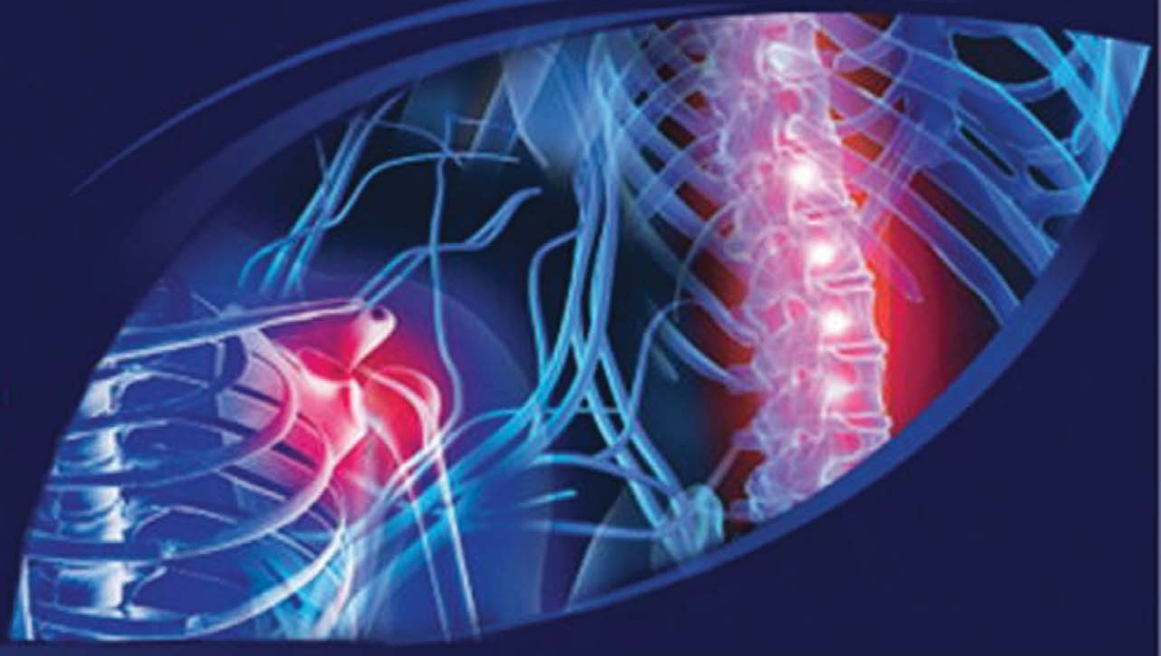
WALL AND MELZACK'S TEXTBOOK OF PAIN



SIXTH EDITION

Stephen B. McMahon
Martin Koltzenburg
Irene Tracey
Dennis Turk

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WALL AND MELZACK'S

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SIXTH EDITION

EDITED BY

Stephen B. McMahon, FMedSci, FSB
Sherrington Professor of Physiology
Director, London Pain Consortium
Academic Lead, Europain
Wolfson Centre for Age-Related Diseases
King's College London
London, UK

Martin Koltzenburg, MD, FRCP
Professor of Clinical Neurophysiology
UCL Institute of Neurology
Co-Director, MRC Centre for Neuromuscular Diseases
University College London
Head of Department
Department of Clinical Neurophysiology
The National Hospital for Neurology and Neurosurgery
UCLH NHS Foundation Trust
Queen Square, London, UK

Irene Tracey, MA (Oxon.), PhD, FRCA
Nuffield Professor of Anaesthetic Science
Director, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
Head, Nuffield Division Anaesthetics
Nuffield Department of Clinical Neurosciences
University of Oxford
Oxford, UK

Dennis C. Turk, PhD
John and Emma Bonica Professor of Anesthesiology and Pain Research
Director, Center for Pain Research on Impact, Measurement, and Effectiveness (C-PRIME)
Department of Anesthesiology and Pain Medicine
University of Washington
Seattle, Washington, USA

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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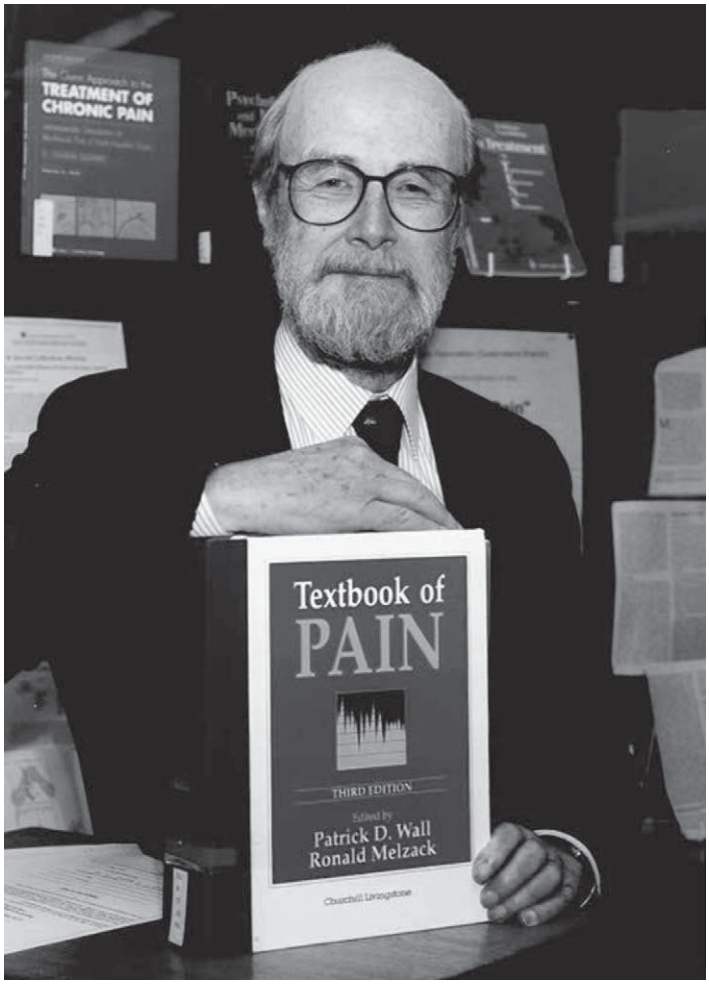

To Patrick Wall
teacher, colleague, and friend

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Contributors

Zahid Ali, PhD
Senior Director
Clinical Research
Pfizer Neusentis
Cambridge, UK

David A. Andersson, PhD
Lecturer in Physiology
Wolfson Centre for Age-Related Diseases
King's College London
London, UK

A. Vania Apkarian, PhD
Professor
Department of Physiology
Northwestern University
Feinberg School of Medicine
Chicago, Illinois, USA

Mark L. Baccei, PhD
Associate Professor
Department of Anesthesiology
University of Cincinnati
Cincinnati, Ohio, USA

Miroslav (Misha) Bačkonja, MD
Medical Director of Neuroscience
CRILifeTree Clinical Research
Salt Lake City, Utah
Emeritus Professor
Department of Neurology
University of Wisconsin
Madison, Wisconsin, USA

Ralf Baron, MD
Professor
Chair of the Division of Neurological Pain Research and Therapy
Department of Neurology
University Hospital Schleswig-Holstein
Kiel, Germany

Simon Beggs, PhD
Research Associate
Assistant Professor
Program in Neurosciences and Mental Health
Hospital for Sick Children, Toronto
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

Inna Belfer, MD, PhD
Associate Professor
Departments of Anesthesiology and Human Genetics
Director
Molecular Epidemiology of Pain Program
University of Pittsburgh/UPMC
Pittsburgh, Pennsylvania, USA

Carlos Belmonte, MD, PhD
Professor
Instituto de Neurociencias de Alicante
Universidad Miguel Hernandez-CSIC
Alicante, Spain

David L.H. Bennett, MB, PhD
Reader in Pain Neurosciences
The Nuffield Department of Clinical Neuroscience
The University of Oxford
Oxford, UK

Charles B. Berde, MD, PhD
Chief
Division of Pain Medicine
Department of Anesthesiology, Perioperative and Pain Medicine
Boston Children's Hospital
Professor of Anesthesia and Pediatrics
Harvard Medical School
Boston, Massachusetts, USA

Odd-Geir Berge, DDS, PhD
Adjunct Professor
Department of Surgical Sciences, Uppsala
Uppsala Berzelii Center
Uppsala, Sweden

Stuart Bevan, PhD
Professor of Pharmacology
Wolfson Centre for Age-Related Diseases
King's College London
London, UK

Klaus Bielefeldt, MD, PhD
Associate Professor of Medicine
Division of Gastroenterology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania, USA

Andreas Binder, MD
Consultant
Division of Neurological Pain Research and Therapy
Department of Neurology
University Clinic Schleswig-Holstein
Kiel, Germany

Harald Breivik, MD, DMedSci
Professor
University of Oslo
Consultant
Department of Pain Management and Research
Oslo University Hospital, Rikshospitalet
Oslo, Norway

Kay Brune, MD, PhD
Doerenkamp Professor
Department of Experimental and Clinical Pharmacology and Toxicology
Friedrich-Alexander University Erlangen-Nuremberg
Erlangen, Germany

M. Catherine Bushnell, PhD
Harold Griffith Professor
Department of Anesthesia
McGill University
Montreal, Quebec, Canada

Asokumar Buvanendran, MD
Director of Orthopedic Anesthesia
Professor of Anesthesiology
Rush University Medical Center
Chicago, Illinois, USA

James N. Campbell, MD
Professor Emeritus
Department of Neurosurgery
The Johns Hopkins University
CEO
Arcion Therapeutics
Baltimore, Maryland, USA

H. Isaac Chen, MD
Resident
Department of Neurosurgery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania, USA

Nathan I. Cherny, MBBS, FRACP, FRCP
Norman Levan Chair of Humanistic Medicine
Cancer Pain and Palliative Medicine Service
Shaare Zedek Medical Center
Jerusalem, Israel

John J. Collins, MBBS, PhD, FAChPM, FFPMANZCA, FRACP
Head of Department
Pain Medicine and Palliative Care
The Children's Hospital at Westmead
Clinical Associate Professor
Discipline of Paediatrics and Child Health
University of Sydney
Sydney, New South Wales, Australia

A.D. (Bud) Craig, PhD
Atkinson Research Scientist
Barrow Neurological Institute
Phoenix, Arizona
Research Professor
Cell Biology and Anatomy
University of Arizona College of Medicine
Tucson, Arizona
Research Professor
Department of Psychology
Arizona State University
Tempe, Arizona, USA

John B. Davis, PhD
Biology Head
Convergence Pharmaceuticals Ltd.
Cambridge, UK

John M. Dawes, PhD
Wolfson Centre for Age-Related Diseases
King's College London
London, UK

Marshall Devor, PhD
Department of Cell and Developmental Biology
Institute of Life Sciences and the Center for Research on Pain
The Hebrew University of Jerusalem
Jerusalem, Israel

Anthony Dickenson, BSc, PhD
Professor of Neuropharmacology
Neuroscience, Physiology, and Pharmacology
University College London
London, UK

Andrew Dickman, DPharm, MSc
Consultant Pharmacist
Department of Palliative Care
Blackpool Teaching Hospitals NHS Foundation Trust
Blackpool, UK
Consultant Pharmacist
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
University of Liverpool
Liverpool, UK

Andrew Dilley, PhD
Lecturer in Anatomy
Division of Clinical and Laboratory Investigation
Brighton and Sussex Medical School
University of Sussex
Falmer, Brighton, UK

Ray J. Dolan, MD
Mary Kinross Professor of Neuropsychiatry
Wellcome Trust Centre for Neuroimaging
University College London
London, UK

Michael J. Dorsi, MD
Neurosurgeon
Ventura County Neurosurgical Associates
Community Memorial Hospital
Ventura, California, USA

Jonathan O. Dostrovsky, BSc, MSc, PhD
Professor Emeritus
Department of Physiology
Faculty of Medicine
Department of Oral Physiology
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

John E. Ellershaw, MBBCh, MA, FRCP
Professor of Palliative Medicine
Marie Curie Palliative Care Institute Liverpool (MCPCIL)
University of Liverpool
Liverpool, UK

Edzard Ernst, MD, PhD, FMedSci, FSB, FRCP, FRCPEd
Professor
Department of Complementary Medicine
Peninsula Medical School, University of Exeter
Exeter, Devon, UK

David Felson, MD, MPH
Professor of Medicine and Epidemiology
Department of Medicine
Boston University School of Medicine
Boston, Massachusetts, USA

Howard L. Fields, MD, PhD
Professor
Department of Neurology
University of California, San Francisco
San Francisco, California, USA

Nanna Brix Finnerup, MD, DrMedSc
Associate Professor
Danish Pain Research Center
Aarhus University
Aarhus, Denmark

David A. Fishbain, BSC (Hon), MSC, MD, Distinguished FAPA
Professor
Department of Psychiatry
Miller School of Medicine
University of Miami
Adjunct Professor
Departments of Neurological Surgery and Anesthesiology
Miller School of Medicine
Professor
Research
Rosomoff Pain Center
Miami, Florida, USA

Maria Fitzgerald, BA, PhD, FMedSci
Professor of Developmental Neurobiology
Department of Neuroscience, Physiology, and Pharmacology
University College London
London, UK

Herta Flor, PhD
Scientific Director
Department of Cognitive and Clinical Neuroscience
Central Institute of Mental Health and University of Heidelberg, Mannheim
Mannheim, Germany

Karen Forbes, MBChB, EdD
Professorial Teaching Fellow
University of Bristol
Honorary Consultant in Palliative Medicine
Department of Palliative Medicine
University Hospitals Bristol NHS Foundation Trust
Bristol, UK

Lucia Gagliese, PhD
Associate Professor
School of Kinesiology and Health Science
York University
Senior Scientist
Ontario Cancer Institute
University Health Network
Scientist
Department of Anesthesia and Pain Management
University Health Network
Toronto, Ontario, Canada

Gerald F. Gebhart, PhD
Director, Center for Pain Research
Department of Anesthesiology
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Jennifer L. Gibbs, MAS, DDS, PhD
Assistant Professor
Department of Endodontics
New York University
New York, New York, USA

Ian Gilron, MD, MSc, FRCPC
Director of Clinical Pain Research
Department of Anesthesiology & Perioperative Medicine
Queen's University
Professor, Departments of Anesthesiology & Perioperative Medicine and Biomedical & Molecular Sciences
Queen's University
Kingston, Ontario, Canada

Peter J. Goadsby, MD, PhD, DSc
Professor
Headache Group–Department of Neurology
University of California, San Francisco
San Francisco, California, USA

Michael S. Gold, PhD
Professor
Department of Anesthesiology
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Veeraindar Goli, MD, MBA, DFAPA
Vice President, Clinical Disease Area Expert–Pain
Primary Care Clinical Sciences
Pfizer, Inc.
Cary, North Carolina
Emeritus Professor
Duke University Medical Center
Durham, North Carolina, USA

Allan Gottschalk, MD, PhD
Associate Professor
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins University
Baltimore, Maryland, USA

Richard H. Gracely, PhD
Professor
Regional Center for Neurosensory Disorders
University of North Carolina
Chapel Hill, North Carolina
Adjunct Professor
Department of Internal Medicine–Rheumatology
University of Michigan
Ann Arbor, Michigan, USA

Jane Greening, PhD, MSc, MCSP
Hon. Senior Research Fellow
Division of Clinical and Laboratory Investigation
Brighton and Sussex Medical School
University of Sussex
Falmer, Brighton, UK

Joel D. Greenspan, PhD
Professor and Chair
Department of Neural and Pain Sciences
University of Maryland School of Dentistry
Professor
Program in Neuroscience
University of Maryland
Baltimore, Maryland, USA

Arpana Gupta, PhD
Postdoctoral Research Fellow
Oppenheimer Family Center for Neurobiology of Stress
Semel Institute of Neuroscience and Human Behavior
Department of Psychiatry and Biobehavioral Sciences
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California, USA

Hermann O. Handwerker, MD
Professor
Department of Experimental and Clinical Pharmacology and Toxicology
Friedrich-Alexander
University Erlangen-Nuremberg
Erlangen, Germany

Kenneth M. Hargreaves, DDS, PhD
Professor
Departments of Endodontics, Pharmacology, Physiology, and Surgery
University of Texas Health Science Center at San Antonio
San Antonio, Texas, USA

Jennifer A. Haythornthwaite, PhD
Professor
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine
Baltimore, Maryland, USA

Mary M. Heinricher, PhD
Professor
Departments of Neurological Surgery and Behavioral Neuroscience
Oregon Health and Science University
Portland, Oregon, USA

Raymond G. Hill, BPharm, PhD, DSc (Hon), FMedSci
Visiting Professor of Pharmacology
Department of Medicine
Imperial College London
London, UK

Andrea G. Hohmann, PhD
Linda and Jack Gill Chair of Neuroscience and Professor
Department of Psychological & Brain Sciences
Indiana University
Bloomington, Indiana, USA

Tomas G.M. Hökfelt, PhD, MD
Professor of Histology and Cell Biology
Department of Neuroscience
Karolinska Institutet
Stockholm, Sweden

