Analgesia

Methods and Protocols

Edited by

Arpad Szallasi

Department of Pathology and Laboratories, Monmouth Medical Center, Long Branch, NJ, USA

Humana Press
We congratulate the editor, Dr. Arpad Szallasi, for enlisting outstanding experts active in important areas of pain research to contribute to this book and for the breadth of topics presented – from the molecular level to clinical application.

Freedom from pain is argued by some to be a fundamental human right. Despite tremendous breakthroughs in our understanding of the biological basis of pain perception and the treatment of pain, freedom from pain cannot be guaranteed. More research that builds upon the current knowledge base will advance the realization of this right for all.

Creativity is essential for scientific investigation, but tools are required to test the validity of creative thought. This book provides a cross discipline view of techniques used to investigate the biological basis for pain perception and to discover new treatments. The techniques themselves reflect great creativity and have strengths and weaknesses. Description in this book of techniques used in pain research by scientists who use them, and in some cases developed or improved them, provide readers of the book the opportunity to benefit from the experience of the authors and to participate in advancing the goal of freedom from pain for everyone.

Gabor Racz  

James E. Heavner
Preface

Analgesia: no pain, lot to gain

Ancient Greeks considered diseases to be penalties sent by gods. Indeed, the English word “pain” has its origin in the Greek word poine (“penalty”). The word analgesia is derived from the Greek adjective analgetos (“not sensing pain”) that, in turn, stems from the verb alego, meaning “to care, look after”. Modern medical dictionaries define analgesia as (1) absence of sensibility to pain, or (2) the relief of pain without loss of consciousness.

Chronic pain is a complex phenomenon, which continues to remain undertreated in the majority of affected patients and thus represents a significant unmet medical need. For any given analgesic drug, the NNT (number needed to treat) number is estimated to be as low as one in seven. Such clinical value (beneficial only in 15% of treated patients) would be unacceptably low for any other disease. Not surprisingly, the medical management of chronic pain remains frustrating both for patients and their clinicians.

Chronic pain is rampant, affecting a major segment of the population. In the US, an estimated 50 million adults are suffering from chronic pain. Chronic pain, however, is not only a health problem. Many patients are in their productive age: the loss of work hours due to pain has grave implications for the economy. As the population is graying, the prevalence of chronic pain is expected to rise. The term “pain epidemic” is hardly unjustified. The US market for treatment of chronic pain is expected to nearly double from today’s $2.6 billion to $5.1 billion in the next ten years. This represents opportunities for the pharmaceutical industry but may strain the resources of the healthcare system. The world-wide prevalence of chronic pain is unknown, but the global pain market was reported to generate total sales of $34 billion in 2007.

Most existing analgesic drugs (painkillers) are derivatives of natural products that had been introduced into clinical practice on a largely empirical basis. The current Decade of Pain Control and Research (2001–2010) has, however, witnessed major changes in analgesia research, progressing from a system level to cellular, subcellular, and molecular. Breakthrough advances in biomedical technologies have allowed us to develop a better understanding of the mechanisms by which pain is generated, transmitted, modulated, and perceived. Genomics (“brain on a chip”) and proteomics have been applied to identify genes and their products that change during pain and thus may represent novel targets for pharmacological manipulation. These genes as pain targets are validated by generation of knockout mice, site-specific mutation, silencing by RNA interference, or knock-down by antisense methods. Cell lines heterogously expressing these genes are generated and used to screen compound libraries for lead analgesic molecules. Then drug candidates are tested in animal models of pain for analgesic activity. Gene transfer by viral vectors represents an attractive alternative strategy for the delivery of antinociceptive substances. Molecular neurosurgery (targeted neurodegeneration by neurotoxins) is another approach for permanent pain relief.
The molecular mechanisms that underlie drug tolerance, dependence, and individual sensitivity are beginning to be understood. Receptor heterogeneity secondary to single nucleotide polymorphism (SNPs) is believed to play an important role. SNPs, however, are not the only source of genetic variability. Copy number variation (CNV) is now emerging as a new source of genomic variation. Indeed, CNVs are now thought to include more nucleotides than SNPs. It is now generally accepted that one size does not fit all: chronic pain patients need individualized therapeutic decisions, a concept popularized in the media as personalized medicine. Enhanced analytic strategies, like microarrays, array-based comparative genomic hybridization and microfluidic chips, may make pain theranostics, the fusion of diagnostics and therapeutics, a reality.

