

Melanin-Concentrating Hormone and Sleep

S. R. Pandi-Perumal • Pablo Torterolo •
Jaime M. Monti
Editors

Melanin-Concentrating Hormone and Sleep

Molecular, Functional and Clinical Aspects

 Springer

Editors

S. R. Pandi-Perumal
Somnogen Canada Inc.
Toronto, Ontario, Canada

Pablo Torterolo
Department of Physiology, School
of Medicine
University of the Republic
Montevideo, Uruguay

Jaime M. Monti
Department of Pharmacology and
Therapeutics, School of Medicine Clinics
Hospital
University of the Republic
Montevideo, Uruguay

ISBN 978-3-319-75764-3 ISBN 978-3-319-75765-0 (eBook)
<https://doi.org/10.1007/978-3-319-75765-0>

Library of Congress Control Number: 2018936749

© Springer International Publishing AG, part of Springer Nature 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature.

The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

*To our families...
for their abundant support, for their patience and
understanding, and for their everlasting love
and affection.*

Preface

The melanin-concentrating hormone (MCH) is a neuropeptide that was initially isolated from the teleost pituitary as a chromophore modulator by Kawauchi et al. (1983). Twenty years later, Verret et al. described that this neuropeptide has a strong relationship with the generation and maintenance of sleep. Since then, several authors have described the anatomy and physiology of the MCHergic system. Regarding sleep, the MCHergic system is now considered a critical player for both REM and NREM sleep generation. In addition, there is preclinical and clinical evidence suggesting a role of MCH in human pathology. Finally, synthetic MCH-receptor ligands are under study for the treatment of different medical conditions.

The first two chapters in this volume deal with anatomy: Bittencourt and Dinitz review the neuroanatomical structure of the MCHergic system, while Lee gives an elaborate account of the projections of the MCHergic neurons toward the structures involved in the regulation of sleep and wakefulness.

The next three chapters focused on the role of MCH in sleep physiology. Gao summarized the evidence supporting the role of MCH in the regulation of sleep homeostasis and also discussed the physiological implications of MCH as a central node of the overall brain circuitry controlling physiological functions and complex behaviors. Monti et al. described the effects of MCH on the neurotransmitter systems involved in the generation and maintenance of wakefulness. Finally, Blanco-Centurion et al. performed a careful analysis of the optogenetic studies that focused on understanding the functions of the MCHergic neurons.

In chapters “Cannabinoids, Sleep, and the MCH System”, “MCH and Thermoregulation”, “MCH, Sleep, and Neuroendocrine Functions” and “Melanin-Concentrating Hormone: Role in Nursing and Sleep in Mother Rats”, the role of the MCHergic system was analyzed in the frame of different physiological functions. Murillo-Rodriguez et al. underlined the interactions between endocannabinoids and MCH in the control of sleep, while Luppi reviewed the role of MCH in thermoregulation, highlighting the hypothesis that the regulation of temperature, metabolism, and sleep is closely linked. D’Almeida and coworkers provide an integrative

discussion of the role of MCH in sleep and neuroendocrine functions. Thereafter, Benedetto et al. evaluated the function of MCH in the postpartum rat, stressing the modulation by MCH of maternal behavior and sleep, functions that are integrated within the preoptic area.

The scope of the last three chapters was to integrate basic with clinical research. Costa et al. examined the state of the art of MCH in medical conditions. Then, Scorza and coworkers discussed the preclinical findings in relation to MCH and depression, a condition where sleep is highly affected. Finally, Chaki reviewed the current knowledge regarding the MCH antagonists for the treatment of depression and anxiety disorders.

We consider that understanding the role of MCH in the control of sleep and related functions is highly relevant for human's health. Investigation in this field is advancing at a rapid pace, and this book reveals novel findings and presents questions for future research.

Montevideo, Uruguay
Toronto, ON, Canada
Montevideo, Uruguay

Jaime M. Monti
S. R. Pandi-Perumal
Pablo Torterolo

References

- Kawauchi et al (1983) Characterization of melanin-concentrating hormone in chum salmon pituitaries. *Nature* 305(5932):321–323
- Verret et al (2003) A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. *BMC Neurosci* 4:19

Credits and Acknowledgements

This volume owes its final shape and form to the assistance and hard work of many talented people. Creating a book, which surveys a broad interdisciplinary field such as sleep and neuropharmacology, involves the collaborative scholarship of many individuals. We express our profound gratitude to the many people who have helped and also to some who have contributed without realizing just how helpful they have been.