Peter Hoskin, MD, FRCP, FRCR
Consultant in Clinical Oncology
Cancer Centre
Mount Vernon Hospital
Northwood, UK
Professor in Clinical Oncology
University College London
London, UK

Stephen P. Hunt, BSc, PhD
Professor of Molecular Neuroscience
Department of Cell and Developmental Biology
University College London
London, UK

Smriti Iyengar, PhD
Senior Research Scientist
Eli Lilly and Company
Indianapolis, Indiana, USA

Wilfrid Jänig, MD
Professor
Department of Physiology
Christian-Albrechts University Kiel
Kiel, Germany

Troels Staehelin Jensen, MD, DMSc
Professor
Department of Neurology and Danish Pain Research Center
Aarhus University Hospital
Aarhus, Denmark

Gareth T. Jones, BSc (Hon), MScEcon, PhD
Senior Lecturer in Epidemiology
Aberdeen Pain Research Collaboration (Epidemiology Group)
School of Medicine and Dentistry
University of Aberdeen
Aberdeen, UK

Joel Katz, PhD
Professor and Canada Research Chair in Health Psychology
Department of Psychology
York University
Professor
Department of Anesthesia
University of Toronto
Director, Acute Pain Research Unit
Department of Anesthesia and Pain Management
Toronto General Hospital
Toronto, Ontario, Canada

Brigitte L. Kieffer, PhD
Translational Medicine and Neurogenetics
Institut de Génétique et de Biologie Moléculaire et Cellulaire
Illkirch, France

H. Richard Koerber, PhD
Professor
Department of Neurobiology
University of Pittsburgh, School of Medicine
Pittsburgh, Pennsylvania, USA

Bart Koes, MSc, PhD
Professor
Department of General Practice
Erasmus MC
Rotterdam, The Netherlands

Martin Koltzenburg, MD, FRCP
Professor of Clinical Neurophysiology
UCL Institute of Neurology
Co-Director, MRC Centre for Neuromuscular Diseases
University College London
Head of Department
Department of Clinical Neurophysiology
The National Hospital for Neurology and Neurosurgery
UCLH NHS Foundation Trust
Queen Square, London, UK

Jeffrey S. Kroin, PhD
Professor
Department of Anesthesiology
Rush Medical College
Chicago, Illinois, USA

Promil Kukreja, MD, PhD
Assistant Professor
Department of Anesthesiology
Medical Director
Regional Anesthesia Pain Service
University of Alabama at Birmingham
Birmingham, Alabama, USA

John Y.K. Lee, MD
Assistant Professor
Department of Neurosurgery
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Fred A. Lenz, MD, PhD, FRCS(C)
A. Earl Walker Professor
Department of Neurosurgery
The Johns Hopkins Hospital
Baltimore, Maryland, USA

Jon D. Levine, MD, PhD
Professor
Department of Medicine
University of California, San Francisco
San Francisco, California, USA

Bengt Linderoth, MD, PhD
Professor
Department of Clinical Neuroscience
Section of Neurosurgery
Karolinska Institutet/Karol University Hospital
Stockholm, Sweden

Arthur G. Lipman, PharmD, FASHP
University Professor
Department of Pharmacotherapy
College of Pharmacy
Adjunct Professor
Department of Anesthesiology
School of Medicine
Director of Clinical Pharmacology
Pain Management Center
University Healthcare
University of Utah Health Sciences Center
Salt Lake City, Utah, USA

Richard Lipton, MD
Edwin S. Lowe Professor
Vice Chair of Neurology
Professor of Epidemiology and Population Health
Professor of Psychiatry and Behavioral Sciences
Albert Einstein College of Medicine
Bronx, New York, USA

Donlin M. Long, MD, PhD
Distinguished Professor of Neurosurgery
Johns Hopkins Medical Institute
Baltimore, Maryland, USA

Timothy R. Lubenow, MD
Professor
Department of Anesthesiology
Rush University Medical Center
Chicago, Illinois, USA

Gary J. Macfarlane, BSc (Hon), MBChB, PhD, CStat, MD (Hon)
Professor of Epidemiology
Aberdeen Pain Research Collaboration (Epidemiology Group)
School of Medicine and Dentistry
University of Aberdeen
Aberdeen, UK

Patrick W. Mantyh, PhD, JD
Professor
Department of Pharmacology
University of Arizona College of Medicine
Tucson, Arizona, USA

†Mitchell B. Max, MD
Departments of Anesthesiology and Human Genetics
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Emeran A. Mayer, MD
Professor
Department of Medicine, Physiology, and Psychiatry
Division of Digestive Diseases
University of California at Los Angeles
Director
Oppenheimer Family Center for Neurobiology of Stress
University of California at Los Angeles
Los Angeles, California, USA

John McBeth, MA, PhD
Reader
Arthritis Research UK Primary Care Centre
Keele University
Keele, UK
Honorary Reader
Arthritis Research UK Epidemiology Unit
University of Manchester
Manchester, UK

Patrick J. McGrath, OC, PhD, FRSC, FCAHS
Professor
Department of Psychology, Pediatrics, Psychiatry
Dalhousie
Vice President
Research and Innovation
IWK Health Centre and Capital District Health Authority
Halifax, Nova Scotia, Canada

Stephen B. McMahon, FMedSci, FSB
Sherrington Professor of Physiology
Director, London Pain Consortium
Academic Lead, Europain
Wolfson Centre for Age-Related Diseases
King's College London
London, UK

Henry J. McQuay, DM, FRCA, FRCP
Emeritus Fellow
Balliol College
Oxford, Oxon, UK

Ronald Melzack, PhD
Professor Emeritus
Department of Psychology
McGill University
Montreal, Quebec, Canada

Siegfried Mense, MD
Professor
Department of Neuroanatomy/Neurophysiology
Heidelberg University, Medical Faculty Mannheim,
Mannheim, Germany

Richard A. Meyer, BSEE, MS
Professor Emeritus
Department of Neurosurgery
The Johns Hopkins University School of Medicine
Baltimore, Maryland, USA

Björn A. Meyerson, MD, PhD
Professor Emeritus
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

Jeffrey S. Mogil, PhD
E.P. Taylor Professor of Pain Studies
Department of Psychology and Alan Edwards Centre for Research on Pain
McGill University
Montreal, Quebec, Canada
Professor
Department of Anesthesiology and Human Genetics
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Andrew Moore, MA, DPhil, CChem, FRSC, FRCA, DSc
Nuffield Division of Anaesthesia
Nuffield Department of Clinical Neuroscience
University of Oxford
Oxford, UK

Valerie Morisset, PhD
Head of Electrophysiology
Convergence Pharmaceuticals Ltd.
Cambridge, UK

Tuhina Neogi, MD, PhD, FRCPC
Associate Professor of Medicine
Clinical Epidemiology Research and Training Unit, and Rheumatology
Boston University School of Medicine
Associate Professor
Department of Epidemiology
Boston University School of Public Health
Boston, Massachusetts, USA

†Deceased

Timothy J. Ness, MD, PhD
Simon Gelman Professor
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, Alabama, USA

Lone Nikolajsen, MD, PhD, DMSc
Clinical Associate Professor
Department of Anesthesiology
Danish Pain Research Center
Aarhus University Hospital
Aarhus, Denmark

Rodrigo Noseda, DVM, PhD
Instructor in Anesthesia
Department of Anesthesia, Critical Care, and Pain Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts, USA

E. Andrew Ochroch, MD, MSCE
Associate Professor
Department of Anesthesiology, Critical Care, and Surgery
University of Pennsylvania
Philadelphia, Pennsylvania, USA

Michael H. Ossipov, PhD
Research Professor
Department of Pharmacology
University of Arizona College of Medicine
Tucson, Arizona, USA

Joanne E. Palmer, BSc (Hon), MSc, PhD
Head of Clinical Operations
Convergence Pharmaceuticals Ltd.
Cambridge, UK

Peter H. Pan, MSEE, MD
Professor and Director of Clinical Research
Section of Obstetric and Gynecologic Anesthesia
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, North Carolina, USA

Bruce G. Pollock, MD, PhD, FRCPC
Professor and Director
Division of Geriatric Psychiatry
University of Toronto
Vice President, Research
Centre for Addiction and Mental Health
Toronto, Ontario, Canada

Frank Porreca, PhD
Professor
Department of Pharmacology
University of Arizona College of Medicine
Tucson, Arizona, USA

Donald D. Price, PhD
Professor Emeritus
Department of Oral and Maxillofacial Surgery
University of Florida
Gainesville, Florida, USA

Pierre Rainville, PhD
Professor
Department of Stomatology
Université de Montréal
Director
Laboratoire de recherche en neuropsychologie de la douleur
Centre de recherche de l'institut universitaire de gériatrie de Montréal
Montreal, Québec, Canada

Srinivasa N. Raja, MD
Professor
Department of Anesthesiology and Critical Care Medicine
Professor
Department of Neurology
Director
Division of Pain Medicine
The Johns Hopkins University
Baltimore, Maryland, USA

Andrew S.C. Rice, MBBS, MD, FRCA, FFPMRCA
Professor of Pain Research
Department of Surgery and Cancer
Imperial College
Hon. Consultant in Pain Medicine
Chelsea and Westminster Hospital NHS Foundation Trust
London, UK

Matthias Ringkamp, MD
Associate Professor
Department of Neurosurgery
The Johns Hopkins University
Baltimore, Maryland, USA

I. Jon Russell, MS, MD, PhD, ACR Master
Director
Fibromyalgia Research and Consulting
Arthritis and Osteoporosis Center of South Texas
Retired Faculty
University of Texas Health Science Center at San Antonio
San Antonio, Texas, USA

Michael W. Salter, MD, PhD
Associate Chief
Science Strategy
Neurosciences & Mental Health Program
Hospital for Sick Children
Professor
Department of Physiology
University of Toronto Centre for the Study of Pain
University of Toronto
Toronto, Ontario, Canada

Jürgen Sandkühler, MD, PhD
Director
Center for Brain Research
Medical University of Vienna
Vienna, Austria

Simona Liliana Sava, MD
Headache Research Unit
University Department of Neurology Citadelle Hospital
University of Liège
Liège, Belgium

John W. Scadding, MD, FRCP
Honorary Consultant Neurologist
The National Hospital for Neurology and Neurosurgery
London, UK

Hans-Georg Schaible, MD
Director
Institute of Physiology 1/Neurophysiology
Jena University Hospital–Friedrich Schiller University Jena
Jena, Germany

Martin Schmelz, MD, PhD
Karl Feuerstein Professorship
Department of Anesthesiology
Heidelberg University
Mannheim, Germany

Jean Schoenen, MD, PhD
Professor
Department of Neurology
Headache Research Unit
University of Liège
Liège, Belgium

Stephan A. Schug, MD, FANZCA, FFPMANZCA
Professor and Chair of Anaesthesiology
Pharmacology and Anaesthesiology Unit
University of Western Australia
Director of Pain Medicine
Department of Anaesthesia and Pain Medicine
Royal Perth Hospital
Perth WA, Australia

Petra Schweinhardt, MD, PhD
Assistant Professor
Alan Edwards Center for Research on Pain
McGill University
Montreal, Quebec, Canada

Ben Seymour, MBChB, MRCP, PhD
Principal Investigator
Center for Information and Neural Networks
National Institute of Communications Technology
Japan
Wellcome Clinical Fellow
Computational and Biological Learning Lab
Department of Engineering
University of Cambridge
Consultant Neurologist
Addenbrookes Hospital
Cambridge, UK

Philip J. Siddall, MBBS, MM (Pain Mgt), PhD, FFPMANZCA
Associate Professor
Department of Pain Management
Greenwich Hospital
HammondCare
University of Sydney
Sydney, New South Wales, Australia

Maree T. Smith, BPharm (Hon), PhD
Director, Centre for Integrated Preclinical Drug Development
Professor of Pharmacy
The University of Queensland
Brisbane, Queensland, Australia

Linda S. Sorkin, PhD
Professor
Department of Anesthesiology
University of California, San Diego
La Jolla, California, USA

Simon N. Tate, BSc
Chief Scientific Officer
Convergence Pharmaceuticals Ltd.
Cambridge, UK

Timo T. Tervo, MD, PhD
Department of Ophthalmology
University of Helsinki
Chief Physician
Helsinki University Central Hospital
Helsinki, Finland

Mick Thacker, PhD
Lecturer
Biomedical Sciences
Centre of Human and Aerospace Physiological Sciences
King's College London
London, UK

Andrew J. Todd, MBBS, PhD
Professor
Institute of Neuroscience and Psychology
University of Glasgow
Glasgow, UK

Thomas R. Toelle, MD, PhD
Professor
Department of Neurology
Technische Universität München
München, Germany

Richard J. Traub, PhD
Professor
Department of Neural and Pain Sciences
University of Maryland School of Dentistry
Baltimore, Maryland, USA

Dennis C. Turk, PhD
John and Emma Bonica Professor of Anesthesiology and Pain Research
Director, Center for Pain Research on Impact, Measurement, and Effectiveness (C-PRIME)
Department of Anesthesiology and Pain Medicine
University of Washington
Seattle, Washington, USA

Anita M. Unruh, PhD, MSW, OT(c), Reg NS
Associate Dean (Research & Academic)
Faculty of Health Professions
Dalhousie University
Halifax, Nova Scotia, Canada

Catherine E. Urch, MRCP, PhD
Palliative Medicine Consultant
Honorary Senior Lecturer
Imperial College Healthcare NHS Trust
Department of Palliative Care
Charing Cross Hospital
London, UK

Maurits van Tulder, PhD
Professor
Department of Health Sciences
Faculty of Earth and Life Sciences
VU University
Amsterdam, The Netherlands

Marcelo Villar, MD, PhD
Professor
Department of Neuroscience
Austral University
Buenos Aires, Argentina

Luis Villanueva, DDS, PhD
Director of Research
CNRS
Head
Pain Group
INSERM
Centre de Psychiatrie et Neurosciences
Paris, France

Tor D. Wager, PhD
Associate Professor
Department of Psychology and Neuroscience
University of Colorado, Boulder
Boulder, Colorado, USA

C. Peter N. Watson, MD, FRCPC
Assistant Professor
Department of Medicine
Division of Neurology
University of Toronto
Toronto, Ontario, Canada

Zsuzsanna Wiesenfeld-Hallin, PhD
Professor and Head of Section of Integrative Pain Research
Department of Physiology and Pharmacology
Karolinska Institutet
Stockholm, Sweden

Heng Yu Wong, MD
Director
HY Wong Gastrointestinal and Liver Specialist Clinic
Mount Elizabeth Medical Center
Singapore

Paul J. Wrigley, MBBS, MM, PhD, FANZCA, FFPMANZCA
Senior Lecturer
Pain Management Research Institute and Kolling Institute of Medical Research
University of Sydney
Pain Medicine Senior Staff Specialist
Pain Management Research Centre
Royal North Shore Hospital
Sydney, New South Wales, Australia

Xiao-Jun Xu, PhD
Associate Professor
Department of Physiology and Pharmacology
Section of Integrative Pain Research
Karolinska Institutet
Stockholm, Sweden

Tony L. Yaksh, PhD
Professor and Vice Chair for Research
Department of Anesthesiology
Professor
Department of Pharmacology
University of California, San Diego
La Jolla, California, USA

Joanna Maria Zakrzewska, MD, FDSRCS, FFDRCSI, FFPMRCA, FHEA
Professor
Head of Facial Pain Unit
Division of Diagnostic, Surgical and Medical Sciences
Eastman Dental Hospital
UCLH NHS Foundation Trust
London, UK

Hanns Ulrich Zeilhofer, MD
Professor
Institute of Pharmacology and Toxicology
University of Zurich
Professor
Institute of Pharmaceutical Sciences
ETH Zurich
Zurich, Switzerland

Xu Zhang, PhD
Professor
Institute of Neuroscience
Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences
Shanghai, China

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Foreword

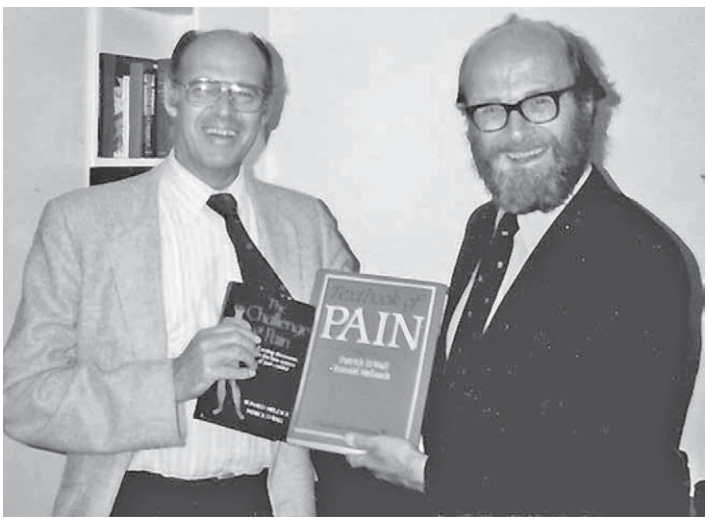
The gate control theory of pain, which Patrick Wall and I published in 1965, led to an explosion of research on pain mechanisms in the spinal cord and brain and provided the rationale for a variety of new approaches to pain therapy. In 1984 we decided to edit a book with the latest information in the rapidly growing field so that clinicians could read about the status of laboratory and clinical research and scientists could learn about major clinical advances in the fight against pain. The first edition of the *Textbook of Pain* in 1984 was sold out in a year. It was followed by new editions that tracked the remarkable advances in the field of pain research and therapy. Shortly after publication of the fourth edition in 1999, Patrick Wall became ill. Our discussions about the *Textbook of Pain* now centered on the need to maintain a balance in presenting the two facets of the field of pain—research and therapy. That goal was achieved in 2006 by Stephen McMahon and Martin Koltzenburg in the fifth edition.