It is hoped that these discoveries will eventually lead to individualized analgesia protocols. Furthermore, new techniques explore low affinity interactions of anesthetics and analgesics with proteins that cannot be detected by traditional binding methodology. Finally, fMRI (functional magnetic resonance imaging) technology creates a unique opportunity for “virtual reality analgesia” by the effects of analgesic drugs on brain functions.

This volume offers comprehensive coverage of molecular analgesia research methods from target discovery through target validation and clinical testing to tolerance and dependence. Emerging receptor classes as targets for analgesic drugs and innovative analgesic strategies are discussed in separate chapters. From the molecular research bench through the animal laboratory to the bed-side, this book is for all those scientists and clinicians who are interested in what the increasingly molecular future has in store for analgesia research.

I used a paraphrase of the title of Robert Herrick’s poem (“No pain, no gain”) in the title of this preface thus it is fitting to close my writing with another poem of his:

96. To Critics
I’ll write, because I’ll give
You critics means to live;
For should I not supply
The cause, th’ effect would die.

Arpad Szallasi
Contents

Foreword ................................................................................................................... v
Preface ..................................................................................................................... vii
Contributors ........................................................................................................... xiii

1 Alternatives to Mammalian Pain Models 1: Use of C. elegans for the Study of Volatile Anesthetics ................................. 1
   Louise M. Steele, Margaret M. Sedensky, and Phil G. Morgan

2 Alternatives to Mammalian Pain Models 2: Using Drosophila to Identify Novel Genes Involved in Nociception ......................... 19
   Jason C. Caldwell and W. Daniel Tracey Jr.

3 Animal Models of Acute Surgical Pain .......................................................... 31
   Hyangin Kim, Backil Sung, and Jianren Mao

4 Animal Models of Acute and Chronic Inflammatory and Nociceptive Pain ................................................................. 41
   Janel M. Boyce-Rustay, Prisca Honore, and Michael F. Jarvis

5 Noxious Heat Threshold Measured with Slowly Increasing Temperatures: Novel Rat Thermal Hyperalgesia Models ................. 57
   Kata Bölcskei, Gábor Pethő, and János Szolcsányi

6 Locomotor Activity in a Novel Environment as a Test of Inflammatory Pain in Rats ............................................................. 67
   David J. Matson, Daniel C. Broom, and Daniel N. Cortright

7 Rationale and Methods for Assessment of Pain-Depressed Behavior in Preclinical Assays of Pain and Analgesia ......................... 79
   S. Stevens Negus, Edward J. Bilsky, Gail Pereira Do Carmo, and Glenn W. Stevenson

8 Animal Models of Orofacial Pain ................................................................ 93
   Asma Khan and Kenneth M. Hargreaves

9 Migraine Models .............................................................................................. 105
   Silvia Benemei, Francesco De Cesaris, Paola Nicoletti, Serena Materazzi, Romina Nassini, and Pierangelo Geppetti

10 Experimental Models of Visceral Pain .......................................................... 115
    Mia Karpitschka and Martin E. Kreis

11 Human Correlates of Animal Models of Chronic Pain ....................... 155
    Arpad Szallasi

12 Human Experimental Pain Models 1: The Ultraviolet Light UV-B Pain Model ................................................................. 159
    James G. Modir and Mark S. Wallace

13 Human Experimental Pain Models 2: The Cold Pressor Model .......... 165
    James G. Modir and Mark S. Wallace
14 Human Experimental Pain Models 3: Heat/Capsaicin Sensitization and Intradermal Capsaicin Models .................................................. 169
James G. Modir and Mark S. Wallace

15 The Value of the Dental Impaction Pain Model in Drug Development ................. 175
Stephen A. Cooper and Paul J. Desjardins

16 Live Cell Imaging for Studying G Protein-Coupled Receptor Activation in Single Cells .............................................................. 191
Deepak Kumar Saini and Narasimhan Gautam

17 Recombinant Cell Lines Stably Expressing Functional Ion Channels ............. 209
Florian Steiner, Sraboni Ghose, and Urs Thomet

18 Ion Channels in Analgesia Research ...................................................... 223
Tamara Rosenbaum, Sidney A. Simon, and Leon D. Islas

19 Electrophysiological and Neurochemical Techniques to Investigate Sensory Neurons in Analgesia Research ........................................... 237
Alexandru Babes, Michael J.M. Fischer, Gordon Reid, Susanne K. Sauer, Katharina Zimmermann, and Peter W. Reeh

