 knockout 182
10.4.2.7 RAMP3 knockout 182
10.5 Conclusions 183
References 183
Part III  Clinical characteristics of migraine  189

11  The clinical characteristics of migraine  191
F. Michael Cutrer, Ryan Smith and David W. Dodick
11.1 Overview of migraine  191
11.2 Migraine prodrome  191
11.3 The migraine headache is the centerpiece of the syndrome  192
11.4 Migraine aura  194
11.4.1 Visual aura  194
11.4.2 Sensory aura  194
11.4.3 Language aura  195
11.4.4 Duration of typical aura  196
11.4.5 Motor aura or hemiplegic migraine  196
11.5 Proposed aura types  197
11.5.1 Brainstem aura  197
11.5.2 Retinal aura  197
11.5.3 Migraine aura versus other causes of neurological deficit  198
11.6 Postdrome  198
11.7 Status migrainosus  199
Summary  199
References  199

12  The premonitory phase of migraine  201
Michele Viana and Peter J. Goadsby
12.1 What is the premonitory phase? Towards a definition  201
12.2 How common are premonitory symptoms?  202
12.3 Do premonitory symptoms reliably predict a migraine attack?  202
12.4 Premonitory symptoms in individuals  203
12.5 Intra-patient variability of the premonitory phase  203
12.6 Difference between patients with and without premonitory symptoms  204
12.7 Premonitory symptoms in children  204
12.8 Premonitory symptoms and migraine triggers  204
12.9 Premonitory symptoms and pathophysiological studies  205
12.10 Treatment during the premonitory phase  206
12.11 Conclusion  206
References  207

Part IV  Migraine genetics and CSD  209

13  The genetic borderland of migraine and epilepsy  211
Isamu Aiba and Jeffrey Noebels
13.1 Introduction  211
13.2 Gene-linked comorbidity  211
13.3 The challenge of dissecting seizure and aura excitability defects 212
13.4 Clinical overlap of migraine with aura and epilepsy phenotypes 214
13.4.1 Classification and co-prevalence 214
13.4.2 Timing 214
13.4.3 Migraine aura and headache arise from distinct pathways and triggers 215
13.4.4 Gender, estrogen, and interictal excitability phenotype in migraine aura and epilepsy 215
13.4.5 Pharmacological overlap 216
13.5 Acquired and genetic etiologies of migraine with aura and epilepsies 216
13.5.1 Epilepsy 216
13.5.2 Migraine 217
13.6 Migraine aura is linked to specific genes with locus and allelic heterogeneity 218
13.7 Correspondence of regional brain susceptibility for migraine in genetic epilepsy syndromes 219
13.8 Are SD thresholds plastic? 220
13.9 Spreading depolarization in cardiorespiratory brainstem regions, a candidate mechanism of SUDEP 221
13.10 Brainstem SD is a “second hit” leading to SUDEP 222
13.11 Tau ablation prevents seizures, SUDEP and brainstem SD threshold in models of SUDEP 223
13.12 Conclusion 223
13.13 Acknowledgements 223

References 223

14 Genetics of monogenic and complex migraine 233
Else A. Tolner, Else Eising, Gisela M. Terwindt, Michel D. Ferrari and Arn M.J.M. van den Maagdenberg
14.1 Migraine is a genetic disease 233
14.2 How to identify genes for migraine? 234
14.3 Gene identification in monogenic Familial Hemiplegic Migraine 234
14.4 Functional studies of gene mutations in monogenic Familial Hemiplegic Migraine 236
14.5 Genetic studies in monogenic disorders in which migraine is a prominent part of the clinical phenotype 239
14.6 Genome-wide association studies in common polygenic migraine 240
14.7 Future directions in genetic migraine research 241
14.7.1 Future avenues of genetic research 242
14.7.2 Novel sequencing strategy for gene identification 243
References 243

15 Lessons from familial hemiplegic migraine and cortical spreading depression 251
Daniela Pietrobon
15.1 Introduction 251
15.2 FHM genes and functional consequences of FHM mutations 252

References 252
15.3 Insights into the mechanisms underlying susceptibility to cortical spreading depression and initiation of migraine attacks from the functional analysis of FHM mouse models 255
15.4 Acknowledgements 260
References 260