The scope of this sixth edition of the *Textbook of Pain* has been expanded by the addition of two new editors—Dennis Turk and Irene Tracey—who have made outstanding contributions to our understanding of the behavioral and brain mechanisms that underlie acute and chronic pain. We are all very grateful to Michael Houston, Elsevier's outstanding publishing manager who ensured the timely publication of this up-to-date edition. I am delighted with it and I know that Patrick, who died on August 8, 2001, would be equally pleased.

Wall and I always aimed to achieve the broadest coverage of the field of pain in order to promote the fight against pain and suffering from every possible angle. Stephen McMahon, Dennis Turk, Irene Tracey, and Martin Koltzenburg have maintained this goal by producing this outstanding new edition. It is up to date and comprises a whole, unified body of knowledge that touches on every aspect of pain. The torch has been handed to an exciting new generation of editors and contributors. Pain—particularly chronic pain—continues to destroy the lives of millions of people worldwide. There is no nobler goal than achieving the relief of pain and suffering. This new edition will bring that day closer.

Ronald Melzack
Professor Emeritus, McGill University
Montreal, Canada

Patrick Wall (left) and Ronald Melzack.



Ronald Melzack (left) and Patrick Wall.

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Preface

The last edition of *Wall and Melzack's Textbook of Pain*–the fifth edition–was published in 2006. There has been a considerable increase in our understanding of the nature and mechanisms of pain since that date. This is reflected in the enormous amount of published literature on pain. PubMed finds more than 160,000 publications since the last edition was published, using the search term "pain." This represents about a 40% increase in publications compared with an equivalent period before publication of the fifth edition. Bibliometric data also shows how some topics within the pain field have become a greater focus of attention than others. For instance, a search for the phrase "neuropathic pain" shows a nearly 90% increase in publication numbers since publication of the last edition of this textbook. "Headache," by contrast, shows a more modest increase, amounting to less than 30%. Technology has allowed some topics to be explored by greater numbers of researchers. The falling cost of DNA and RNA sequencing and associated technologies is likely to have contributed to some of the 60% increase in publications found with the search terms "genetics" and "pain." Between the beginning of 2001 and the end of 2006, PubMed finds but a single publication with the search terms "epigenetics" and "pain." Since then, 19 papers have emerged, and one suspects this will be the beginning of a new flood of interest.

The current edition of *Wall and Melzack's Textbook of Pain,* the sixth, tries to capture and report on the most important developments in the field over the last 6 years. Collectively, the 147 authors who contribute to the current edition have probably read a large proportion of those 160,000 new publications. In this new edition we have retained the same general structure that we created for the fifth edition, but we have added some chapters to reflect new developments and merged others. The increasing body of literature also places burdens on the editors. For that reason I am tremendously grateful that Irene Tracey and Dennis Turk have joined the editorial team and applied their distinct expertise to refining this textbook.

Despite advancing knowledge in the field, the burden of pain remains unacceptably high. Epidemiological studies, many reviewed in this book, point to the high prevalence of chronic pain across the world associated with staggering socioeconomic costs. Unfortunately, existing therapies fail to offer good (let alone complete) pain relief to the majority of these sufferers. There have been some modest advances with the approval of some new therapies, such as topical capsaicin patches in some countries. A step chance in analgesic drug efficacy seems possible, too, as evidenced by the dramatic pain relief offered by blockers of NGF in a series of clinical trials–also reviewed in this book. We are still waiting to find out if side effects will limit or block this initiative. But the example serves to illustrate that a good understanding of pain and pain mechanisms can lead to effective therapies.

This is a difficult time for pharmaceutical companies, who have struggled with the many problems associated with translating new knowledge into new therapies in this area and many others. We hope that this new edition of *Wall and Melzack's Textbook of Pain* will help all those interested in this field–academic scientists, clinicians, and industry leaders–to do their work more effectively. We sincerely hope they succeed in their efforts to bring about a positive change for another group of stakeholders here–the sufferers of pain.

Stephen B. McMahon, FMedSci, FSB
London

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Abbreviations and Acronyms

ABC	ATP-binding cassette
AC	adenylate cyclase
ACC	anterior cingulate cortex
ACG	anterior cingulate gyrus
ACh	acetylcholine
ACL	anterior cruciate ligament
ACOG	American College of Obstetricians and Gynecologists
ACPA	anti–cyclic citrulated peptide antibody
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADAPT	Arthritis Diet and Activity Promotion Trial
ADEPT	attitude, diagnosis, education, physical treatment, living
ADP	adenosine diphosphate
AEA	arachidonyl ethanol amide
AED	antiepileptic drug
2-AFC	two alternative forced choice (method)
AFP	atypical facial pain
2-AG	2-acylglycerol; 2-arachidonoylglycerase
AIA	antigen-induced monarthritis
AIM	ancestry informative marker
AIP	acute inflammatory polyneuropathy
AMH	A-fiber mechano-heat–sensitive nociceptor; A fibers responsive to mechanical and heat stimuli
AMI	acute myocardial infarction
AMP	adenosine monophosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANS	autonomic nervous system
AO	atypical odontalgia
AP	action potential
APF	antiproliferative factor
APM	Association for Palliative Medicine of Great Britain and Ireland
APML	acute promyelocytic leukemia
APSF	Anesthesia Patient Safety Foundation
AS	anxiety sensitivity
ASA	American Society of Anesthesiologists
ASIC	acid-sensing ion channel
ATF3	activated transcription factor 3
ATL	aspirin-triggered lipoxin
ATP	adenosine triphosphate
AU	action unit
AUA	American Urological Society
AVM	arteriovenous malformation
BBB	blood–brain barrier
BCG	bacille Calmette-Guérin
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
BH_4	tetrahydrobiopterin
bHLH	basic helix–loop–helix
BKN	bradykinin
BMD	bone mineral density
BMI	body mass index
BMS	burning mouth syndrome
BOCF	baseline observation carried forward
BOLD	blood oxygenation level–dependent
BPI	Brief Pain Inventory
BPS	bladder pain syndrome
BTcP	breakthrough cancer pain
CABG	coronary artery bypass grafting
CAIEB	clinician-administered intermittent bolus
CAM	complementary and alternative medicine; constitutively activated mutant
CAMKII	calcium–calmodulin–dependent kinase II protein
CASPAR2	contactin-associated protein 2
CAV	cyclophosphamide, Adriamycin (doxorubicin), and vincristine
CBF	cerebral blood flow
CBT	cognitive–behavioral therapy
CCI	chronic constriction injury (model)
CCK	cholecystokinin
CDH	chronic daily headache
CEI	continuous epidural infusion
CEP	cortical evoked potential
CER	control event rate
CES-D	Center for Epidemiological Studies–Depression Scale
CFA	complete Freund's adjuvant
CFACS	Child Facial Action Coding System
CFS	chronic fatigue syndrome
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene–related peptide
CH	cluster headache
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CHEP	contact heat–evoked potential
CI	confidence interval
CIA	collagen-induced polyarthritis
CIBP	cancer-induced bone pain
CIDP	chronic inflammatory demyelinating polyneuropathy
CIPA	congenital insensitivity to pain with anhidrosis
CISS	constructive interference steady state (MRI)
CL	centralateral
CLASS	Celecoxib Long-term Arthritis Safety Study
CMH	C-fiber mechano–heat–sensitive nociceptors
CMM	conventional medical management
CMT	Charcot–Marie–Tooth (disease)
CNCP	chronic non-cancer pain
CNS	central nervous system
COMT	catechol *O*-methyltransferase

CONSORT Consolidated Standards of Reporting Trials
Cox, COX cyclooxygenase
CP chronic prostatitis
CPCI Chronic Pain Coping Inventory
CPM conditional pain modulation
CPP chronic pain patient; chronic pelvic pain; conditioned place preference
CPPS chronic pelvic pain syndrome
CPR cardiopulmonary resuscitation
CPSP central poststroke pain
CR conditional response
CREB cyclic AMP response element–binding protein
CRF corticotropin-releasing factor
CRH corticotropin-releasing hormone
CRHCS complexity regarding the health care system
CRPS complex regional pain syndrome
CS conditioned stimulus
CSCI continuous subcutaneous infusion
CSD cortical spreading depression
CSE combined spinal epidural (technique)
CSF cerebrospinal fluid; colony-stimulating factor
CSQ Coping Strategies Questionnaire
CSS CRPS severity score
CT computed tomography
CTB cholera toxin B
CTS carpal tunnel syndrome
CTTH chronic tension-type headache
CWP chronic widespread pain
CXCL1 C-X-C motif ligand 1
DA dopamine
DAG diacylglycerol
DAP depolarizing afterpotential
DAT dopamine transporter
DBS deep brain stimulation
DC dendritic cell
DCN dorsal column nuclei
ddC 2′,3′-dideoxycytidine
ddI 2′,3′-dideoxyinosine
DDS-I Descriptor Differential Scale: intensity dimension
DEG/ENac degenerin/epithelial sodium channel
DGL (DAGL) diacylglycerol lipase
DH dorsal horn
DHE dihydroergotamine
DHPG dihydroxyphenylglycine
DLPFC dorsolateral prefrontal cortex
DMARD disease-modifying antirheumatic drug
DMSO dimethylsulfoxide
DN4 Douleur Neuropathique en 4 questions
DNI distal nerve injury (model)
DNIC diffuse noxious inhibitory control
DOMS delayed-onset muscle soreness
DOR δ-opiate receptor
DPN diabetic painful neuropathy
DREAM downstream regulatory element antagonistic modulator
DREZ dorsal root entry zone
DRG dorsal root ganglion
DRR dorsal root reflex
DSM-IV *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition
d4t stavudine
DTI diffusion tensor imaging
DVT deep vein thrombosis
DZ dizygotic
EAACI excitatory amino acid carrier 1
EC epidural compression
EDTMP ethylene diamine tetramethylene phosphonate
EEG electroencephalogram
EER experimental event rate
EERW enrolled enrichment with randomized withdrawal
EET epoxyeicosatrienoic acid
EGF epidermal growth factor
eGFR estimated GFR
EII embryonic day II
EM extensive metabolizer
EMDR eye movement desensitization and reprocessing
EMEA European Medicines Evaluation Agency
EMG electromyography
ENaC epithelial Na^+ channel
ENF epidermal nerve fiber
eNOS endothelial nitric oxide synthase
EP etoposide and cisplatin
EPH episodic paroxysmal hemicrania
EPSC excitatory post-synaptic current
EPSP excitatory post-synaptic potential
EQ European Quality of Life instrument
ERK extracellular signal–regulated kinase
ERP event-related potential
ES1 exteroreceptive suppression (silent) period 1
ESR erythrocyte sedimentation rate
ESSIC European Society for the Study of Interstitial Cystitis
ET-1 endothelin 1
ET_a endothelin receptor A
ETTH episodic tension-type headache
EULAR European League Against Rheumatism
FA fractional anisotropy
FAAH fatty acid amide hydrolase
FAI femoral acetabular impingement (syndrome)
FAPS functional abdominal pain syndrome
FBSS failed back surgery syndrome
FCA Freund's complete adjuvant
FD functional dyspepsia
FDA Food and Drug Administration
FGF fibroblast growth factor
FGID functional gastrointestinal disorder
FHM familial hemiplegic migraine
FIESTA fast imaging employing steady-state acquisition (MRI)
FIQ Fibromyalgia Impact Questionnaire
FISH fluorescence in situ hybridization
FLACC Face, Legs, Activity, Cry, Consolability
FM fibromyalgia
FMH familial hemiplegic migraine
FMPL *N*-formylmethionyl-leucyl-phenylalanine
fMRI functional magnetic resonance imaging
FMS fibromyalgia syndrome
FPS focal pain scale
FRAP fluoride-resistant acid phosphatase
5-FU 5-fluorouracil
GA gestational age

GABA γ-aminobutyric acid
GAD glutamic acid decarboxylase
GAT-1 GABA transporter type 1
GBS Guillain-Barré syndrome
G-CSF granulocyte colony-stimulating factor
GDNF glial cell line–derived neurotrophic factor
GEn gabapentin enacarbil
GERD gastroesophageal reflux disease
GFAP glial fibrillary acidic protein
GHQ General Hospital Questionnaire
GI gastrointestinal
GIRK G-protein–coupled inward rectifying potassium channel
Gly-IR glycine immunoreactivity
GlyR glycerine receptor
GM-CSF granulocyte–macrophage colony-stimulating factor
GON greater occipital nerve
GP general practitioner
GPCR G protein–coupled receptor
GpER extended-release gabapentin
GPN glossopharyngeal neuralgia
GREP Gender Role Expectations in Pain
GRPR gastrin-releasing peptide receptor
GS gastrocnemius–soleus
GW gestational weeks
GWAS genome-wide association study
HAART highly active antiretroviral therapy
HADS Hospital Anxiety and Depression Scale
HC hemicrania continua
hCG human chorionic gonadotropin
HCN hyperpolarization-activated cyclic nucleotide–gated (ion channel)
HD homeodomain
HETE hydroxyeicosatetraenoic acid
HGF hepatocyte growth factor
HIT Headache Impact Test
HIV human immunodeficiency virus
HLA human leukocyte antigen
HNC healthy normal control
HPC polymodal nociceptive cells
HPETE hydroperoxyeicosatetraenoic (acid)
HPOA hypertrophic pulmonary osteoarthropathy
HR heart rate
HRQoL health-related quality of life
HRT hormone replacement therapy
HSAN hereditary sensory and autonomic neuropathy
HSMN hereditary sensory and motor neuropathy
HSV herpes simplex virus
HT high-threshold (stimuli)
5-HT 5-hydroxytryptamine
HTN high-threshold (mechanoreceptor) mechanosensitive
5-HTP 5-hydroxytryptophan
IA intra-articular
IADR International Association for Dental Research
IASP International Association for the Study of Pain
IB4 isolectin B4
IBD inflammatory bowel disease
IBS irritable bowel syndrome
IBS-C irritable bowel syndrome with constipation
IBS-D irritable bowel syndrome with diarrhea
IBS-M irritable bowel syndrome with mixed bowel habits
IC insular cortex; interstitial cystitis
IC_{50} inhibitive concentration of 50%
ICC intraclass correlation coefficient
ICD-9 *International Classification of Diseases,* ninth revision
ICHD International Classification of Headache Disorders
ICSS intracranial self-stimulation
IENF intraepithelial nerve fiber
IGLE intraganglionic laminar ending
IHS International Headache Society
IL interleukin
IM intermediate metabolizer
iMA intramuscular array
IMMPACT Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials
INCB International Narcotics Control Board
iNOS inducible nitric oxide synthase
INR international normalized ratio
IP_3 inositol triphosphate
IPG implantable pulse generator
IPL inferior parietal lobule
IPSC inhibitory post-synaptic current
IPSP inhibitory post-synaptic potential
ISB interscalene brachial plexus blockade
IT intrathecal
ITS iontophoretic transdermal system
IVRS intravenous regional sympatholysis
JCAHO Joint Commission on Accreditation of Healthcare
JNK c-Jun N-terminal kinase
K/C kaolin and carrageenan
KCC2 potassium–chloride co-transporter-2
K/L Kellegren–Lawrence (OA grading system)
LANSS Leeds Assessment of Neuropathic Symptoms and Signs (pain scale)
LASIK laser in situ keratomileusis
LBP low back pain
LC locus coeruleus; Langerhans cell
LCP Liverpool Care Pathway for the Dying Patient
LEP laser-evoked potential
LFS low-frequency stimulation
LGI1 leucine-rich inactivated 1
LHRF luteinizing hormone–releasing factor
LHRH luteinizing hormone–releasing hormone
LIDSI lack of information about diagnosis or severity of the illness
LIF leukemia inhibitory factor
LIG leucine-rich repeat and immunoglobulin
LLI leg length inequality
LLLT low-level laser therapy
L-NAME *N*-nitro-L-arginine methyl ester
L-NMA N^G-methyl-L-arginine
L-NMNA N^G-monomethyl-L-arginine hydrochloride
LOCF last observation carried forward
LOX lipoxygenase
5-Lox 5-lipoxygenase
LP lumbar puncture
LPb lateral parabrachial area
LPS lipopolysaccharide