20 The Genetics of Pain and Analgesia in Laboratory Animals ......................... 261
William R. Lariviere and Jeffrey S. Mogil

21 RT-PCR Analysis of Pain Genes: Use of Gel-Based RT-PCR for Studying Induced and Tissue-Enriched Gene Expression ....................... 279
Kendall Mitchell and Michael J. Iadarola

22 Gene-Based Approaches in the Study of Pathological Pain ......................... 297
Elisa Dominguez, Alice Meunier, and Michel Pohl

23 Linkage Analysis and Functional Evaluation of Inherited Clinical Pain Conditions .......................................................... 309
Johannes J. Krupp, Dennis Hellgren, and Anders B. Eriksson

24 Rat Bone Marrow Stromal Cells and Oligonucleotides in Pain Research ........ 327
Maria Florencia Coronel, Norma Alejandra Chasseing, and Marcelo José Villar

25 Transplantation of Human Mesenchymal Stem Cells in the Study of Neuropathic Pain .......................................................... 337
Dario Siniscalco

26 Delivery of RNA Interference to Peripheral Neurons In Vivo Using Herpes Simplex Virus .......................................................... 347
Anna-Maria Anesti

27 Combination of Cell Culture Assays and Knockout Mouse Analyses for the Study of Opioid Partial Agonism ........................................ 363
Soichiro Ide, Masabumi Minami, Ichiro Sora, and Kazutaka Ikeda

28 Assessing Potential Functionality of Catechol-O-methyltransferase (COMT) Polymorphisms Associated with Pain Sensitivity and Temporomandibular Joint Disorders ..................................................... 375
Andrea G. Nackley and Luda Diatchenko

29 Genetic Polymorphisms and Human Sensitivity to Opioid Analgesics ............. 395
Daisuke Nishizawa, Masakazu Hayashida, Makoto Nagashima, Hisashi Koga, and Kazutaka Ikeda
30 Molecular Assays for Characterization of Alternatively Spliced Isoforms of the Mu Opioid Receptor (MOR) .................................................. 421
Pavel Gris, Philip Cheng, John Pierson, William Maixner, and Luda Diatchenko

31 Inhalational Anesthetic Photolabeling ........................................... 437
Roderic G. Eckenhoff, Jin Xi, and William P. Dailey

32 Measuring Membrane Protein Interactions Using Optical Biosensors .................................................. 445
Joseph Rucker, Candice Davidoff, and Benjamin J. Doranz

33 Proteomics and Metabolomics and Their Application to Analgesia Research .................................................. 457
Nichole A. Reisdorph and Richard Reisdorph

34 Preemptive Analgesia: Problems with Assessment of Clinical Significance .................................................. 475
Igor Kissin

35 Standardization of Pain Measurements in Clinical Trials .................................................. 483
William K. Sietsema

36 Procedural Sedation and Analgesia Research .................................................. 493
James R. Miner

37 Non-invasive Transcranial Direct Current Stimulation for the Study and Treatment of Neuropathic Pain .................................................. 505
Helena Knotkova and Ricardo A. Cruciani

38 Pain Imaging in the Emerging Era of Molecular Medicine .................................................. 517
Christian S. Stohler and Jon-Kar Zubieta

39 Current and Emerging Pharmacologic Therapies for Pain and Challenges Which Still Lay Ahead .................................................. 539
Christopher Noto and Marco Pappagallo

Concluding Remarks .................................................. 555
Index .................................................. 557
Contributors