The editors wish to express their sincere appreciation and owe endless gratitude to all our distinguished contributors for their scholarly contribution that facilitated the development of this volume. Our greatest debt is obviously to our outstanding authors who, regardless of how busy they were, managed to find time for this project. They, in a most diligent and thoughtful way, have brought a wide range of interests and disciplines to this volume entitled *Melanin-Concentrating Hormone and Sleep: Molecular, Functional and Clinical Aspects*. They accepted our submission deadlines and tolerated with great patience our repeated reminders, our frequent phone calls, and our bombardment with high-priority e-mail messages.

We would like to thank our secretarial and administrative staffs of our respective institutions, for helping us to stay on task and for their attention to detail.

No volume can be completed without the untiring efforts of many publishing professionals. Producing a volume such as this is a team effort, and we acknowledge with gratitude the work of the editorial department of Springer International Publishing AG, Switzerland. We are especially indebted to Dr. Beatrice Menz, Senior Editor, Biomedicine, Springer International Publishing AG, who was an enthusiastic and instrumental supporter from the start to the end. Our profound gratitude is also offered to Hannah Dean, Editorial Assistant, Biomedicine, whose equally dedicated efforts promoted a smooth completion of this important project. Both Beatrice and Hannah provided unflagging dedication, invaluable help, and encouragement. We appreciate their intellectual rigor and personal commitment to our project.

We also thank the Springer International Publishing AG production department colleagues for their meticulous work. They all gave unstintingly of their time, energy, and enthusiasm. This talented and dedicated team of copy and production

editors strengthened, polished, trimmed, and conscientiously checked the text for errors.

The editors would also like to acknowledge the close cooperation we have received from each other. We think we made a good team, even if we say it ourselves!

Every effort has been made by the authors, editors, and publishers to contact the copyright holders to obtain their permission for the reproduction of borrowed material. Regrettably, it remains possible that this process could have been incomplete. Thus, if any copyrights have been overlooked, the publisher will ensure correction at the first opportunity for a subsequent reprint of this volume.

Last, but certainly not least, we are most grateful to our wonderful wives and families, who provided love and support too valuable to measure. We owe everything to them. Their understanding and patience, wisdom, creativity, constant support, and encouragement while the book was being developed are immeasurably appreciated. Without the love and support of our families and friends, we could not have completed this project. Being able to spend more time with them is our chief reward for finishing. They saw the work through from the conception of an idea to the completion of an interesting project with unwavering optimism and encouragement. They were the source of joy and inspiration for us, and we thank them for their continuing support and for understanding the realities of academic life!

To all the people who contributed to this project, we want to say “thank you!” Their willingness to contribute their time and expertise made this work possible, and it is to them that the greatest thanks are due. They make our work possible and pleasurable.

For this, and for so much else, we are ever grateful.

Montevideo, Uruguay
Toronto, ON, Canada
Montevideo, Uruguay

Jaime M. Monti
S. R. Pandi-Perumal
Pablo Torterolo

Contents

Neuroanatomical Structure of the MCH System	1
Jackson C. Bittencourt and Giovanne B. Diniz	
Projections of the MCH System to Structures Involved in the Regulation of Sleep and Wakefulness	47
Hyun Sook Lee	
The Role of Melanin-Concentrating Hormone in the Regulation of the Sleep/Wake Cycle: Sleep Promoter or Arousal Modulator?	57
Xiao-Bing Gao	
Optogenetic Control of the Melanin-Concentrating Hormone Expressing Neurons	75
Carlos Blanco-Centurion, Meng Liu, and Priyattam Shiromani	
The Effects of Melanin-Concentrating Hormone on Neurotransmitter Systems Involved in the Generation and Maintenance of Wakefulness	109
Jaime M. Monti, Seithikurippu R. Pandi-Perumal, and Pablo Torterolo	
Cannabinoids, Sleep, and the MCH System	121
Eric Murillo-Rodríguez, Daniela Morales-Lara, José Carlos Pastrana-Trejo, Lorena Macías-Triana, Karen Romero-Cordero, Miriel de-la-Cruz, and Clelia De-la-Peña	
MCH and Thermoregulation	131
Marco Luppi	
MCH, Sleep, and Neuroendocrine Functions	139
Carlos Eduardo Neves Girardi, Débora Cristina Hipólido, and Vânia D’Almeida	
Melanin-Concentrating Hormone: Role in Nursing and Sleep in Mother Rats	149
Luciana Benedetto, Pablo Torterolo, and Annabel Ferreira	

Melanin-Concentrating Hormone in Medical Conditions 171
Alicia Costa, Luciana Benedetto, Patricia Lagos, Jaime M. Monti,
and Pablo Torterolo

MCH and Depression 195
Jessika Urbanavicius, Patricia Lagos, Ximena López, Pablo Torterolo,
and Cecilia Scorza

**MCH Receptor 1 Antagonists: Antidepressant/Anxiolytic Potential
in Animal Models** 207
Shigeyuki Chaki

Editors and Contributors

About the Editors

Jaime Monti is Doctor of Medicine at the University of the Republic, Uruguay. He has completed postdoctoral studies at the National Institutes of Health, USA. He is full professor of Pharmacology and Therapeutic and the School of Medicine of the Republic University, professor of the Basic Sciences Development Program (PEDECIBA), and researcher of the National system of Researchers. His research has been awarded the Claude Bernard Prize (France government) and the Schering Award for Basic Sleep Research. He is an internationally recognized expert in the neuropharmacology of sleep and wakefulness, with more than a hundred of papers in this topic.