LS lumbosacral
LT low-threshold (stimuli)
LTB_4 leukotriene B_4
LTD long-term depression
LTM low-threshold mechanoreceptive/mechanosensitive (cell, afferent)
LTP long-term potentiation
M1 primary motor cortex
MA mechanically activated
MAO monoamine oxidase
MAP mitogen-activated protein (kinase)
MAPK mitogen-activated protein kinase
mBSA methylated bovine serum albumin
MCP-1 monocyte chemoattractant protein-1
MCS motor cortex stimulation
MD medial dorsal (nucleus)
MDD major depressive disorder
MDvc medial dorsal (nucleus), ventral caudal portion
MeCP2 methyl CpG binding protein 2
M3G morphine-3-glucuronide
M6G morphine-6-glucuronide
MEG magnetoencephalogram
MEK mitogen-activated protein/ERK kinase
MELAS mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
MEP magnetic evoked potential
mEPSC miniature excitatory post-synaptic current
MFG medial frontal gyrus
MFPS myofascial pain syndrome
MGL monoacylglycerol lipase
mGlu metabotropic glutamate (receptor)
MGS mouse grimace scale
MGUS monoclonal gammopathy of undetermined significance
MHC major histocompatibility complex
MIA mechanically insensitive afferent (afferent fibers); mono-iodoacetate (model)
MIDAS Migraine Disability Assessment Scale
MINI Mini International Neuropsychiatric Interview
mIPSC miniature inhibitory post-synaptic current
MMPI Minnesota Multiphasic Personality Inventory
MOR μ-opioid receptor
MPEP 2-methyl-6-(phenylethynyl) pyridine
MPI Multidimensional Pain Inventory
MPQ McGill Pain Questionnaire
MPS myofascial pain syndrome
mPP mitochondrial permeability pore
MRA magnetic resonance angiography
mRFF minimum rhythmic firing frequency
Mrgprd Mas-related G protein–coupled
MRI magnetic resonance imaging
MRS magnetic resonance spectroscopy
MS multiple sclerosis
MSA mechanically sensitive afferent
MSG monosodium glutamate
mTOR mammalian target of rapamycin
MVD microvascular decompression
MZ monozygotic
N noradrenergic
NAA *N*-acetylaspartate
NA_c nucleus accumbens
NAC *N*-acetylcysteine
nAChR nicotinic acetylcholine receptor
NADPH nicotinamide adenine dinucleotide phosphate
NAPE *N*-arachidonylphosphatidylethanolamine
nBR nociceptive component of the blink reflex
NCCP non-cardiac chest pain
NDPH new daily persistent headache
NDSA non-dermatomal sensory abnormality
NE norepinephrine
NET norepinephrine transporter
NF200 neurofilament 200
NFACS Neonatal Facial Action Coding System
NFCI non-freezing cold injury
NF-κB nuclear factor κB
NGF nerve growth factor
Ngn1 neurogenin 1
NGT nitroglycerin (glyceryl trinitrate)
NHANES National Health and Nutrition Examination Survey
NHP Nottingham Health Profile
NICU neonatal intensive care unit
NK natural killer (cell)
NK1 neurokinin 1
NKA neurokinin A
NMDA *N*-methyl-D-aspartate
NNH number needed to harm
nNOS neuronal nitric oxide synthase
NNQ number needed to harm
NNT number needed to treat
NO nitric oxide
NOS nitric oxide synthase
NP neuropathic pain
NPQ Neuropathic Pain Questionnaire
NPS Neuropathic Pain Scale
NPFF neuropeptide FF
NPY neuropeptide Y
NRS numerical rating scale
NS nociceptive-specific (cell)
NSAID non-steroidal anti-inflammatory drug
NSAP non-specific arm pain
NSRI serotonin–norepinephrine reuptake inhibitor
NT3 neurotrophin 3; neurotrophic factor 3
NYHA New York Heart Association
OA osteoarthritis
OARSI Osteoarthritis Research Society International
OFC orbitofrontal cortex
OIH opioid-induced hyperalgesia
OMERACT Objective Measures of Randomized Clinical Trials
OMIM Online Mendelian Inheritance in Man (database)
ONJ osteonecrosis of the jaw
OR odds ratio
OSA obstructive sleep apnea
PACAP pituitary adenyl cyclase–activating peptide
PAD primary afferent depolarization
PAF platelet-activating factor
PAG periaqueductal gray
PAOD peripheral arterial occlusive disease
PAP prostatic acid phosphatase
PAR protease-activated receptor
PASS Pain Anxiety Symptoms Scale
PB parabrachial nucleus (of the dorsolateral pons)

PBMC peripheral blood mononuclear cell
PCA patient-controlled analgesia
PCEA patient-controlled epidural analgesia
PCIA patient-controlled intravenous analgesia
PD personality disorder; Parkinson's disease
PDA personal digital assistant
PDI Pain Disability Index
PDN painful diabetic neuropathy
PDPH post–dural puncture headache
PEA palmitoylethanolamine
PEPD paroxysmal extreme pain disorder
PET positron emission tomography
Pf parafascicular (nucleus)
PFC prefrontal cortex
PFMS primary fibromyalgia syndrome
PG prostaglandin
pgACC perigenual anterior cingulate cortex
PGP protein gene product (e.g., PGP 9.5)
PH paroxysmal hemicrania
PHN post-herpetic neuralgia
PI3K phosphatidyl-3′-kinase
PIEB programmed intermittent epidural bolus
PI-IBS postinfectious IBS
PIP_2 phosphatidylinositol 4,5-bisphosphate
PIPP Premature Infant Pain Profile
PKA protein kinase A
PKC protein kinase C
PLA_2 phospholipase A_2
PLD phospholipase D
PLC phospholipase C
PLP phantom limb pain
PLS phantom limb sensation
PM poor metabolizer
PMN polymorphonuclear
PNB peripheral nerve block
PNI peripheral nerve injury
PNS parasympathetic nervous system; peripheral nervous system
Po posterior complex (nucleus)
POMS Profile of Mood States
PONV postoperative nausea and vomiting
PoT posterior triangular (nucleus)
PPAR-γ peroxisome proliferator–activated receptor γ
PPT pressure pain threshold
PQAS Pain Quality Assessment Scale
Pr5 primary sensory trigeminal nucleus
PREP pain-related electrically evoked potential
PRI pain rating index
PRI-A pain rating index (affective)
PRI-S pain rating index (sensory)
PRI-T pain rating index (total)
PRK photorefractive keratectomy
PROMIS Patient-Reported Outcome Measurement Information System
PROSPECT Procedure-Specific Postoperative Pain Management
PSDC post-synaptic dorsal column pathway
PSNL partial sciatic nerve ligation (model)
PSQI Pittsburgh Sleep Quality Index
PT physical therapy
PTCA percutaneous transluminal coronary angioplasty
PTSD post-traumatic stress disorder
PV partial ventral
PVAS pain visual analog scale
PVB *cis*-platinum–vinblastine–bleomycin
PVD peripheral vascular disease
PVG periventricular gray
QC quick C (fiber)
QoL quality of life
QSART quantitative sudomotor axon reflex test
QST quantitative sensory test/testing; quantitative somatosensory thermotest
QTL quantitative trait locus
RA rheumatoid arthritis
rACC rostral anterior cingulate cortex
RAIC rostral anterior insular cortex
RANK receptor activator of NF-κB
RANKL RANK ligand
rCBF regional cerebral blood flow
RCT randomized controlled trial
REM rapid eye movement (sleep)
RET receptor tyrosine kinase
RF receptive field
RFT radiofrequency thermorhizotomy
r-HuEPO alfa recombinant human epoetin alfa
RLS restless legs syndrome
RR relative risk
RSD reflex sympathetic dystrophy
RSI repetitive strain injury
rTMS repetitive transcranial magnetic stimulation
RVM rostral ventromedial medulla; rostroventral medulla
S serotonergic
SC slow C (fiber)
SCI spinal cord injury
SCL-90R Symptom Checklist–90 Revised
SCORE Serious Complication Repository
SCR skin conductance response
SCS spinal cord stimulation
SCT spinocervicothalamic
SDH superficial dorsal horn
SDT sensory decision theory
SEP somatosensory evoked potential
SERP somatosensory event-related potential
SERT serotonin transporter
SF-36 36-item short form of the Medical Outcomes Society
SFL spontaneous foot-lifting (behavior)
SF-MPQ short-form McGill Pain Questionnaire
SFMS secondary fibromyalgic syndrome
SG substantia gelatinosa
SHT spinohypothalamic tract
SI, SII primary and secondary somatosensory cortices
sIL-6R soluble IL-6 receptor
SIP Sickness Impact Profile; sympathetically independent pain
siRNA small interfering RNA
sLORETA source analysis method of low-resolution brain electromagnetic tomography; standardized low-resolution brain electromagnetic tomography
Sm submedius (nucleus)
SMA supplementary/supplemental motor area

SMON subacute myelo-optic neuropathy
SMP sympathetically maintained pain
SNI spared nerve injury (model)
SNL spinal nerve ligation (model)
SNP single nucleotide polymorphism
SNRI serotonin–noradrenaline reuptake inhibitor
SNS sympathetic nervous system
SNSR sensory neuron–sensitive receptor
SOPA Survey of Pain Attitude
SP substance P
Sp5 spinal sensory trigeminal nucleus
Sp5C spinal sensory trigeminal nucleus caudalis subnucleus
Sp5I spinal sensory trigeminal nucleus interpolaris subnucleus
Sp5O spinal sensory trigeminal nucleus oralis subnucleus
SPECT single-photon emission computed tomography
SP–SAP substance P–saporin
SQUID superconductivity quantum induction device
SRD subnucleus reticularis dorsalis
SRF serum response factor
SSRI selective serotonin reuptake inhibitor
SSS Somatic Symptoms Score
sst/SST somatostatin
STAI State–Trait Anxiety Inventory
STD short-term depression
StEP Standardized Evaluation of Pain
STh sensory thalamic (nuclei)
STP soft tissue pain (syndrome)
STT spinothalamic tract
SUNA short-lasting unilateral neuralgiform headache attacks
SUNCT short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
SV2A synaptic vesicle 2A
SVC superior vena cava
TA treatment adherence
TAC trigeminal autonomic cephalgia
TASK TWIK-related acid-sensitive K^+ channel
TBNS trigeminal brain stem nuclear complex
TCA tricyclic antidepressant
TCM traditional Chinese medicine
TENS transcutaneous electric nerve stimulation
TGF transforming growth factor
TGVS trigeminovascular system
THC tetrahydrocannabinol
TL thoracolumbar
TLR toll-like receptor
Tm transmembrane
TMD temporomandibular disorder
TMJ temporomandibular joint
TN trigeminal neuralgia
TNF-α tumor necrosis factor-α
TRAAK TWIK-related arachidonic acid K^+ channel
TRAK-1 TWIK-related K^+ channel 1
TRESK TWIK-related spinal cord potassium channel
trkA tyrosine kinase receptor A; tropomyosin-related kinase A
TRP transient receptor potential
TRPA1 transient receptor potential ankyrin 1
TRPV1 transient receptor potential vanilloid 1
TST sectioning of the tibial and sural nerves while leaving the common peroneal nerve intact (model)
TTH tension-type headache
TTS total tenderness score
TTX tetrodotoxin
TTXr tetrodotoxin-resistant
TUNEL terminal deoxynucleotidyl transfer nick end labeling
TWIK tandem of P domains in a weak inward rectifying K^+ channel
UK United Kingdom
UM ultrarapid metabolizer
UR unconditioned response
US unconditioned stimulus; United States
UTP uridine triphosphate
UVB ultraviolet B
VAS visual analog scale
Vc ventral caudal (nerve)
VCAM vascular cell adhesion molecule
Vcpc parvicellular part of the ventral caudal (nucleus)
VDS verbal descriptor scale
VGAT vesicular GABA transporter
VGCC voltage-gated calcium channel
VGLUT vesicular glutamate transporter
VGSL voltage-gated sodium channel
VIP vasoactive intestinal polypeptide
VL ventral lateral (nerve)
VLO ventral lateral orbital (cortex)
VMb basal part of the ventral medial (nucleus)
VMl ventromedial (thalamus)
VMpo posterior part of the ventral medial (nucleus)
VP ventral posterior (nucleus)
VPI ventroposterior inferior (nucleus)
VPL ventral posterior lateral (nucleus)
VPM ventral posterior medial (nucleus)
VRP ventral root potential
VRS verbal rating scale
VTA ventral tegmental area
VZV varicella-zoster virus
WDR wide–dynamic range (cell neuron)
WHO World Health Organization
WPI Widespread Pain Index
WC workers' compensation
WOMAC Western Ontario and McMaster (Universities) Osteoarthritis Index
WS Waddell's sign
YAG yttrium–aluminum–garnet

Contents

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Section I

Neurobiology of Pain

Chapter 1

Peripheral Mechanisms of Cutaneous Nociception

Matthias Ringkamp, Srinivasa N. Raja, James N. Campbell, and Richard A. Meyer

SUMMARY

Nociceptors are a specialized class of primary afferents that respond to intense, noxious stimuli. Unmyelinated nociceptors signal the burning pain from intense heat stimuli applied to the glabrous skin of the hand, as well as the pain from sustained pressure. Myelinated nociceptors signal the sharp pain from heat stimuli applied to hairy skin and from sharp mechanical stimuli. Both myelinated and unmyelinated nociceptors signal pain from chemical stimuli. Following a cutaneous injury, enhanced pain in response to cutaneous stimuli, called *hyperalgesia*, develops at the site of injury (primary hyperalgesia) and in the surrounding uninjured skin (secondary hyperalgesia). Tissue injury leads to enhanced responsiveness of nociceptors, called *sensitization*, which accounts for primary hyperalgesia. This sensitization is due to the local release of inflammatory mediators. Secondary hyperalgesia is due to sensitization of neurons in the central nervous system. When nerves are severed, spontaneous activity and ectopic mechanical, thermal, and chemical sensitivity develop in the injured nociceptors. The properties of nearby, uninjured nociceptors are also changed. In both injured and uninjured nociceptors, responsiveness to adrenergic agents can develop, which may account for involvement of the sympathetic nervous system in certain forms of neuropathic pain.

INTRODUCTION

One of the vital functions of the nervous system is to provide information about the occurrence or threat of injury. The sensation of pain, by its inherent aversive nature, contributes to this function. In this chapter we consider the peripheral neural apparatus that responds to noxious (injurious or potentially injurious) stimuli and thus provides a signal to alert the organism to potential injury. Investigators have studied cutaneous sensibility by recording from single nerve fibers in different species, including humans. Stimuli are applied to the receptive field (i.e., area of the tissue responsive to the applied stimulus) of single fibers, and the characteristics of the neural response are noted. We concentrate on the skin for three reasons. First, sensory receptors in the skin have been more thoroughly studied than receptors in any other tissue. Second, the opportunity to perform correlative psychophysical studies in animals and humans allows powerful inferences to be made regarding function. Third, cutaneous pain sensation is of great clinical significance. Diseases such as post-herpetic neuralgia and others associated with small-fiber neuropathies have profound effects on cutaneous sensory function and often lead to severe pain.

Highly specialized sensory fibers, alone or in concert with other specialized fibers, provide information to the central nervous system (CNS) not only about the environment but also about the state of the organism itself. In the case of the sensory capacity of the skin, cutaneous stimuli may evoke a sense of cooling, warmth, or touch. Accordingly, certain sensory fibers are selectively sensitive to these stimuli. Warm fibers, which are predominately unmyelinated, are exquisitely sensitive to gentle warming of their punctate receptive fields. These fibers have been shown to exclusively signal the quality and intensity of the warmth sensation (Johnson et al 1979). Similarly, a subpopulation of the thinly myelinated, Aδ fibers respond selectively to gentle cooling stimuli and encode the sense of cooling (Darian-Smith et al 1973). For the sense of touch, different classes of mechanoreceptive afferent fibers are exquisitely sensitive to deformations of the skin. These low-threshold mechanoreceptors encode such features as texture and shape.

A relatively high threshold for an adequate stimulus distinguishes the remaining class of cutaneous receptors. Because these receptors respond preferentially to noxious stimuli, they are termed nociceptors (Sherrington 1906). Among the many varieties of sensory receptors, nociceptors are distinctive in that they typically respond to the multiple energy forms that produce injury (thermal, mechanical, and chemical stimuli) and provide information to the CNS regarding the location and intensity of noxious stimuli. Nociceptors may be subclassified with respect to four criteria: (1) unmyelinated C-fiber afferents (conduction velocity <2 m/sec) versus myelinated A-fiber afferents (conduction velocity >2 m/sec), (2) modalities of stimulation that evoke a response, (3) response characteristics, and (4) distinctive chemical markers (e.g., receptors expressed on the membrane). We first consider the properties of cutaneous nociceptors and then review how their function is thought to relate to the sensation of pain.

Tissue damage results in a cascade of events that lead to enhanced pain in response to natural stimuli, termed *hyperalgesia*. A corresponding increase in the responsiveness of nociceptors, called *sensitization*, occurs. The characteristics of hyperalgesia and its neurophysiological counterpart sensitization are discussed in a later section. Finally, we consider how nociceptors may play a role in accounting for the often severe pain that accompanies nervous system injury and disease.

PROPERTIES OF NOCICEPTORS IN UNINJURED SKIN

Nature might have designed nociceptors such that each had the capacity to respond to the full complement of stimulus energy forms that pose potential risks to the organism (thermal, mechanical, and chemical). What nature has adopted instead is a mixed strategy whereby many nociceptors respond to multiple stimulus modalities (polymodal) and others have more specialized response properties. These specialized response properties probably at least in part account for different aspects of nociceptive sensory function (e.g., burning, aching, pricking, prickle, itch). As delineated later, nociceptors have distal effector functions as well, and specialization may also play a role here. The end result is that nociceptors have a complex biology and heterogeneous properties.

