VITAMINS AND HORMONES

Anandamide an Endogenous Cannabinoid

Editor-in-Chief

GERALD LITWACK

Chair, Department of Basic Sciences
The Commonwealth Medical College
Scranton, Pennsylvania
CONTENTS

Contributors xv
Preface xxv

1. Enzymatic Formation of Anandamide 1
   Yasuo Okamoto, Kazuhito Tsuboi, and Natsuo Ueda
     I. The Transacylation–Phosphodiesterase Pathway for Anandamide Formation 2
     II. NAT 4
     III. NAPE-PLD 9
     IV. Alternative Pathways Forming NAEs from NAPEs 15
     V. Conclusions 18
     References 19

2. Organized Trafficking of Anandamide and Related Lipids 25
   Marla L. Yates and Eric L. Barker
     I. AEA and the Endocannabinoid System 26
     II. AEA Transport 31
     Acknowledgment 45
     References 45

3. Biosynthesis of Oleamide 55
   Gregory P. Mueller and William J. Driscoll
     I. Introduction 56
     II. Fatty Acid Amide Messengers: Structural Considerations 56
     III. Natural Occurrence of Oleamide 57
     IV. Biologic Actions of Oleamide 58
     V. Proposed Mechanisms for the Biosynthesis of Oleamide 59
     VI. Oleamide Biosynthesis by Peptidylglycine Alpha-amidating Monooxygenase 60
     VII. Discovery of Cytochrome c as an Oleamide Synthase 62
     VIII. Cytochrome c also Catalyzes the Formation of Oleoylglycine and Other Long-Chain Fatty Acylamino Acids 64
     IX. Proposal for an Oleamide Synthesome 66
7. Cannabinoid Receptor CB1 Antagonists: State of the Art and Challenges 159

Maurizio Bifulco, Antonietta Santoro, Chiara Laezza, and Anna Maria Malfitano

I. Introduction 160
II. Endocannabinoid System: Control of Energy Balance 161
III. Cannabinoid CB1 Receptors and CB1 Antagonists 162
IV. CB1 Antagonists in the Treatment of Obesity and Related Comorbidities 169
V. Other Emerging Effects of CB1 Antagonists 176
VI. Therapeutic Prospects 179
VII. Conclusions 180
Acknowledgments 181
References 181


Heather B. Bradshaw, Neta Rimmerman, Sherry S.-J. Hu, Sumner Burstein, and J. Michael Walker

I. Historical View of Lipid Signaling Discoveries 192
II. The Identification of Endogenous Signaling Lipids with Cannabimimetic Activity 192
III. Identification of Additional N-Acyl Amides 193
IV. N-Arachidonoyl Glycine Biological Activity 194
V. N-Arachidonoyl Glycine Biosynthesis 194
VI. N-Palmitoyl Glycine Biological Activity 195
VII. N-Palmitoyl Glycine Biosynthesis 197
VIII. PalGly Metabolism 197
IX. Identification and Characterization of Additional Members of the N-Acyl Glycines 198
X. Biological Activity of Novel N-Acyl Glycines 200
XI. Conclusions 201
References 203

9. The Endocannabinoid Anandamide: From Immunomodulation to Neuroprotection. Implications for Multiple Sclerosis 207

Fernando G. Correa, Leyre Mestre, Fabián Docagne, José Borrell, and Carmen Guaza

I. Introduction 208
II. AEA as a Neuroimmune Signal 212
III. Anandamide and Multiple Sclerosis 219
IV. Concluding Remarks 223
Acknowledgment 224
References 224

10. Modulation of the Endocannabinoid-Degrading Enzyme Fatty Acid Amide Hydrolase by Follicle-Stimulating Hormone 231
Paola Grimaldi, Gianna Rossi, Giuseppina Catanzaro, and Mauro Maccarrone

I. Follicle-Stimulating Hormone: Signal Transduction and Molecular Targets 232
II. Sertoli Cells: Activities and Biological Relevance 237
III. Overview of the Endocannabinoid System 239
IV. The ECS in Sertoli Cells 241
V. Regulation of FAAH by FSH in Sertoli Cells 243
VI. FAAH Is an Integrator of Fertility Signals 244
VII. Conclusions 254
Acknowledgments 255
References 255

Renato Malcher-Lopes and Marcelo Buzzi

I. Introduction 264
II. The Arachidonic Acid Cascade 266
III. Glucocorticoid-Mediated Inhibition of cPLA₂-Dependent AA Release from Membrane Phospholipids 269
IV. Biosynthesis of the AA-Containing Endocannabinoids AEA and 2-AG 271
V. Nongenomic Glucocorticoid-Induced Activation of Endocannabinoid Biosynthesis 274
VI. Endocannabinoids Metabolization 278
VII. Crosstalk Between GCs and COX₂ in the Control of Neuroinflammation and Neuroprotection 282
VIII. Crosstalk Between GCs and COX₂ in the Control of Synaptic Plasticity and Learning Processes 285
IX. Coordination of GC-Mediated Control of the Neuroimmune Response and Energy Homeostasis Control 288
Acknowledgments 295
References 295
12. Modulation of the Cys-Loop Ligand-Gated Ion Channels by Fatty Acid and Cannabinoids

Li Zhang and Wei Xiong

I. CB Receptor-Dependent and -Independent Effects of Endocannabinoids
II. Structure and Function of the Cys-Loop LGICs
III. Inhibition of 5-HT$_3$ Receptors by Cannabinoids
IV. Modulation of Gly Receptor Function by Cannabinoids
V. Inhibition of nACh Receptors by Endocannabinoids
VI. Modulation of GABA$_A$ Receptor Function by Fatty Acids
VII. Concluding Discussion
References