S. R. Pandi-Perumal is the president and chief executive officer of Somnogen Canada Inc, a Canadian Corporation. He is a well-recognized sleep researcher, both nationally and internationally, and has authored over 200 publications. His general area of research interest includes sleep and biological rhythms. He is a well-known editor in the field of sleep medicine and has edited over 25 volumes dealing with various sleep-related topics. He received an honorable mention in the *New York Times* in 2004. The India International Friendship Society awarded him the prestigious Bharat Gaurav award on January 12, 2013. The Bharat Gaurav Award is usually given in recognition of a person who has made achievements in a particular field, which in turn will have a positive impact on society at large.

Pablo Torterolo is Doctor of Medicine and Doctor of Neurosciences at the University of the Republic, Montevideo, Uruguay. He has completed postdoctoral studies at the University of Bologna and at the University of California, Los Angeles. He is currently associate professor of the Department of Physiology of the School of Medicine, University of the Republic. He is also professor of the Basic Sciences Development Program (PEDECIBA) and researcher of the National System of Researchers. His research has been awarded the Prize of the National

Academy of Medicine and the Elio García-Austt Award. His studies focus on the neurobiology and pathophysiology of sleep.

Contributors

Luciana Benedetto Department of Physiology, School of Medicine, University of the Republic, Montevideo, Uruguay

Jackson C. Bittencourt Laboratory of Chemical Neuroanatomy, Department of Anatomy, Institute of Biomedical Sciences, University of Sao Paulo, Brazil

Centre for Neuroscience and Behavior, Institute of Psychology, University of Sao Paulo, Brazil

Carlos Blanco-Centurion Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Shigeyuki Chaki Research Headquarters, Taisho Pharmaceutical Co., Ltd, Saitama, Japan

Alicia Costa Department of Physiology, School of Medicine, University of the Republic, Montevideo, Uruguay

Miriél de-la-Cruz Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Clelia De-la-Peña Centro de Investigación Científica de Yucatán A.C., Unidad de Biotecnología, Mérida, Yucatán, México

Giovanne B. Diniz Laboratory of Chemical Neuroanatomy, Department of Anatomy, Institute of Biomedical Sciences, University of Sao Paulo, Brazil

Vânia D'Almeida Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil

Annabel Ferreira Facultad de Ciencias, Sección de Fisiología y Nutrición, Universidad de la República, Montevideo, Uruguay

Xiao-Bing Gao Department of Comparative Medicine, Program on Integrative Cell Signaling and Neurobiology of Metabolism (ICSNM), Yale University School of Medicine, New Haven, CT, USA

Carlos Eduardo Neves Girardi Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil

Master Program in Psychology/Psychosomatics, Universidade Ibirapuera, São Paulo, Brazil

Débora Cristina Hipólido Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil

Patricia Lagos Department of Physiology, School of Medicine, University of the Republic, Montevideo, Uruguay

Hyun Sook Lee Department of Anatomy, College of Medicine, Konkuk University, Seoul, Republic of Korea

Meng Liu Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Ximena López Department of Experimental Neuropharmacology, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay

Marco Luppi Dipartimento di Scienze Biomediche e NeuroMotorie, Università degli Studi di Bologna, Bologna, Italy

Lorena Macías-Triana Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Jaime M. Monti Department of Pharmacology and Therapeutics, School of Medicine Clinics Hospital, University of the Republic, Montevideo, Uruguay

Daniela Morales-Lara Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Eric Murillo-Rodríguez Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Seithikurippu R. Pandi-Perumal Somnogen Canada Inc., Toronto, ON, Canada

José Carlos Pastrana-Trejo Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Karen Romero-Cordero Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Grupo de Investigación en Envejecimiento, División Ciencias de la Salud, Universidad Anáhuac Mayab, Mérida, Yucatán, Mexico

Intercontinental Neuroscience Research Group, Mérida, Yucatán, Mexico

Cecilia Scorza Department of Experimental Neuropharmacology, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay

Priyattam Shiromani Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Ralph Johnson Medical Center, US Department of Veterans Affairs, Charleston, SC, USA

Pablo Torterolo Department of Physiology, School of Medicine, University of the Republic, Montevideo, Uruguay

Jessika Urbanavicius Department of Experimental Neuropharmacology, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay