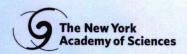


NEUROBIOLOGICAL BASIS OF MIGRAINE

EDITED BY

TURGAY DALKARA AND MICHAEL A. MOSKOWITZ



Neurobiological Basis of Migraine

Edited by
Turgay Dalkara, MD, PhD
Hacettepe University
Ankara
Turkey

Michael A. Moskowitz, MD Harvard Medical School Massachusetts General Hospital Boston Massachusetts USA



This edition first published 2017 © 2017 John Wiley & Sons, Inc.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at http://www.wiley.com/go/permissions.

The right of Turgay Dalkara and Michael A Moskowitz to be identified as the authors of the editorial material in this work has been asserted in accordance with law.

Registered Offices John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

Editorial Office 111 River Street, Hoboken, NJ 07030, USA

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Limit of Liability/Disclaimer of Warranty

The publisher and the authors make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties; including without limitation any implied warranties of fitness for a particular purpose. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for every situation. In view of on-going research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or website is referred to in this work as a citation and/or potential source of further information does not mean that the author or the publisher endorses the information the organization or website may provide or recommendations it may make. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this works was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising here from.

Library of Congress Cataloguing-in-Publication Data applied for.

ISBN: 9781118967195

Cover Design: Wiley

Cover Images: Courtesy of Rami Burstein; (Background) © Tetra Images/Gettyimages

Set in 10/12pt Warnock Pro by SPi Global, Chennai, India Printed and bound in Malaysia by Vivar Printing Sdn Bhd 10 9 8 7 6 5 4 3 2 1 We dedicate this book to our wives, Sevim and Mary as well as to our children and grandchildren, Deniz Dalkara-Mourot, Defne Dalkara, Jenna Moskowitz, Ozan and Esin Dalkara-Mourot, Mattia and Talia Farmer. Their unconditional support and encouragement continue as our inspiration

List of Contributors

Isamu Aiba

Developmental Neurogenetics Laboratory Department of Neurology Baylor College of Medicine Houston Texas USA

Messoud Ashina

Danish Headache Center, Department of Neurology Rigshospitalet, Glostrup Faculty of Health and Medical Sciences University of Copenhagen Copenhagen Denmark

Christopher W. Atcherley

Department of Collaborative Research and Neurology Mayo Clinic Scottsdale Arizona USA

Cenk Ayata

Stroke Service and Neuroscience Intensive Care Unit Department of Neurology Massachusetts General Hospital Harvard Medical School Boston Massachusetts USA

David A. Boas

Martinos Center for Biomedical Imaging MGH Harvard Medical School Charlestown Massachusetts USA

David Borsook

P.A.I.N. Group
Department of Anesthesiology
Perioperative & Pain Medicine
Boston Children's Hospital, Harvard
Medical School
Boston
Massachusetts
USA

K.C. Brennan

Headache Physiology Laboratory Departments of Neurology University of Utah Utah USA

Rami Burstein

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center Harvard Medical School Boston Massachusetts USA

Shih-Pin Chen

Department of Neurology Taipei Veterans General Hospital Taipei Taiwan

F. Michael Cutrer

Department of Neurology Mayo Clinic Rochester Minnesota USA

Markus A. Dahlem

Department of Physics Humboldt University of Berlin Berlin Germany

Turgay Dalkara

Department of Neurology Faculty of Medicine and Institute of Neurological Sciences and Psychiatry Hacettepe University Ankara Turkey

Milena De Felice

School of Clinical Dentistry University of Sheffield South Yorkshire United Kingdom

Anna Devor

Departments of Neurosciences and Radiology **UCSD** La Jolla California USA

David W. Dodick

Mayo Clinic Hospital Phoenix Arizona USA

Gregory Dussor

Behavioral and Brain Sciences BSB-14, The University of Texas at Dallas Richardson Texas **USA**

Mária Dux

Department of Physiology University of Szeged Szeged Hungary

Else Eising

Department of Human Genetics Leiden University Medical Center Leiden The Netherlands

Michel D. Ferrari

Department of Neurology Leiden University Medical Center Leiden The Netherlands

G.F. Gebhart

Center for Pain Research Department of Anesthesiology School of Medicine University of Pittsburgh Pittsburgh Pennsylvania **USA**

Peter J. Goadsby

Headache Group - NIHR-Wellcome King's Clinical Research Facility King's College London London UK