13. Endogenous Cannabinoids and Neutrophil Chemotaxis

Douglas McHugh and Ruth A. Ross

I. Cellular Motility and Neutrophils
II. The Endogenous Cannabinoid System
III. Cannabinoids Modulate Cell Migration
IV. Endocannabinoid Effects on Basal Locomotion of Neutrophils
V. Endocannabinoid Effects on Induced Migration of Neutrophils
VI. Cannabinoid Receptor Expression in Neutrophils
VII. Inhibition of Induced Migration: Which Receptors are Involved?
VIII. Inhibitory Signal Transduction Mechanisms: Receptor Crosstalk
IX. Inhibitory Signal Transduction Mechanisms: Disruption of the Actin Cytoskeleton
X. Conclusion
References

14. CB1 Activity in Male Reproduction: Mammalian and Nonmammalian Animal Models

Riccardo Pierantoni, Gilda Cobellis, Rosaria Meccariello, Giovanna Cacciola, Rosanna Chianese, Teresa Chioccarelli, and Silvia Fasano

I. Introduction
II. Receptor Properties
III. Brain–Pituitary Axis
IV. Testis
V. Excurrent Duct System
VI. Concluding Remarks
References
### 15. Anandamide and the Vanilloid Receptor (TRPV1)

Attila Tóth, Peter M. Blumberg, and Judit Boczán

<table>
<thead>
<tr>
<th>Section Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Cannabinoid and Vanilloid Receptors</td>
<td>390</td>
</tr>
<tr>
<td>II. Biochemistry of Anandamide</td>
<td>392</td>
</tr>
<tr>
<td>III. Anandamide as Vanilloid Receptor (TRPV1) Ligand</td>
<td>396</td>
</tr>
<tr>
<td>IV. Other Anandamide Receptors</td>
<td>404</td>
</tr>
<tr>
<td>V. Physiological Actions of Anandamide on TRPV1</td>
<td>404</td>
</tr>
<tr>
<td>VI. Future Directions</td>
<td>410</td>
</tr>
<tr>
<td>References</td>
<td>411</td>
</tr>
</tbody>
</table>

### 16. Endocannabinoid System and Fear Conditioning

Leonardo B. M. Resstel, Fabrício A. Moreira, and Francisco S. Guimarães

<table>
<thead>
<tr>
<th>Section Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>421</td>
</tr>
<tr>
<td>II. Fear Conditioning</td>
<td>423</td>
</tr>
<tr>
<td>III. Influence of Endocannabinoids on Fear Conditioning</td>
<td>426</td>
</tr>
<tr>
<td>IV. Brain Regions in which Endocannabinoids may Modulate Fear Conditioning</td>
<td>429</td>
</tr>
<tr>
<td>V. Conclusion</td>
<td>433</td>
</tr>
<tr>
<td>References</td>
<td>433</td>
</tr>
</tbody>
</table>

### 17. Regulation of Gene Transcription and Keratinocyte Differentiation by Anandamide

Nicoletta Pasquariello, Sergio Oddi, Marinella Malaponti, and Mauro Maccarrone

<table>
<thead>
<tr>
<th>Section Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>442</td>
</tr>
<tr>
<td>II. Epidermis</td>
<td>445</td>
</tr>
<tr>
<td>III. Transcriptional Control of Skin Differentiation</td>
<td>453</td>
</tr>
<tr>
<td>IV. Endocannabinoid System in Epidermis</td>
<td>455</td>
</tr>
<tr>
<td>V. Modulation of the Endocannabinoid System in Differentiating Keratinocytes</td>
<td>456</td>
</tr>
<tr>
<td>VI. Repression of Gene Transcription by Anandamide</td>
<td>457</td>
</tr>
<tr>
<td>VII. Conclusions</td>
<td>459</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>460</td>
</tr>
<tr>
<td>References</td>
<td>461</td>
</tr>
</tbody>
</table>

### 18. Changes in the Endocannabinoid System May Give Insight into new and Effective Treatments for Cancer

Gianfranco Alpini and Sharon DeMorrow

<table>
<thead>
<tr>
<th>Section Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>470</td>
</tr>
<tr>
<td>II. Changes in the Endocannabinoid System in Cancer</td>
<td>471</td>
</tr>
</tbody>
</table>
III. Antiproliferative Effects of Anandamide 473
IV. Effects of AEA on Migration, Invasion, and Angiogenesis 476
V. Targeting Degradation Enzymes of Cannabinoids as an Anticancer Therapy 479
VI. Tumor Promoting Effects of Anandamide 480
VII. Conclusions 480
Acknowledgments 481
References 481

19. Use of Cannabinoids as a Novel Therapeutic Modality Against Autoimmune Hepatitis 487
   Rupal Pandey, Venkatesh L. Hegde, Narendra P. Singh, Lorne Hofseth, Uday Singh, Swapan Ray, Mitzi Nagarkatti, and Prakash S. Nagarkatti

   I. Introduction 488
   II. The Endogenous Cannabinoid System 489
   III. The Biosynthesis of Endocannabinoids 490
   IV. Endocannabinoid System is Autoprotective 490
   V. Autoimmune Hepatitis 492
   VI. Treatment Drawbacks 494
   VII. Cannabinoid/Endocannabinoid System in Hepatitis 494
   VIII. Conclusions and Future Directions 499
Acknowledgments 500
References 500

Index 505