The receptive field of a nociceptor is often first localized by use of mechanical stimuli. Various other stimulus modalities are then applied to this receptive field. In most early studies of nociceptors, only heat and mechanical stimuli were used to study nociceptors. Therefore, the nomenclature of CMH and AMH is often used to refer to C-fiber mechano-heat–sensitive nociceptors and A-fiber mechano-heat–sensitive nociceptors, respectively. If a fiber responds to heat and mechanical stimuli, the fiber will in most cases respond to chemical stimuli as well (Davis et al 1993b). Thus, CMHs and AMHs may also be referred to as polymodal nociceptors.

The issue of whether a given nociceptor responds to a particular stimulus modality is perilous because the presumed lack of response to a given modality may in fact represent failure to apply the stimulus with sufficient intensity. The problem with the application of high-intensity stimuli is that the stimulus may alter the properties of the nociceptor in an enduring manner. A selection bias occurs: nociceptors with lower thresholds are more likely to be studied. The easiest way to find a nociceptor for electrophysiological study is to apply squeezing (mechanical) stimuli to the skin and thus identify the receptive field. This selection process identifies what are termed *mechanically sensitive afferents* (MSAs). In time it has become apparent that selection bias from this approach has led to oversight of an important class of nociceptors: *mechanically insensitive afferents* (MIAs). Because these fibers by definition have high mechanical thresholds (or are unresponsive to mechanical stimuli), finding the mechanical receptive field of these fibers is difficult. An alternative technique described by Meyer and colleagues (1991) has been to apply electrical stimuli to the skin to identify the putative receptive field. With this technique it turns out that about half of the Aδ-fiber nociceptors and 30% of the C-fiber nociceptors are MIAs, with MIAs being defined as afferents that have very high mechanical thresholds (>6 bar = 600 kPa = 60 g/mm^2) or are unresponsive to mechanical stimuli (Handwerker et al 1991, Meyer et al 1991). MIAs have also been reported in the knee joint (Schaible and Schmidt 1985), viscera (Häbler et al 1988), and cornea (Tanelian 1991). As will be seen, this MIA–MSA distinction is of significance with regard to distinguishing nociceptor types. From the perspective of nomenclature, it is well to emphasize that MIAs are not defined as fibers that have no response to mechanical stimuli but rather as fibers that have a very high threshold (or no sensitivity at all) such that demonstration of a response to mechanical stimuli in electrophysiological studies is difficult.

C-Fiber Nociceptors

CMHs are commonly encountered cutaneous afferents, and activity of sufficient magnitude in these fibers is thought to evoke a burning pain sensation. The size of the receptive field appears to scale with the size of the animal. Typical values for monkey are between 15 and 20 mm^2 (LaMotte and Campbell 1978), and for human they are near 100 mm^2 (Schmidt et al 1997). There are often discrete areas of mechanical sensitivity (hot spots) within the receptive field, but in many fibers the areas of mechanical responsiveness tend to fuse over the region of the receptive field. Most CMHs respond to chemical stimuli (though not as well as A-fiber nociceptors; Davis et al 1993b) and can therefore be considered polymodal.

Responses to heat stimuli have been studied in considerable detail. The response of a typical CMH to a random sequence of heat stimuli ranging from 41–49°C is shown in Figure 1-1A. It can be seen that the response increases monotonically with stimulus intensity over this temperature range, which encompasses the pain threshold in humans. One ion channel involved in the transduction of heat at nerve terminals is thought to be the neuronal transient receptor potential ion channel V1 (TRPV1); activity in this channel increases with increasing temperature (Caterina et al 1997). A detailed description of the neuronal ion channels involved in stimulus transduction is presented in Chapter 2 (for review see Dubin and Papapoutian 2010). Signal transduction molecules on keratinocytes may also play a role in heat transduction by inducing the release of adenosine triphosphate (ATP), which activates purinergic receptors ($P2X_3$ and $P2Y_2$) on the free nerve endings (see Fig. 1-4).

Two types of heat response are observed following a stepped heat stimulus. Quick C (QC) fibers exhibit their peak discharge during the rising phase of the heat stimulus, whereas slow C (SC) fibers exhibit their peak discharge during

the plateau phase (Fig. 1-2B). The heat thresholds (Fig. 1-2C) and mechanical thresholds of QC fibers are significantly lower than those of SC fibers, thus suggesting that they may be located more superficially in the epidermis. QC fibers respond more vigorously to pruritic stimuli than do SC fibers, which suggests that they may be important in itch sensations (Johanek et al 2008).

Thermal modeling studies combined with electrophysiological analysis have indicated that (1) the heat threshold of CMHs depends on the temperature at the depth of the receptor and not the rate of increase in temperature, (2) transduction of heat stimuli (conversion of heat energy to action potentials) occurs at different skin depths for different CMHs (Tillman et al 1995b), and (3) suprathreshold responses of CMHs vary directly with the rate of increase in temperature (Tillman et al 1995a, 1995b; Yarnitsky et al 1992). The depth of the heat-responsive terminals of CMHs varies quite widely (ranging from 20–570 μm; Tillman et al 1995b). When a stepped temperature stimulus is applied to the skin, the temperature increases in the subsurface levels more slowly because of thermal inertia. The disparity in the surface temperature and the temperature at the level of the receptor varies directly with depth and indirectly with time. Given that the depth of CMH terminals varies widely, true heat thresholds are obtained when the rate of increase in temperature is very gradual or when the duration of the stimulus is very long. Although the literature reflects a wide range of heat thresholds for CMHs, when tested with these types of heat stimuli, the heat threshold of the majority of CMHs is in a remarkably narrow range of 39–41°C (Tillman et al 1995b).

The response of CMHs is also strongly influenced by the stimulus history. Both fatigue and sensitization are observed. One example of fatigue is the observation that the response to the second of two identical heat stimuli is substantially less than the response to the first stimulus. This fatigue is dependent on the time between stimuli, with full recovery taking longer than 10 minutes. A similar reduction in the intensity of pain after repeated heat stimuli is observed in human subjects (LaMotte and Campbell 1978). Fatigue is also apparent in Figure 1-1A, where the response to a given stimulus varied inversely with the intensity of the preceding stimulus. A decrease in the response to heat is also observed following mechanical stimuli applied to the receptive field or electrical stimuli applied to the nerve trunk (Peng et al 2003). This suggests that fatigue in response to a given stimulus modality can be induced by heterologous stimulation, that is, by excitation with a stimulus of a different modality. Interestingly, recovery from cross-modal or heterologous fatigue is faster than recovery from fatigue induced by a stimulus of the same modality. Presumably, this is because these heterologous stimuli do not activate and therefore do not fatigue the stimulus transduction apparatus in the same way. Alternatively, fatigue may arise from independent effects on spike initiation (from antidromic stimulation) and transduction (from natural stimulation at the receptive field). Fatigue in response to heat stimuli is also seen in vitro when small (and presumably nociceptive) dorsal root ganglion (DRG) cells are repetitively tested with heat stimuli (Greffrath et al 2002). The enhanced response, or sensitization, that may occur in CMHs after tissue injury is described below in the section on hyperalgesia.

Responses to mechanical stimuli are covered in more detail later. Suffice it here to indicate that CMHs usually display a slowly adapting response to mechanical stimuli of a given force. As noted later, MSA CMHs have a graded response to punctate stimuli, but their stimulus–response functions become saturated at levels substantially below the threshold for pain.

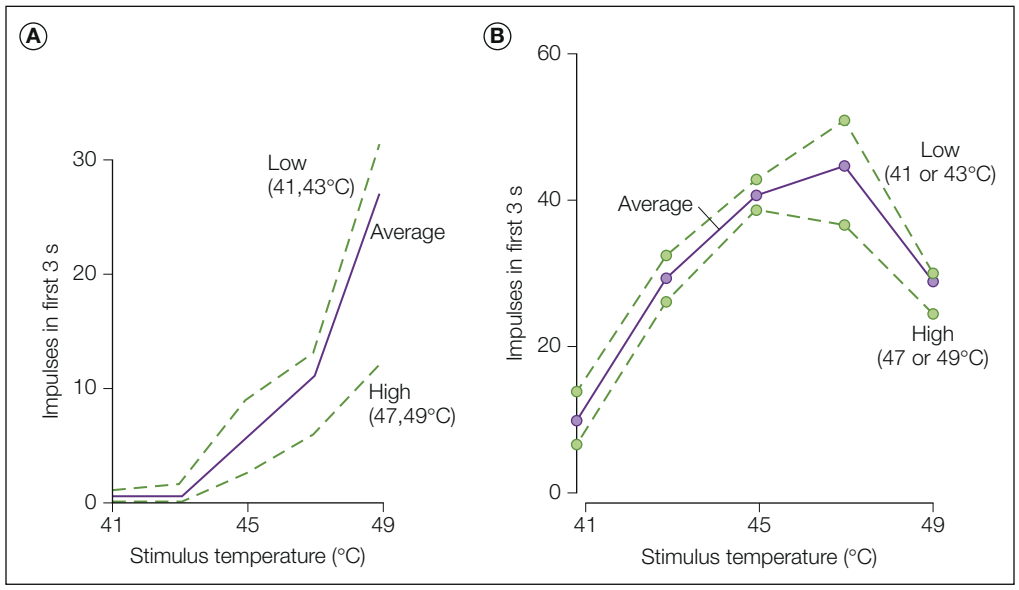

Figure 1-1. Responses of a typical C-fiber nociceptor and a warm fiber to heat stimuli. Heat stimuli ranging from 41-49°C and lasting 3 seconds were presented at 25-second interstimulus intervals to the glabrous skin of the monkey hand. Each stimulus occurred with equal frequency and was preceded by every other stimulus an equal number of times. Within these constraints, the order of stimulus presentation was randomized. Base temperature between stimuli was 38°C. **A,** Monotonic stimulus–response function for a typical nociceptor. **B,** Non-monotonic stimulus–response function for a typical warm fiber. The solid line represents the total response to a given temperature averaged across all presentations. The dotted lines represent the stimulus–response functions obtained when the preceding temperature was of low (41 and 43°C) or high (47 and 49°C) intensity. *(Reproduced with permission from LaMotte RH, Campbell JN 1978 Comparison of responses in warm and nociceptive C-fiber afferents in monkey with human judgements of thermal pain. Journal of Neurophysiology 41:509–528.)*

C-fiber MIAs are heterogeneous with regard to responses to chemical and heat stimuli, and some respond only to mechanical stimuli (but of course with a very high mechanical threshold). The sensitivity to mechanical stimuli has no obvious correlation to the heat threshold (Davis et al 1993b). In contrast to CMH afferents, some C-fiber MIAs in humans are vigorously excited when challenged with histamine or capsaicin. In addition, the activity observed in these C-fiber MIAs parallels the duration of the perception of itch (histamine) or burning pain (capsaicin) (Schmelz et al 1997, 2000b). C-fiber MIAs may therefore act as chemosensors. In addition to pronounced chemosensitivity, these fibers have some other interesting properties that could account for pain in response to tonic pressure stimuli or the neurogenic flare response (see below).

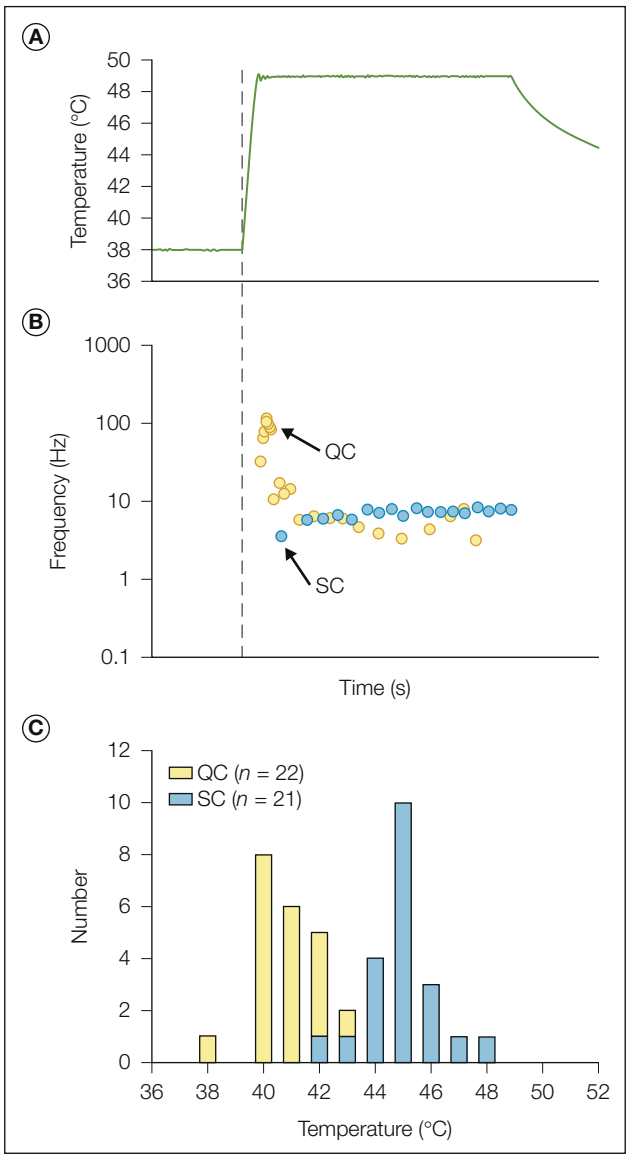

Figure 1-2. Two types of heat responses are observed in C-fiber nociceptors. A, Stepped heat stimulus (49°C, 3 seconds) used to classify heat response. **B,** The quick C (QC) fiber (yellow circles) exhibits a high-frequency discharge during the rising phase of the stimulus that adapts quickly (within 1 second). The slow C (SC) fiber (blue circles) exhibits a relatively uniform discharge throughout the stimulus period. Each circle represents the time of occurrence of an action potential. **C,** A histogram of the heat thresholds reveals that the distributions of QC and SC fibers are almost non-overlapping. *(From Johanek LM, Meyer RA, Friedman RM, et al 2008 A role for polymodal C-fiber afferents in nonhistaminergic itch. Journal of Neuroscience 28:7659–7669.)*

Low-threshold C-fiber mechanoreceptors that do not respond to heat have been described in the cat (Bessou and Perl 1969) and rabbit (Shea and Perl 1985). In primates, including humans, these fibers have been found in proximal areas of the body (Kumazawa and Perl 1977, Nordin 1990) and the hairy skin on the forearm (Vallbo et al 1999). These afferents are strongly activated by innocuous mechanical stimuli moved slowly across the receptive field, but they also respond to pinprick stimuli. The neuronal activity in these fibers is not critical for the perception of touch and, according to one imaging study, leads to the activation of the insular but not the sensory cortex (Olausson et al 2003). Low-threshold C-fiber mechanoreceptors are thought to mediate the sensation of "pleasant" touch and may therefore play an important role in "affiliative" behavior (Vallbo et al 1999, Wessberg et al 2003, Löken et al 2009).

Some mechano-insensitive C fibers are reported to be activated by non-noxious and noxious cold and hot stimuli. It has been hypothesized that activity in these afferents may mediate the "hot–burning" sensations caused by such stimuli. These afferents may also be involved in mediating psychophysical phenomena such as "paradoxical heat" or the thermal grill illusion (Campero et al 2009).

C-fiber afferents differ not only in their receptive features but also in their conductive properties. In fact, their conductive and receptive properties appear to correlate. When unmyelinated C-fiber afferents are activated repetitively by electrical stimuli, their conduction latency increases gradually (i.e., the conduction velocity of the afferent decreases). In addition, with increasing stimulation frequency, the amount of this activity-dependent slowing increases. Slowing in C-fiber MIAs is greater than in C-fiber MSAs (Weidner et al 1999), and mechanosensitive nociceptive afferents show more pronounced slowing than do cold-sensitive C fibers, low-threshold C fibers, or sympathetic efferent C fibers (Gee et al 1996, Serra et al 1999, Obreja et al 2010, Ringkamp et al 2010). This difference in slowing properties indicates that the ion channels responsible for conduction may be different and suggests that the ion channels responsible for spike initiation at the receptive terminal may also differ between C-fiber classes.

A-Fiber Nociceptors

A-fiber nociceptors are thought to evoke pricking pain, sharpness, and perhaps aching pain. As a general rule, A-fiber nociceptors do what C-fiber nociceptors do, but do it more robustly. They respond at higher discharge frequencies, and the discriminable information supplied to the CNS is greater (e.g., Slugg et al 2000).

Two types of A-fiber nociceptors are apparent (Dubner et al 1977, Treede et al 1998). A summary of their properties is presented in Table 1-1. Type I fibers are typically responsive to heat, mechanical, and chemical stimuli and may therefore be referred to as AMHs or polymodal nociceptors. Because the heat thresholds are high with short-duration stimuli (typically >53°C), the responsiveness of these fibers to heat has in some studies been overlooked. Consequently, these fibers

have been called high-threshold mechanoreceptors (HTMs) by many investigators (e.g., Burgess and Perl 1967). Heat sensitivity in type I fibers is most likely mediated by the vanilloid receptor–like protein 1 (VRL1, renamed TRPV2) since it has a similar high threshold for activation by heat and is expressed in neurons with small myelinated axons (Caterina et al 1999). When heat thresholds are determined with long-duration temperature stimuli, however, thresholds are in the mid-40–50°C range (Treede et al 1998). Type I AMHs are seen in hairy and glabrous skin (Campbell et al 1979) and have also been described in the cat and rabbit (Fitzgerald and Lynn 1977, Roberts and Elardo 1985). The mean conduction velocity of type I AMHs in the monkey is 25 m/sec and extends as high as 55 m/sec. Thus, by conduction velocity criteria, type I AMHs fall into a category between that of Aδ and Aβ fibers. Nearly all type I AMHs are MSAs. Their receptive field size is similar to that of CMHs, but the presence of "hot spots" in response to mechanical stimuli is much more obvious.

Type II A-fiber nociceptors were encountered only infrequently in early studies. It turns out that this is because the thresholds to mechanical stimuli place the majority of these fibers in the MIA category. Many have no demonstrable response to mechanical stimuli. When an unbiased electrical search stimulus is used, however, the prevalence of type I and type II A-fiber nociceptors in the hairy skin of the primate is similar. They do not occur in the glabrous skin of the hand (where type I AMHs are prevalent). Their mean conduction velocity, 15 m/sec, is also lower than that of type I AMHs. Their responses to heat resemble those observed in CMHs, and they may also be mediated by the vanilloid receptor 1 (VR1 or TRPV1). Responses to endogenous inflammatory/algesic mediators resemble those seen with type I A-fiber nociceptors (Davis et al 1993b).

Examples of the differing responses of the two types of A-fiber nociceptors to a heat stimulus are shown in Figure 1-3. Type I fibers exhibit a distinctive, gradually increasing response to heat. They sensitize to burn and chemical injury and probably play a role in the development of hyperalgesia. Type II fibers respond to heat in similar fashion to CMHs: early peak frequency and a slowly adapting response (Treede et al 1995). As noted later, type II A-fiber nociceptors are thought to signal first pain sensation in response to heat and may also contribute to pain caused by the application of capsaicin to the skin (Ringkamp et al 2001).

The conduction velocity of small myelinated Aδ fibers is, by definition, faster than that of unmyelinated C fibers. However, the terminal cutaneous branches of nociceptive Aδ fibers may conduct at a velocity characteristic of unmyelinated fibers (i.e., <2 m/sec) (Peng et al 1999). In addition, these unmyelinated terminals may branch off the main axon several centimeters proximal to their cutaneous receptive field.

Table 1-1 Comparison of Type I and Type II A-Fiber Nociceptors

CHARACTERISTIC	TYPE I	TYPE II
Heat threshold to short stimuli	High	Low
Heat threshold to long stimuli	Low	Low
Response to intense heat	Slowly increasing	Adapting
Response latency to intense heat	Long	Short
Peak latency to intense heat	Late	Early
Mechanical threshold	Most are MSAs	Most are MIAs
Conduction velocity	Aδ and Aβ fibers	Aδ fibers
Sensitization to heat injury	Yes	No
Location	Hairy and glabrous skin	Hairy skin

MIAs, mechanically insensitive afferents; MSAs, mechanically sensitive afferents.

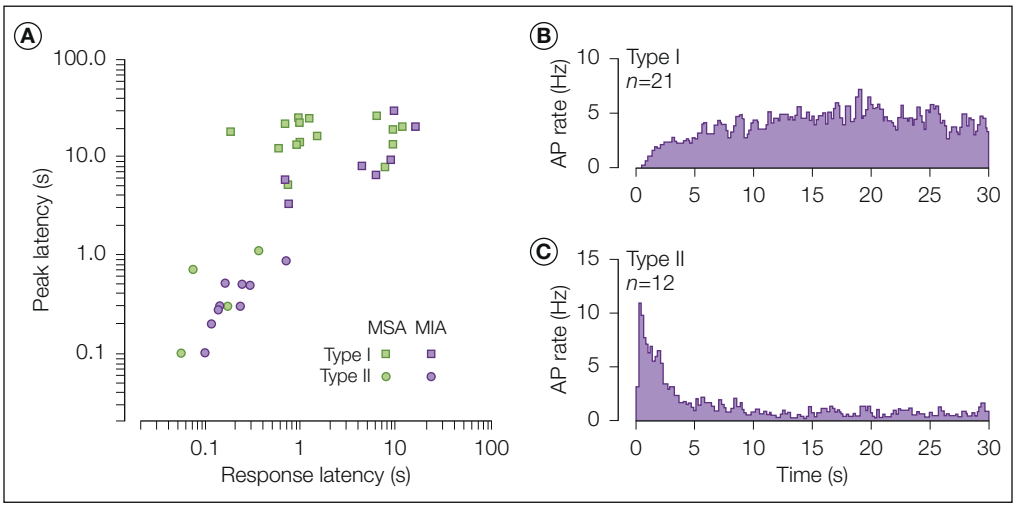

Figure 1-3. A-fiber nociceptors exhibit two types of responses to a heat stimulus. A, Scatter plot of peak discharge latency versus response latency for mechanically insensitive afferents (MIAs; purple symbols) and mechanically sensitive afferents (MSAs; green symbols) in response to a 53°C, 30-second stimulus. Receptors that had a long peak discharge latency were considered to have a type I heat response (squares). Receptors that had a short response latency and a peak discharge near stimulus onset were considered to have a type II heat response (circles). The type II heat response was found more frequently in the MIA group ($p \leq 0.05$, χ^2-test). **B,** Average peristimulus frequency histogram (obtained with a 0.2-second bin width) of the response to the 53°C, 30-second stimulus for A-fiber nociceptors that had a type I heat response. **C,** Average peristimulus frequency histogram for A-fiber nociceptors that had a type II heat response. *(Reproduced with permission from Treede RD, Meyer RA, Campbell JN 1998 Myelinated mechanically insensitive afferents from monkey hairy skin: heat-response properties. Journal of Neurophysiology 80:1082–1093.)*

Nociceptors Can Be Classified by Molecular Markers

The anatomical and biochemical features of nociceptive afferents have been studied extensively to correlate these features with their receptive properties. A wide range of cell markers have been used to classify nociceptive afferents and to study their peripheral and central projections. These markers include molecules expressed on the cell surface (e.g., receptors, glycoconjugates), molecules stored and released from nociceptive afferents (e.g., peptides), and enzymes. Expression of receptors for neurotrophic factors is of interest since these factors may regulate the sensitivity of nociceptive afferents in physiological and pathological states such as inflammation and neuropathy. The size of neuronal populations expressing or co-expressing different markers varies between species (Zwick et al 2002) and changes with the developmental stage (Molliver et al 1997, Guo et al 2001). Inflammation of the innervated tissue or a peripheral nerve lesion can cause substantial changes in the expression of these molecules. With the ongoing discovery of new marker molecules and the refinement of histological techniques, classification of nociceptive afferents is undergoing constant change and revision. Despite these "challenges," however, classification of nociceptive afferents based on the expression of biochemical markers is instructive inasmuch as certain different neuronal populations are distinguishable across species. Sophisticated genetic manipulations have allowed the peripheral and central projections of defined neuronal populations to be studied in great detail. In addition, ablation experiments have been used to study the role of defined neuronal populations in animal behavior.

The cell bodies of nociceptive somatic and visceral afferents are located in DRGs. Slowly conducting Aδ and C fibers, including nociceptors, have small cell bodies (Lawson and Waddell 1991). Some of these are labeled with an antibody directed against a neurofilament protein (NF200) and are therefore thought to correspond to the somata of small myelinated Aδ afferents.

Small DRG cells are subdivided into peptidergic neurons (i.e., neurons containing peptides such as substance P [SP], calcitonin gene–related peptide [CGRP], and somatostatin [SST]) and "non-peptidergic" neurons. In the rat, about 40% of DRG cells, 50% of C fibers, and 20% of Aδ fibers are classified as peptidergic (McCarthy and Lawson 1989, Lawson et al 1996). Non-peptidergic, nociceptive neurons contain fluoride-resistant acid phosphatase (FRAP) (Silverman and Kruger 1988a), and their somata and axons bind the plant isolectin B4 (IB4) from *Griffonia simplicifolia* (Silverman and Kruger 1988b). It is common practice to classify neurons as "peptidergic" or "non-peptidergic" based on their binding of IB4. However, considerable co-localization of SP or CGRP and IB4 or FRAP has been reported in rats but less so in mice (Carr et al 1990, Wang et al 1994, Bergman et al 1999, Price and Flores 2007). In vivo intracellular recordings combined with immunohistochemistry have shown that cells containing SP or CGRP or cells binding IB4 are nociceptive and that non-nociceptive cells do not label with these markers (Lawson et al 1997, 2002; Gerke and Plenderleith 2001).

A group of mas-related genes (Mrgs) have been discovered that are selectively expressed in small DRG neurons and encode G protein–coupled receptors (GPCRs) (Dong et al 2001). Independently, sensory neuron–specific GPCRs (so-called sensory neuron–specific receptors [SNSRs]) in which the encoding genes were identical to some of the previously described Mrgs were identified shortly thereafter (Lembo et al 2002). For some Mrgs (MrgA–C) identified in mice, no ortholog genes exist in human or non-human primates, but closely related Mrgs (so-called MrgXs) have been identified. For other Mrgs (MrgD–G), however, ortholog genes exist in humans. Mrgs are expressed mainly in non-peptidergic, IB4-positive neurons, with some Mrgs being expressed in distinct IB4 subpopulations. In in vitro recordings, MrgD$^+$ DRG cells showed characteristics typical of nociceptors (e.g., broad action potentials, expression of tetrodotoxin [TTX]-resistant sodium channels) (Drussor et al 2008). Receptors encoded by Mrgs respond to a variety of ligands, including β-alanine, cortistatin, peptides derived from different opioid precursors, and different RFamide peptides (Dong et al 2001, Han et al 2002, Lembo et al 2002, Robas et al 2003, Shinohara et al 2004), and they probably modulate excitability and sensitivity in this class of nociceptive afferents.

Expression of some markers appears to be related to the peripheral target tissue innervated by the neuron. Thus, almost all visceral afferents are peptidergic, but only about half the afferents projecting to the skin are (e.g., Perry and Lawson 1998) and only a small percentage of afferents projecting to muscle are labeled with IB4 (Plenderleith and Snow 1993, Ambalavanar et al 2003). MrgD-positive fibers exclusively innervate the skin, and they terminate in more superficial skin layers than do their peptidergic counterparts (Fig. 1-4) (Zylka et al 2005). Peptidergic and non-peptidergic afferents project to distinct dorsal horn laminae, with peptidergic fibers projecting mainly to lamina I and lamina II outer and IB4-binding afferents projecting preferentially to lamina II inner (e.g., Hunt and Rossi 1985, Silverman and Kruger 1988b; but see also Woodbury et al 2000).

Although all nociceptive neurons depend on nerve growth factor (NGF) during early development, in the adult only peptidergic neurons express its receptor TrkA (tropomyosin-related kinase A) (Averill et al 1995). In contrast, most IB4-positive DRG cells do not express TrkA (Molliver et al 1995, but see also Kashiba et al 2001) but express one of the glial-derived neurotrophic factor (GDNF) family receptors (GDNFRα1–4) together with receptor tyrosine kinase Ret (Bennett et al 1998, Orozco et al 2001).

Peptidergic and non-peptidergic neurons express different receptors involved in signal transduction, and they may therefore display different sensitivity to a given stimulus. Thus the $P2X_3$ receptor, which mediates nociceptor excitation by ATP, is primarily expressed in IB4-positive neurons (Vulchanova et al 1998). In contrast, TRPV1, which mediates responses to heat, capsaicin, and protons, is expressed in only a minority of IB4-positive cells in mice (Zwick et al 2002). In rats, however, this segregation is less obvious since about half of both IB4-positive and -negative cells express TRPV1 (Caterina et al 1997; Michael and Priestley 1999; Guo et al 1999, 2001). Species differences also exist in the co-expression of different Mrgs and their co-expression with other markers of nociceptive neurons (Zylka et al 2003).

Coupling between C-Fiber Nociceptors

Activation of one fiber by action potential activity in another is referred to as *coupling*. Coupling of action potential activity occurs between C fibers in the normal

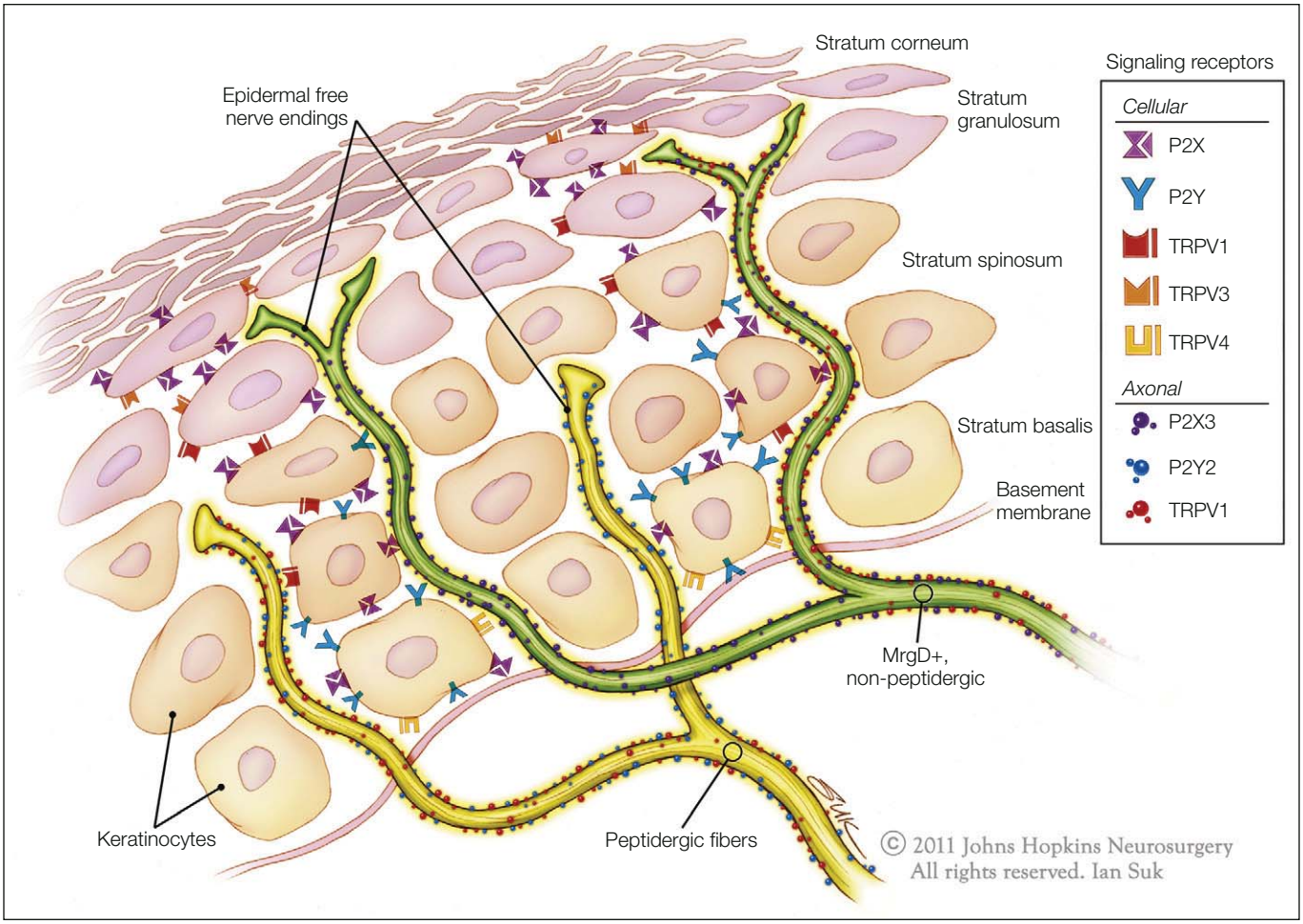

Figure 1-4. Schematic illustration of unmyelinated fiber terminations in the epidermis. Non-peptidergic, MrgD+ neurons terminate as free nerve endings in the most superficial layers of the epidermis. Peptidergic neurons terminate in deep layers of the epidermis. Some of the signaling receptors found on keratinocytes and free nerve endings are also illustrated. *(Artwork by Ian Suk, Johns Hopkins University; adapted from Dussor G, Koerber HR, Oaklander AL, et al 2009 Nucleotide signaling and cutaneous mechanisms of pain transduction. Brain Research Reviews 60:24–35.)*

peripheral nerve of the monkey (Meyer et al 1985a). Coupling frequently involves conventional CMHs. Coupling is eliminated by injecting small amounts of local anesthetic at the receptive field of the CMH, thus indicating that the site of coupling is near the receptor. Collision studies indicate that the coupling is bidirectional. Sympathetic fibers do not appear to be involved in this coupling as demonstrated by experiments in which the sympathetic chain is stimulated or ablated (Meyer and Campbell 1987). The role of coupling is unknown but it may relate to the flare response or other efferent functions of nociceptors (see below). Coupling between peripheral nerve fibers is also one of the pathological changes associated with nerve injury (e.g., Blumberg and Jänig 1982, Meyer et al 1985b). In this case, coupling occurs at the site of axotomy.

Anatomical Studies of Cutaneous Nociceptors

Immunostaining for protein gene product (PGP) 9.5, a carboxy-terminal ubiquitin hydrolase, has proved particularly sensitive in identifying small-diameter afferents in the skin (Hsieh et al 1996). Vertical sections reveal that epidermal axons emerge from the superficial dermal nerve plexuses running beneath the epidermis. Schwann cells encase the axons at the dermal level, but as the axons rise into the epidermis between keratinocytes, the Schwann cell encasements are lost (Kruger et al 1981). Both clear round and large dense-core vesicles are noted at the epidermal penetration site. The vesicles are similar morphologically to vesicles present in other cells involved in hormone and neurotransmitter secretion. It is presumed that these vesicles secrete their contents into tissues on activation (see the efferent role of nociceptors below). Some of these fibers appear to innervate Langerhans cells. In small-fiber neuropathies in which patients have pain and deficits in cutaneous pain sensibility, these axonal terminals stained by PGP 9.5 are markedly decreased (Holland et al 1998).

As illustrated in Figure 1-4, free nerve endings can be traced far into the epidermal layer. These free nerve endings are probably sensory and serve the sensations of pain, temperature, and itch. The parent axons of these unmyelinated terminals are probably both myelinated and unmyelinated. Some of these free nerve endings are peptidergic and contain SP or CGRP (Gibbons et al 1987). Others are non-peptidergic and reach into the superficial layers of the epidermis.

RELATIONSHIP OF NOCICEPTOR ACTIVITY TO ACUTE PAIN SENSATIONS

Nociceptors and Pain in Response to Heat Stimuli

CMHs Signal Pain from Heat Stimuli to Glabrous Skin

We now examine the evidence that CMHs signal pain. In glabrous skin of the hand, two types of fibers, CMHs (not AMHs) and warm fibers, respond to short-duration heat stimuli (≤5 seconds) at temperatures near the pain threshold in humans (i.e., around 45°C). It is of interest, therefore, to compare how warm fibers and CMHs encode information about noxious heat stimuli. Warm fibers respond vigorously to gentle warming of the skin and are thought to signal the sensation of warmth (Johnson et al 1979). An example of the response of a warm fiber to stimuli in the noxious heat range is shown in Figure 1-1B. The response of warm fibers is not monotonic over this temperature range. In the example shown in Figure 1-1B, the total response evoked at 49°C was less than that at 45°C. Psychophysical studies in humans demonstrate that pain increases monotonically with stimulus intensities between 40 and 50°C. Because the responses of CMHs increase monotonically over this temperature range (Fig. 1-1A) and the responses of warm fibers do not (Fig. 1-1B), it follows that CMHs probably signal the sensation of heat pain to the glabrous skin of the hand (LaMotte and Campbell 1978).

Other evidence in support of a role for CMHs in pain sensation includes the following: (1) human judgments of pain in response to stimuli over the range of 41–49°C correlate well with the activity of CMH nociceptors over this range (Fig. 1-5, Meyer and Campbell 1981b); (2) selective A-fiber ischemic blocks or C-fiber (local anesthetic) blocks indicate that C-fiber function is necessary for perception of thermal pain near the pain threshold (Torebjörk and Hallin 1973); (3) the stimulus interaction effects observed in psychophysical experiments (LaMotte and Campbell 1978) are also observed in recordings from CMHs (Fig. 1-1A); (4) the latency to pain sensation on glabrous skin following stepped changes in temperature is long and consistent with input from CMHs (Campbell and LaMotte 1983); and (5) in patients with congenital insensitivity to pain, microscopic examination of peripheral nerves indicates an absence of C fibers (Bischoff 1979).

Human Microneurographic Recordings

Microneurography has been used to record from nociceptive afferents in awake humans and allows correlations between the discharge of afferents and the reported sensations of the subject. The technique involves percutaneous insertion of a microelectrode into fascicles of nerves such as the superficial radial nerve at the wrist. These studies have demonstrated that the properties of nociceptors in humans and monkeys are similar. In some experiments the microelectrode is also used to stimulate an identified, single nerve fiber in awake human subjects to evoke specific sensations. Some, however, argue that the size of the stimulating electrode is too large to stimulate individual units (Wall and McMahon 1985). Given this reservation, the following evidence from microneurographic studies in humans points to the capacity of CMH activity to evoke pain: (1) intraneural electrical stimulation of presumed single identified CMHs in humans elicits pain (Torebjörk and Ochoa 1980), (2) the heat threshold for activation of CMHs recorded in awake humans is just below the pain threshold (Van Hees and Gybels 1981), and (3) a linear relationship exists between responses of CMHs recorded in awake humans and ratings of pain over the temperature range 39–51°C (Torebjörk et al 1984).

Correlations between Psychophysical Measures of the Heat Pain Threshold and Neurophysiological Results

We noted above that the heat threshold of CMHs is dependent on temperature at the level of the receptor and is independent of the rate of change in temperature. At the same time when threshold temperature is measured at the surface of skin, CMHs have a lower threshold when the rate of increase in temperature is slow. As discussed earlier, the reason for this relates to thermal inertia.

Human pain thresholds are sometimes measured as the temperature that corresponds to the first report of pain as skin temperature is increased linearly (Marstock technique). Investigators have noted that faster rates of change in temperature lead to lower estimates of the heat pain threshold (Yarnitsky and Ochoa 1990, Tillman et al 1995a). This is the opposite of the situation with the surface temperature threshold of CMHs but fits with the finding that suprathreshold responses of CMHs vary directly with the rate of increase in

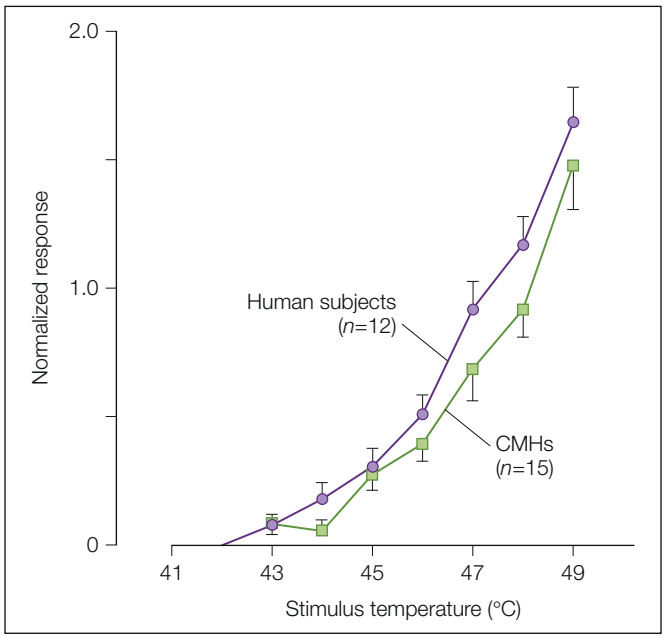

Figure 1-5. Correlation of the response of C-fiber nociceptors in the monkey with pain ratings in human subjects. The close match between the curves supports a role for C-fiber nociceptors in heat pain sensation from glabrous skin. The first stimulus of the heat sequence was always 45°C. The remaining nine stimuli ranged from 41–49°C in 1°C increments and were presented in random order. Human judgments of pain were measured with a magnitude estimation technique: subjects assigned an arbitrary number (the modulus) to the magnitude of pain evoked by the first 45°C stimulus and judged the painfulness of all subsequent stimuli as a ratio of this modulus. The response to a given stimulus was normalized by dividing by the modulus for each human subject or by the average response to the first 45°C stimulus for the C-fiber mechano-heat–sensitive nociceptors (CMHs). *(Originally published in Meyer RA, Campbell JN 1981 Peripheral neural coding of pain sensation. Johns Hopkins APL Technical Digest 2:164–171. Copyright 1981 AAAS.)*

temperature. Thus it is unlikely that the threshold responses of CMHs are responsible for the heat pain thresholds. Rather, it appears that nociceptors must reach a certain discharge frequency (about 0.5 impulses/sec) for pain to be perceived (Van Hees 1976, Yarnitsky et al 1992, Tillman et al 1995a).

A-Fiber Nociceptors and Heat Pain

As shown in Figure 1-6, a long-duration heat stimulus applied to the glabrous skin of the hand in human subjects evokes substantial pain for the duration of the stimulus. CMHs exhibit a prominent discharge during the early phase of the stimulus, but this response adapts within seconds to a low level. In contrast, type I AMHs are initially unresponsive but then discharge vigorously. Therefore, type I AMHs probably contribute to the pain during a sustained, high-intensity heat stimulus (Meyer and Campbell 1981a).

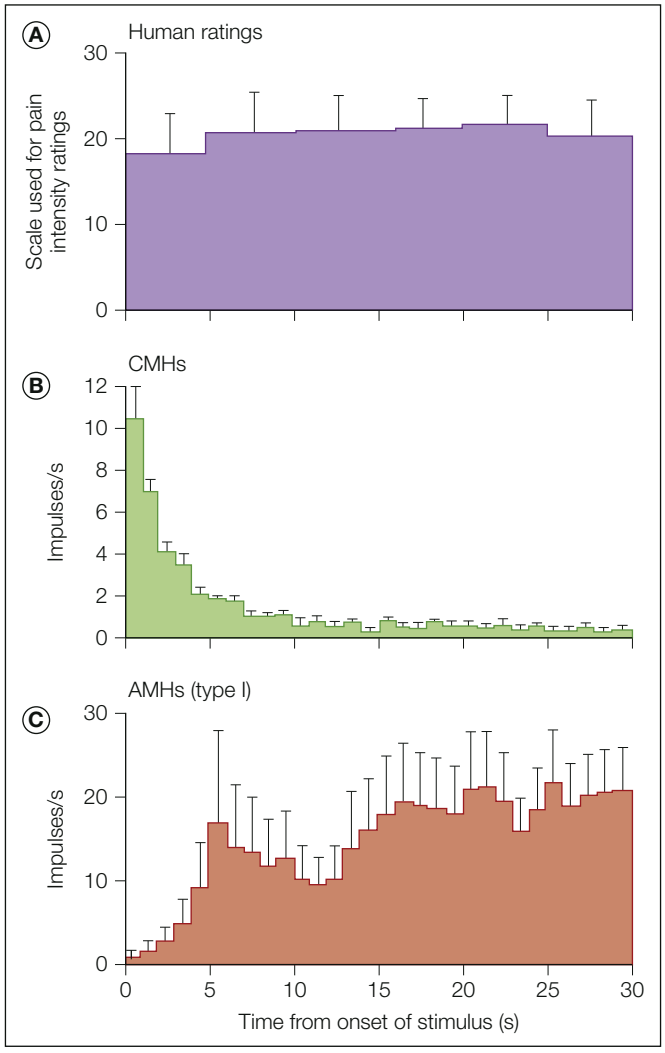

Figure 1-6. Ratings of pain by human subjects during a long-duration, intense heat stimulus (53°C, 30 seconds) applied to the glabrous skin of the hand compared with responses of C-fiber mechano-heat–sensitive nociceptors (CMHs) and type I A-fiber mechano-heat–sensitive nociceptors (AMHs). **A,** Pain was intense throughout the stimulus. **B,** The brisk response of CMHs at the beginning of the stimulus changed to a low rate of discharge after 5 seconds. **C,** The response of AMHs increased during the first 5 seconds and remained high throughout the stimulus. *(Reprinted with permission from Meyer RA, Campbell JN 1981 Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. Science 213:1527–1529.)*

In hairy skin, stepped heat stimuli evoke a double pain sensation (Lewis and Pochin 1937). The first perception is a sharp pricking sensation, and the second sensation is a burning feeling that occurs after a momentary lull during which little if anything is felt. Myelinated afferent fibers must signal the first pain since the latency of response to the first pain is too small to be carried by C fibers (Campbell and LaMotte 1983). Type II A-fiber nociceptors (see Fig. 1-3) are ideally suited to signal this first pain sensation: (1) the thermal threshold is near the threshold temperature for the first pain (Dubner et al 1977), (2) the receptor utilization time (time between onset of the stimulus and activation of the receptor) is short (Treede et al 1998), and (3) the burst of activity at the onset of the heat stimulus is consistent with the perception of a momentary pricking sensation. The absence of a first pain sensation to heat stimuli applied to the glabrous skin of the human hand correlates with the failure to find type II A-fiber nociceptors on the glabrous skin of the hand in the monkey.

The preceding discussion indicates that nociceptors may signal pain in response to heat stimuli. However, two caveats are in order: (1) This does not mean that activity in nociceptors always signals pain. It is clear that low-level discharge rates in nociceptors do not always lead to sensation (e.g., Van Hees and Gybels 1981, Cervero et al 1993). Central mechanisms, including attentional and emotional states, quite obviously play a crucial role in whether and how much nociceptor activity leads to the perception of pain. (2) It is probable that receptors other than nociceptors signal pain in certain circumstances. For example, the pain in response to light touch that occurs after certain nerve injuries or with tissue injury appears to be signaled by activity in low-threshold mechanoreceptors (see below).

Nociceptors and Pain in Response to Controlled Mechanical Stimuli

A-Fiber Nociceptors Signal Sharp Pain

A-fiber and C-fiber MSAs respond well to punctate mechanical stimuli. When a controlled-force stimulus is applied to the receptive field, the response is greatest at the onset of the stimulus and then slowly adapts. Like heat, repeated presentations of a mechanical stimulus lead to pronounced fatigue. A-fiber nociceptors recover faster from fatigue than do C-fiber nociceptors (Fig. 1-7).

Much has been learned about the features of a mechanical stimulus that determine the response of nociceptors to mechanical stimuli. The discharge of nociceptors increases with increased force and pressure, but these functions vary depending on probe size: the smaller the probe, the greater the response (Garell et al 1996). For cylindrical probes of different diameter, the discharges are comparable if the intensity of the stimulus is calculated according to force per length of the perimeter of the cylindrical probe. This suggests that the stress/strain maximum that occurs at the edge of the cylindrical stimulus is the critical parameter for excitation of nociceptor terminals.

For a given probe size, the response of A-fiber nociceptors increases monotonically with force, whereas the response of C-fiber nociceptors becomes saturated at higher force levels (Fig. 1-8A; Slugg et al 2000). In general, the discharge in A fibers is greater than that in C fibers.

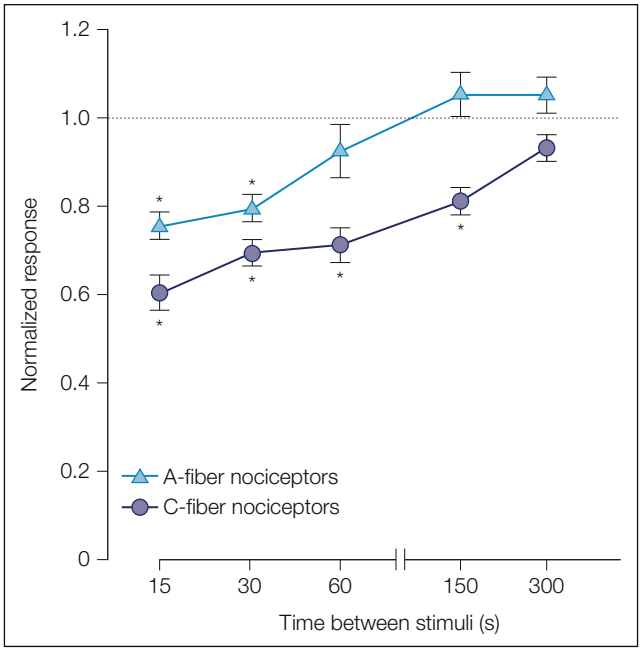

Figure 1-7. A-fiber nociceptors recover faster from fatigue than do C-fiber nociceptors. Mechanical stimuli were presented to the receptive field of A-fiber and C-fiber nociceptors at different interstimulus intervals (with 10 minutes between stimulus pairs). The A-fiber response (triangles) recovered within 60 seconds, whereas the C-fiber response (circles) took more than 150 seconds to recover. To normalize the data, the response to the test stimulus was divided by the response to the immediately preceding conditioning stimulus. *(Adapted from Slugg RM, Meyer RA, Campbell JN 2000 Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. Journal of Neurophysiology 83:2179–2191.)*