Michael S. Gold

Center for Pain Research Department of Neurobiology School of Medicine University of Pittsburgh Pittsburgh Pennsylvania **USA**

Jakob Møller Hansen

Danish Headache Center Department of Neurology Rigshospitalet Glostrup Faculty of Health and Medical Sciences University of Copenhagen Copenhagen Denmark

Richard J. Hargreaves

Biogen Cambridge Massachusetts USA

Duncan J. Hodkinson

P.A.I.N. Group Department of Anesthesiology Perioperative & Pain Medicine Boston Children's Hospital, Harvard Medical School Boston Massachusetts USA

Kıvılcım Kılıç

Department of Neurosciences **UCSD** La Iolla California USA

Jonghwan Lee

Martinos Center for Biomedical Imaging Harvard Medical School Charlestown Massachusetts USA

Dan Levy

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center Harvard Medical School Boston Massachusetts USA

Agustin Melo-Carrillo

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center Harvard Medical School Boston Massachusetts USA

Karl Messlinger

Institute of Physiology and Pathophysiology Friedrich-Alexander University Erlangen-Nürnberg Erlangen Germany

Michael A. Moskowitz

Departments of Radiology and Neurology Massachusetts General Hospital Harvard Medical School Boston Massachusetts USA

Kelsey Nation

Department of Pharmacology University of Arizona

Tucson Arizona USA

Jeffrey Noebels

Developmental Neurogenetics Laboratory Department of Neurology Baylor College of Medicine Houston Texas

Rodrigo Noseda

USA

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center Harvard Medical School Boston Massachusetts USA

Michael H. Ossipov

Department of Pharmacology University of Arizona Tucson Arizona **USA**

Daniela Pietrobon

Department of Biomedical Sciences University of Padova

and

CNR Institute of Neuroscience Padova Italy

Frank Porreca

Department of Collaborative Research and Neurology Mayo Clinic Scottsdale Arizona USA

and

Department of Pharmacology University of Arizona Tucson Arizona **USA**

Andrew F. Russo

Neuroscience Program Department of Molecular Physiology and **Biophysics** VA Center for the Prevention and Treatment of Visual Loss University of Iowa Iowa City Iowa **USA**

Payam A. Saisan

Department of Neurosciences **UCSD** La Iolla California USA

Sava Sakadžić

Martinos Center for Biomedical Imaging MGH Harvard Medical School Charlestown Massachusetts **USA**

Aaron Schain

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center. Harvard Medical School Boston Massachusetts USA

Ryan Smith

Department of Molecular Physiology and **Biophysics** VA Center for the Prevention and Treatment of Visual Loss Iowa City Iowa **USA**

Levi P. Sowers

Department of Molecular Physiology and **Biophysics** VA Center for the Prevention and Treatment of Visual Loss University of Iowa **Iowa City** Iowa USA

Andrew M. Strassman

Department of Anesthesia Critical Care and Pain Medicine Beth Israel Deaconess Medical Center Harvard Medical School Boston Massachusetts USA

Gisela M. Terwindt

Department of Neurology Leiden University Medical Center Leiden The Netherlands

Jeremy Theriot

Headache Physiology Laboratory Department of Neurology University of Utah Salt Lake City Utah USA

Peifang Tian

Department of Physics John Carroll University University Heights Ohio **USA**

Else A. Tolner

Department of Neurology Leiden University Medical Center Leiden The Netherlands

Annie E. Tye

Neuroscience Program University of Iowa Iowa City Iowa **USA**

Hana Uhlirova

Department of Radiology **UCSD** La Iolla California USA

Arn M.J.M. van den Maagdenberg

Department of Human Genetics Leiden University Medical Center Leiden The Netherlands

Michele Viana

Headache Science Center C. Mondino National Neurological Institute Pavia Italy

Luis Villanueva

Institut National de la Santé et de la Recherche Médicale/Université Paris Descartes Centre de Psychiatrie et Neurosciences Paris France

Sergei A. Vinogradov

Departments of Biochemistry and Biophysics and Chemistry University of Pennsylvania Philadelphia Pennsylvania **USA**

Sophie L. Wilcox

P.A.I.N. Group Department of Anesthesiology Perioperative & Pain Medicine Boston Children's Hospital Harvard Medical School Boston Massachusetts **USA**

Jennifer Y. Xie

Department of Pharmacology University of Arizona Tucson Arizona USA

Mohammad Abbas Yaseen

Martinos Center for Biomedical Imaging MGH Harvard Medical School Charlestown Massachusetts USA

Foreword

When I studied psychology between 1969 and 1975, I took a course on psychosomatic diseases. The professor presented migraine as a typical example of disease which was clearly a psychological problem without a biological basis. There were compelling arguments, like migraine attacks triggered by stress and a strong co-morbidity with anxiety disorders. How much has changed since these times?