Anna-Maria Anesti • BioVex Inc., Woburn, MA, USA
Alexandru Babes • Department of Physiology and Biophysics, University of Bucharest, Bucharest, Romania
Silvia Benemei • Department of Preclinical and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
Edward J. Bilsky • Department of Pharmacology, University of New England College of Osteopathic Medicine, Biddeford, ME, USA
Janel M. Boyce-Rustay • Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA
Kata Bölcskei • Analgesic Research Laboratory, University of Pécs, Gedeon Richter Plc., Pécs, Hungary
Daniel C. Broom • Branford, CT, USA
Jason C. Caldwell • Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA
Norma Alejandra Chasseing • Instituto de Biologia y Medicina Experimental, CONICET, Buenos Aires, Argentina
Philip Cheng • Center for Neurosensory Disorders, University of North Carolina, Chapel Hill, NC, USA
Stephen A. Cooper • Senior VP Clinical and Medical Affairs (retired), Palm Beach Gardens, FL, USA
Maria Florencia Coronel • Facultad de Ciencias Biomedicas, Universidad Austral, Buenos Aires, Argentina
Daniel N. Cortright • Science Foundry LLC, Orange, CT, USA
Ricardo A. Cruciani • Research Division, Department of Pain Medicine and Palliative Care, Beth Israel Medical, Center Institute for Non-Invasive Brain Stimulation of New York, New York, NY, USA; Departments of Neurology and Anesthesiology, Albert Einstein College of Medicine, Bronx, NY, USA
William P. Dailey • Department of Chemistry, University of Pennsylvania School of Arts and Sciences, Philadelphia, PA, USA
Candice Davidoff • Integral Molecular, Inc., Philadelphia, PA, USA
Francesco De Cesaris • Department of Preclinical and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
Paul J. Desjardins • Senior VP Clinical and Medical Affairs, Wyeth Consumer Healthcare, Madison, NJ, USA
Luda Diatchenko • Center for Neurosensory Disorders, Carolina Center for Genome Sciences, University of North Carolina, Chapel Hill, NC, USA
Elisa Dominguez • Faculty of Medicine Pitié-Salpêtrière, Brain and Spinal Cord Research Institute, INSERM UMRS 975, Pain Group, Paris, France
Benjamin J. Doranz • Integral Molecular, Inc., Philadelphia, PA, USA
Roderic G. Eckenhoff • Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
Anders B. Eriksson • Department of Molecular Pharmacology, AstraZeneca R&D, Södertälje, Sweden
Michael J.M. Fischer • Institute of Physiology and Pathophysiology, University of Erlangen – Nuremberg, Erlangen, Germany
Narasimban Gautam • Departments of Anesthesiology and Genetics, Washington University School of Medicine, St. Louis, MO, USA
Pierangelo Geppetti • Department of Preclinical and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
Sraboni Ghose • Genionics AG, Schlieren, Switzerland
Pavel Gris • Center for Neurosensory Disorders, University of North Carolina, Chapel Hill, NC, USA
Kenneth M. Hargreaves • Departments of Endodontics, Pharmacology, Physiology and Surgery, University of Texas Health Science Center, San Antonio, TX, USA
Masakazu Hayashida • Department of Anesthesiology, Saitama Medical University International Medical Center, Hidaka, Japan
Denis Hellgren • Department of Disease Biology, AstraZeneca R&D, Södertälje, Sweden
Prisca Honore • Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA
Michael J. Iadarola • Neurobiology and Pain Therapeutics Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA
Soichiro Ide • Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan
Kazutaka Ikeda • Division of Psychobiology, Tokyo Institute of Psychiatry, Tokyo, Japan
León D. Islas • Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico
Michael F. Jarvis • Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA
Mia Karptischka • Walter-Brendel Institute for Surgical Research, Ludwig-Maximilian’s University, Munich, Germany
Asma Khan • Department of Endodontics, University of North Carolina, Chapel Hill, NC, USA
Hyangin Kim • Department of Anesthesia and Critical Care, Massachusetts General Hospital Center for Translational Pain Research, Harvard Medical School, Boston, MA, USA
Igor Kissin • Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
Helena Knotkova • Research Division, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, Institute for Non-Invasive Brain Stimulation of New York, New York, NY, USA; Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA
Contributors

Hisashi Koga • Laboratory of Medical Genomics, Department of Human Genome Technology, Kazusa DNA Research Institute, Kisarazu, Japan
Martin E. Kreis • Department of Surgery, Hospital Grosshadern, Ludwig-Maximilian’s University, Munich, Germany
Johannes J. Krupp • Department of Molecular Pharmacology, AstraZeneca R&D, Södertälje, Sweden
William R. Lariviere • Departments of Anesthesiology and Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
William Mainzer • Center for Neurosensory Disorders, Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Jianren Mao • Department of Anesthesia and Critical Care, Massachusetts General Hospital Center for Translational Pain Research, Harvard Medical School, Boston, MA, USA
Serena Materazzi • Department of Preclinical and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
David J. Matson • Amgen Inc., Cambridge, MA, USA
Alice Meunier • Pitié-Salpêtrière Hospital, Brain and Spinal Cord Research Institute, INSERM UMRS 975, Neuron-Glia Interactions Group, Paris, France
Masabumi Minami • Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan
James R. Miner • Department of Emergency Medicine, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, MN, USA
Kendall Mitchell • Neurobiology and Pain Therapeutics Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, USA
James G. Modir • Department of Anesthesiology, University of California (UCSD), San Diego, CA, USA
Jeffrey S. Mogil • Department of Psychology, Alan Edwards Center for Research on Pain, McGill University, Montreal, QC, Canada
Phil G. Morgan • Center for Developmental Therapeutics, Seattle Children’s Research Institute, Seattle, WA, USA; Department of Anesthesiology & Pain Medicine, University of Washington, Seattle, WA, USA
Andrea G. Nackley • Center for Neurosensory Disorders, University of North Carolina, Chapel Hill, NC, USA
Makoto Nagashima • Department of Surgery, Toho University Sakura Medical Center, Sakura, Japan
Romina Nassini • Department of Preclinical, and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
S. Stevens Negus • Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA
Paola Nicoletti • Department of Preclinical and Clinical Pharmacology, Headache Center, University of Florence, Florence, Italy
Daisuke Nishizawa • Division of Psychobiology, Tokyo Institute of Psychiatry, Tokyo, Japan
Christopher Noto • Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY, USA
Marco Pappagallo • Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY, USA
Gail Pereira do Carmo • School of Social and Behavioral Sciences, Marist College, Poughkeepsie, NY, USA
Gábor Petthő • Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pécs, Pécs, Hungary
John Pierson • Center for Neurosensory Disorders, University of North Carolina, Chapel Hill, NC, USA
Michel Pohl • Pitié-Salpêtrière Hospital, Brain and Spinal Cord Research Institute, INSERM UMRS 975, Neuron–Glia Interactions Group, Paris, France
Peter W. Reeh • Institute of Physiology and Pathophysiology, University of Erlangen – Nuremberg, Erlangen, Germany
Gordon Reid • Department of Physiology, University College, Cork, Ireland
Nichole A. Reisdorph • Department of Immunology, National Jewish Health, University of Colorado, Denver, CO, USA
Richard Reisdorph • Departments of Pediatrics and Immunology, National Jewish Health, University of Colorado, Denver, CO, USA
Tamara Rosenbaum • Departamento de Biofísica, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Mexico City, Mexico
Joseph Rucker • Integral Molecular, Inc., Philadelphia, PA, USA
Deepak Kumar Saini • Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA
Susanne K. Sauer • Institute of Physiology and Pathophysiology, University of Erlangen – Nuremberg, Erlangen, Germany
Margaret M. Sedensky • Center for Developmental Therapeutics, Seattle Children’s Research Institute, Seattle, WA, USA; Department of Anesthesiology & Pain Medicine, University of Washington, Seattle, WA, USA
William K. Sietsema • Regulatory Consulting and Submissions, Kendle International Inc., and College of Pharmacy, University of Cincinnati, Cincinnati, OH, USA
Sidney A. Simon • Department of Neurobiology, Center for Neuroengineering, Duke University Medical Center, Durham, NC, USA
Dario Siniscalco • Department of Experimental Medicine, Section of Pharmacology “L. Donatelli,” Second University of Naples, Naples, Italy
Ichiro Sora • Division of Psychobiology, Department of Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Japan
Louise M. Steele • Center for Developmental Therapeutics, Seattle Children’s Research Institute, Seattle, WA, USA
Florian Steiner • Genionics AG, Schlieren, Switzerland
Glenn W. Stevenson • Department of Psychology, University of New England, Biddeford, ME, USA
Christian S. Stohler • University of Maryland Dental School, Baltimore, MD, USA
Backil Sung • Department of Anesthesia and Critical Care, Massachusetts General Hospital Center for Translational Pain Research, Harvard Medical School, Boston, MA, USA
Arpad Szallasi • Department of Pathology and Laboratories, Monmouth Medical Center, Long Branch, NJ, USA; Drexel University College of Medicine, Philadelphia, PA, USA

János Szolcsányi • Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pécs, Pécs, Hungary

Urs Thomet • Genionics AG, Schlieren, Switzerland

W. Daniel Tracey, Jr. • Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA

Marcelo Jose Villar • Faculdad de Ciencias Biomedicas, Universidad Austral, Buenos Aires, Argentina

Mark S. Wallace • Department of Anesthesiology, University of California (UCSD), San Diego, CA, USA

Jin Xi • Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Katharina Zimmermann • Institute of Physiology and Pathophysiology, University of Erlangen – Nuremberg, Erlangen, Germany

Jon-Kar Zubieta • Departments of Psychiatry and Radiology, University of Michigan Medical School, Ann Arbor, MI, USA