16 From cortical spreading depression to trigeminovascular activation in migraine 267

Turgay Dalkara and Michael A. Moskowitz
16.1 CSD causes the visual aura 267
16.2 SD may underlie transient neurological dysfunctions preceding attacks 269
16.3 Does SD cause headache? 270
16.4 Human data supporting the parenchymal inflammatory signaling 274
16.5 Meningeal neurogenic inflammation amplifies the parenchymal signal 275
16.6 Understanding human CSD and migraine without aura 276
16.7 Potential of CSD models to understand migraine and drug development 278
References 278

Part V Modeling and imaging in migraine 285

17 Mathematical modeling of human cortical spreading depression 287

Markus A. Dahlem
17.1 Introduction 287
17.2 Microscopic models: cellular and cytoarchitectonic detail 288
17.2.1 Physiological observations: persistent depolarization 288
17.2.2 Working model: sustained inward currents 288
17.2.3 Physiological mechanism: excitability 289
17.2.4 Results, modeling iterations, and interpretation 291
17.2.4.1 Increasing physiological detail 291
17.2.4.2 Model reconciliation 291
17.3 Macroscopic models: large scale spatiotemporal phenomenology 292
17.3.1 Clinical manifestation: march of migraine aura symptoms 292
17.3.2 Working model: activator inhibitor type description in two spatial dimensions 293
17.3.3 Physiological mechanism: spatiotemporal self-organization 294
17.3.4 Results of modeling iterations: from fronts to pulses to solitary localized structures 295
17.3.4.1 The speed of the front 295
17.3.4.2 Propagation and zigzag percepts 296
17.3.4.3 Propagation of solitary localized patterns 298
17.3.5 Interpretation of pattern formation principles 299
17.3.6 Clinical predictions 300
References 301
18 Tools for high-resolution in vivo imaging of cellular and molecular mechanisms in cortical spreading depression and spreading depolarization 307
Kuvlicm Kilić, Hana Uhlírova, Peifang Tian, Payam A. Saisan, Mohammad Abbas Yaseen, Jonghwan Lee, Sergei A. Vinogradov, David A. Boas, Sava Sakadžić and Anna Devor
18.1 Introduction 307
18.2 Large-scale imaging of vascular dynamics with microscopic resolution 308
18.3 Combining measurements of single-vessel diameter with imaging and quantification of intracellular Ca^{2+} in neurons and astrocytes 309
18.4 NADH autofluorescence: an endogenous marker of energy metabolism 311
18.5 Direct imaging of molecular O_{2} in blood and tissue 312
18.6 Employing optogenetics to study inter-cellular communication 314
18.7 Conclusions and outlook 314
References 315

19 Animal models of migraine aura 321
Shih-Pin Chen, Jeremy Theriot, Cenk Ayata and KC Brennan
19.1 Introduction: spreading depression and migraine 321
19.2 In vivo and in vitro models of SD susceptibility 322
19.3 Experimental preparations 324
19.3.1 In vivo preparations 324
19.3.2 In vitro preparations 324
19.4 Methods to trigger SD 327
19.5 Methods to detect CSD 329
19.6 SD susceptibility attributes 331
19.7 Recommended quality measures for experimental models of migraine aura 333
19.7.1 Anesthesia 333
19.7.2 Systemic physiology 333
19.7.3 Surgical preparation and maintenance 333
19.7.4 Pharmacokinetic factors 333
19.7.5 Induction and recording considerations 334
19.8 Future directions 334
References 335

20 Human models of migraine 347
Jakob Møller Hansen and Messoud Ashina
20.1 Introduction 347
20.2 The first steps: GTN and the NO-hypothesis 347
20.3 Calcitonin gene-related peptide (CGRP) 351
20.4 Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP) 353
20.4.1 Prostaglandin model 353
20.5 Can we gain from the use of experimental models to study functional consequences of migraine mutations? 354
20.6 Conclusion 355
References 355
21  Imaging pain and headache  363
   Duncan J. Hodkinson, Sophie L. Wilcox and David Borsook
21.1  Introduction  363
21.2  Functional brain changes in migraine  363
21.2.1  Headache  363
21.2.2  Aura  364
21.2.3  Allodynia and hyperalgesia  365
21.2.4  Photophobia, phonophobia, and olfactory discomfort  365
21.2.5  Habituation  365
21.2.6  Autonomic dysfunction and other non-pain symptoms  365
21.2.7  Cerebrovascular and metabolic dysfunction  367
21.3  Structural brain changes in migraine  367
21.3.1  Grey matter alterations in migraine  368
21.3.2  White matter alterations in migraine  370
21.4  Insights from orofacial pain  370
21.5  Conclusions  371
References  372

Index  377