When I started to see migraine patients as a young neurology resident, it became immediately clear to me that migraine was clearly more than a psychological problem. Why had the psychologists neglected the results from twin studies? The phenotype of migraine attacks was extremely homogeneous across patients.

Now is the time to summarize the progress in the neurobiological basis of migraine we have made in the last 40 years. The editors have recruited the best scientists and clinicians in the field of migraine research for a display of amazing research results. We are now able to assign all phases of a migraine attack, from prodromes, aura, headache, autonomic symptoms, photo- and phonophobia and postdromes, to anatomical structures, modifications in the pain transmission and modulation system and higher cortical functions.

A major challenge is still the treatment of acute migraine attacks and migraine prevention. Triptans were developed as attack treatment, under the assumption that they would constrict dilated vessels in the dura and the base of the brain. Later, it turned out that they have major effects on pain transmission in the trigemino-thalamic pathways. We desperately need more effective and better tolerated drugs for migraine prevention. The migraine-preventive properties of available medications like beta-blockers, flunarizine, valproic acid, topiramate, amitriptyline and onabotulinum-toxin A were detected "by chance" when these drugs were used for other indications in patients with migraine. CGRP was identified as a major player in the pathophysiology of migraine. At present, four antibodies against CGRP or the CGRP receptor are under development for migraine prevention. This is a good example of translational research, where observations from pathophysiological studies have resulted in new treatment approaches.

xxiv Foreword

Who should read this book? Anyone who is interested in migraine as a disease and in migraine patients. I hope that many young researchers and clinicians will become motivated to move into the very promising field of headache research.

Hans-Christoph Diener
Senior Professor of Clinical Neurosciences
Department of Neurology
University Duisburg-Essen
Essen Germany
E-Mail: hans.diener@uk-essen.de

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
1.5.0	nucleus 16
	References 17
	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

viii	Contents	
	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
	2.0	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
	2.0	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

The cortex as a major source of descending modulation 81

4.3.3 4.3.4

4.4

Conclusions 82

References 83

Part II Special features of migraine pain 91

5	Visceral pain 93
5.1	Michael S. Gold and G.F. Gebhart
5.1	Organization of innervation 93
5.2 5.2.1	Common features of visceral pain and headache 96
	Referred sensations 96 Sensitization 98
5.2.2	
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

х	Contents	
	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

11.1 11.2 11.3 11.4 11.4.1 11.4.2 11.4.3 11.4.4 11.4.5 11.5.1 11.5.2 11.5.3 11.6 11.7	The clinical characteristics of migraine 191 F. Michael Cutrer, Ryan Smith and David W. Dodick Overview of migraine 191 Migraine prodrome 191 The migraine headache is the centerpiece of the syndrome 192 Migraine aura 194 Visual aura 194 Sensory aura 194 Language aura 195 Duration of typical aura 196 Motor aura or hemiplegic migraine 196 Proposed aura types 197 Brainstem aura 197 Retinal aura 197 Migraine aura versus other causes of neurological deficit 198 Postdrome 198 Status migrainosus 199
11.7	Summary 199 References 199
12	The premonitory phase of migraine 201 Michele Viana and Peter J. Goadsby
12.1 12.2 12.3 12.4 12.5 12.6 12.7 12.8 12.9 12.10 12.11	What is the premonitory phase? Towards a definition 201 How common are premonitory symptoms? 202 Do premonitory symptoms reliably predict a migraine attack? 202 Premonitory symptoms in individuals 203 Intra-patient variability of the premonitory phase 203 Difference between patients with and without premonitory symptoms 204 Premonitory symptoms in children 204 Premonitory symptoms and migraine triggers 204 Premonitory symptoms and pathophysiological studies 205 Treatment during the premonitory phase 206 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 13.2	Introduction 211 Gene-linked comorbidity 211