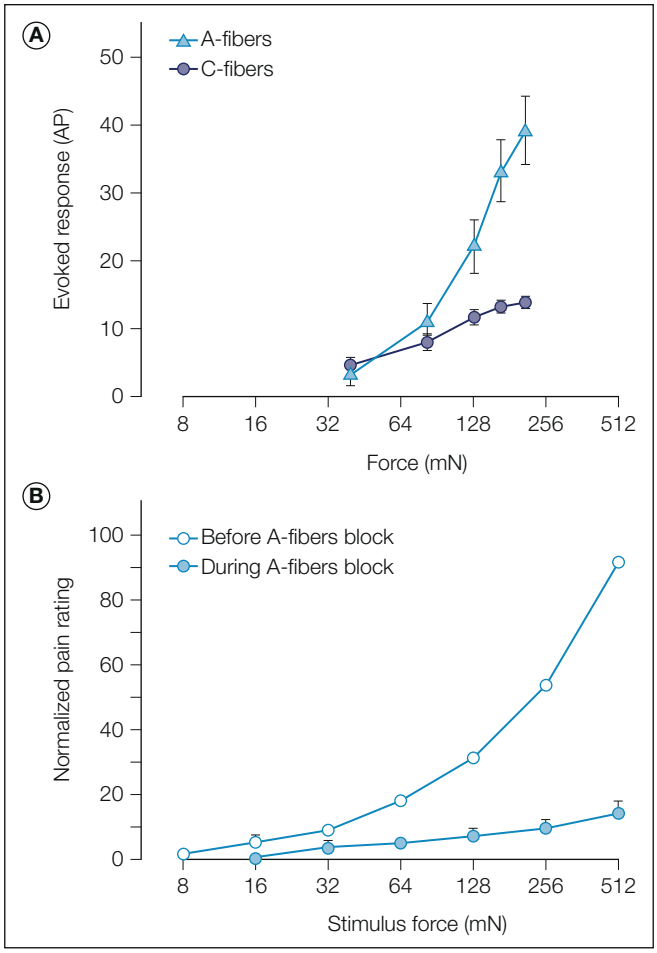

Figure 1-8. Comparison of responses of nociceptors to mechanical stimuli in the monkey with pain ratings in human subjects. These data provide evidence that A-fiber nociceptors signal the pain reported from sharp probes. **A,** Average responses of A-fiber nociceptors (triangles) and C-fiber nociceptors (circles) to controlled-force stimuli. The A fibers exhibited a monotonically increasing response, whereas the response of the C fibers reached a plateau at the higher force levels (0.4-mm-diameter cylindrical probes; the total response to a stimulus 3 seconds in duration is plotted). **B,** Average pain ratings in response to controlled-force stimuli (open circle) increased monotonically in a manner comparable to that observed for the A-fiber nociceptors. Selective block of A-fiber function led to a significant decrease in pain ratings (filled circles). All pain ratings for a given subject were normalized by dividing by that subject's average rating of the maximum stimulus (0.2-mm-diameter cylindrical probes, stimulus duration of 1 second). *(**A**, Adapted from Slugg RM, Meyer RA, Campbell JN 2000 Response of cutaneous A- and C-fiber nociceptors in the monkey to controlled-force stimuli. Journal of Neurophysiology 83:2179–2191; **B**, adapted from Magerl W, Fuchs PN, Meyer RA, et al 2001 Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. Brain 124:1754–1764.)*

The area of the receptive field that responds to mechanical stimuli also responds to heat stimuli (Treede et al 1990). However, the transducer elements that account for mechanosensitivity are probably different from those responsible for heat. For example, the heat response of nociceptors is readily sensitized by a heat injury, whereas the mechanical response is not (see below).

A-fiber nociceptors appear to be responsible for the sharp pain reported in response to punctate mechanical stimuli: (1) the reaction time to perception of pain is short, (2) the stimulus–response function of A-fiber nociceptors (Fig. 1-8A) is comparable to the pain ratings of human subjects (Fig. 1-8B) over a similar force range, and (3) the pain in response to sharp probes is dramatically reduced during selective blockade of A-fiber function (Fig. 1-8B; Magerl et al 2001).

Pretreatment of the skin with capsaicin abolishes heat pain sensitivity but does not greatly affect mechanical pain (Magerl et al 2001). This suggests that the A-fibers involved in sharp pain are capsaicin insensitive; they could be type I AMHs or HTMs.

C-Fiber MIAs Signal Pain in Response to Tonic Pressure

When long-duration mechanical stimuli are applied to human subjects, the pain increases throughout the stimulus (Adriaensen et al 1984). However, the response of MSAs to long-duration suprathreshold stimuli adapts with time. Although C-fiber MIAs are, by definition, normally insensitive to mechanical stimuli, they develop a response to prolonged mechanical stimulation (Schmidt et al 2000). In addition, the pain associated with a tonic stimulus persists through selective A-fiber blockade (Andrew and Greenspan 1999b). Thus it appears that C-fiber MIAs signal the pain associated with tonic pressure.

Nociceptors and Cold Pain Sensation

Cold pain differs from heat pain in a number of important factors: (1) the cold pain threshold (≈14°C on hairy skin; Harrison and Davis 1999) is much farther from resting skin temperature (33°C) than the heat pain threshold (about 45°C), (2) the slope of the stimulus–response function is much steeper for heat pain than for cold pain (Morin and Bushnell 1998), and (3) the lag

in response between stimulus onset and pain report suggests that cold pain is subserved by deeper receptors whereas heat pain seems to be subserved by superficial receptors. Klement and Arndt (1992) demonstrated that cold pain could be evoked by cold stimuli applied within the veins of human subjects. A local anesthetic applied within the vein, but not in the overlying skin, abolished cold pain sensibility. It is therefore possible that cold pain is served, at least in part, by vascular receptors.

Just as the sensation of warmth is served by a specific set of primary afferents (predominantly C fibers), the sense of cooling is served by a specific set of primary afferents (i.e., cold fibers). Cold fibers are predominantly of the A type. They exhibit ongoing activity at room temperature, and their response increases markedly with gentle cooling. Stimuli that induce cold pain are not encoded well by these cold fibers. Although the majority of nociceptors have some response to ice stimuli applied to the skin, Simone and Kajander (1997) showed that all A-fiber nociceptors respond to cold stimuli below 0°C. C-fiber nociceptors may play a role in signaling cold pain sensation as well (LaMotte and Thalhammer 1982). A non-selective cation channel has been identified (called ANKTM1 or transient receptor potential ankyrin 1 [TRPA1]) that has an activation threshold (17.5°C) comparable to the cold pain threshold (Story et al 2003). This channel is found in a subset of nociceptive sensory neurons that are responsive to intense heat and capsaicin. However, the role of TRPA1 in mediating noxious cold is still debated.

Nociceptors and Chemically Evoked Sensations

Many chemical agents produce pain when applied to the skin. In many cases the pain from these agents probably results from tissue injury and is therefore indirect. (Chemical mediators associated with inflammation are described later.) One exception that has received a lot of attention is capsaicin. Intradermal injection of capsaicin produces intense burning pain that lasts for several minutes. When capsaicin is injected into the receptive field of C-fiber MSAs, the response is weak (relative to the heat response) and of short duration (Baumann et al 1991). In contrast, A-fiber and C-fiber MIAs exhibit a long-lasting, vigorous response to capsaicin (Schmelz et al 2000b, Ringkamp et al 2001), thus suggesting that these fibers are responsible for the pain induced by capsaicin. The pungent effects of capsaicin appear to be mediated by the TRPV1 receptor expressed on nociceptive fibers. This receptor appears to be activated by heat and protons (acid) as well.

Another chemical of interest is histamine, which produces a long-lasting itch when applied to the skin. Injection of histamine into the receptive field of C-fiber MSAs leads to a lasting response (Johanek et al 2008). Iontophoresis of histamine into the receptive field of a subpopulation of C-fiber MIAs also produces a vigorous, long-lasting response (Schmelz et al 1997), which suggests that both CMHs and C-fiber MIAs may play a role in histamine-induced itch. Histamine probably activates nociceptors via the H_1 receptor located on peripheral terminals.

Because cowhage spicules produce an intense itch that is not blocked by topical antihistamines (Johanek et al 2008), and they provide a useful tool to investigate the chronic itch in patients that is resistant to antihistamine treatment. In about half of normal subjects, cowhage-induced itch is greatly attenuated during selective blockade of myelinated fibers. Although C-fiber MIAs do not respond to cowhage, QC fibers and A-fiber nociceptors respond vigorously to cowhage (Ringkamp et al 2011). The active ingredient in cowhage is the cysteine protease mucunain, which activates nociceptive terminals via protease-activated receptor 2 (PAR-2) and PAR-4 (Reddy et al 2008).

HYPERALGESIA: ROLE OF NOCICEPTORS AND OTHER AFFERENT FIBERS

To understand the peripheral neural mechanisms of pain induced by noxious stimuli is to understand only one aspect of pain sensibility. There is, in fact, a dynamic plasticity that relates stimulus intensity and sensation. Of great biological importance in this regard is the phenomenon of hyperalgesia. Hyperalgesia is defined as a leftward shift of the stimulus–response function that relates the magnitude of pain to stimulus intensity. An example of this is seen in Figure 1-9A, which shows human judgments of pain induced by heat stimuli before and after a burn. It is evident that the threshold for pain is lowered and pain in response to suprathreshold stimuli is enhanced.

Hyperalgesia is a consistent feature of somatic and visceral tissue injury and inflammation. Pharyngitis is associated with hyperalgesia in pharyngeal tissues such that merely swallowing induces pain. Micturition in the presence of a urinary tract infection is painful, again reflecting the presence of hyperalgesia. In arthritis, slight motion of the joint results in pain. A sunburn leads to pain with light touch and gentle heating.

The peripheral neural mechanisms of hyperalgesia have been studied in various tissues, including the joints, cornea, testicle, gastrointestinal tract, and bladder. Much of the theoretical work on hyperalgesia, however, has evolved from studies of the skin, and it is this work that will receive attention here.

Hyperalgesia occurs not only at the site of injury but also in the surrounding uninjured area. Hyperalgesia at the site of injury is termed *primary hyperalgesia*, whereas hyperalgesia in the uninjured skin surrounding the injury is termed *secondary hyperalgesia* (Lewis 1935). Hyperalgesia exemplifies the functional plasticity of the nervous system. As we will see, the neural mechanisms for primary and secondary hyperalgesia differ.

In discussing hyperalgesia, it is useful to consider the following variables: (1) energy form of the injury, (2) type of tissue involved, (3) energy form of the test stimulus, and (4) location of the testing relative to the area injured. These variables interact in complex ways. For example, it will be shown that nociceptors will become sensitized to mechanical stimuli (the energy form of the test stimulus), but only after certain forms of injury (i.e., injection of inflammatory mediators).

An experimental design frequently used for study of the neural mechanisms of hyperalgesia is to characterize the response properties of a given fiber, then apply a manipulation that under usual circumstances would produce hyperalgesia, and finally assess whether this manipulation has altered the response properties of the fiber in question. Cutaneous hyperalgesia has been studied after thermal injury (burn or freeze lesions), after local administration of chemicals (e.g., capsaicin, mustard oil, or menthol), after a mechanical injury to the skin (e.g., incision, crushing), and after exposure to ultraviolet radiation. The main features of the hyperalgesia that develops after these various injuries are quite similar.

As shown in Figure 1-10, the relative locations of the injury site, the test site, and the receptive field of the sensory neuron

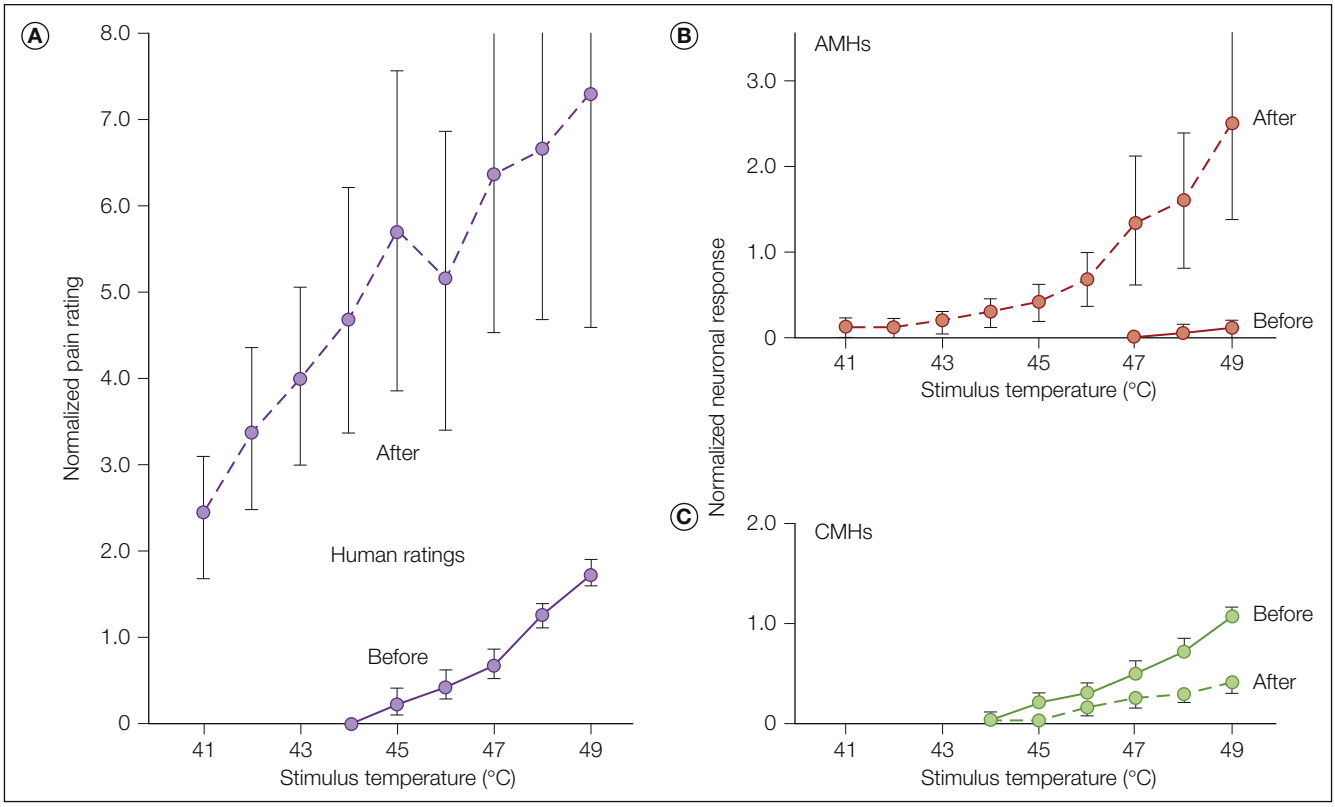

Figure 1-9. Hyperalgesia and nociceptor sensitization after a cutaneous burn injury. Responses to heat stimuli were obtained 5 minutes before and 10 minutes after a 53°C, 30-second burn on the glabrous skin of the hand. The burn resulted in increases in the magnitude of pain (hyperalgesia) in human subjects that were matched by enhanced responses (sensitization) in type I A-fiber mechano-heat–sensitive nociceptors (AMHs) in the monkey. In contrast, C-fiber mechano-heat–sensitive nociceptors (CMHs) exhibited decreased sensitivity after the burn. **A,** Human judgments of pain. **B,** Responses of type I AMHs in the monkey. **C,** Responses of CMHs in the monkey. The same type of random heat sequence and normalization described in Figure 1-5 was used. Because the AMHs did not respond to the 45°C stimulus before the burn, the AMH data were normalized by dividing by the response to the first 45°C stimulus after the burn. *(Reprinted with permission from Meyer RA, Campbell JN 1981 Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. Science 213:1527–1529.)*

being studied dictate whether the experiment provides information regarding the mechanisms of primary or secondary hyperalgesia (Treede et al 1992). These three variables may interact in any of six ways. As shown in Figure 1-10, when the injury and the test site coincide (Fig. 1-10A and B), the study has provided a basis by which to consider the mechanism of primary hyperalgesia, whereas when the test site and the injury site diverge (Fig. 1-10C–F), the study has provided a basis by which to account for secondary hyperalgesia.

When the paradigms shown in Figure 1-10A and B are used, it is found that under certain circumstances, nociceptors exhibit an increased response to the test stimulus. Thus, peripheral neural mechanisms are likely to account for at least some aspects of primary hyperalgesia. In contrast, primary afferent nociceptors do not develop an enhanced response to the test stimulus when the paradigms shown in Figure 1-10C–F are investigated. By default, therefore, the mechanism for secondary hyperalgesia must reside within the CNS.

PRIMARY HYPERALGESIA

Hyperalgesia to Heat Stimuli

We first consider the situation in which a burn injury is applied to the skin and the test stimulus is heat applied to the location of the burn injury. When a burn is applied to the glabrous skin of the hand, marked hyperalgesia to heat develops as shown in Figure 1-9A (Meyer and Campbell 1981a). The hyperalgesia is manifested as a leftward shift of the stimulus–response function that relates the magnitude of pain to stimulus intensity. For example, the 41°C stimulus was not painful before the burn but after the injury was as painful as the 49°C stimulus before the injury.

Peripheral Sensitization as a Mechanism for Primary Hyperalgesia to Heat Stimuli

Substantial evidence favors the concept that the primary hyperalgesia to heat stimuli that develops at the site of a burn injury is mediated by sensitization of nociceptors (Meyer and Campbell 1981a, LaMotte et al 1982). Sensitization is defined as a leftward shift of the stimulus–response function that relates the magnitude of the neural response to stimulus intensity. Sensitization is characterized by a decrease in threshold, an augmented response to suprathreshold stimuli, and ongoing spontaneous activity. These properties correspond to the properties of hyperalgesia (Table 1-2).

To explain the hyperalgesia that occurs with a burn on the glabrous skin of the hand, a correlative analysis of subjective ratings of pain in humans with responses of nociceptors (CMHs and type I AMHs) in anesthetized monkeys was

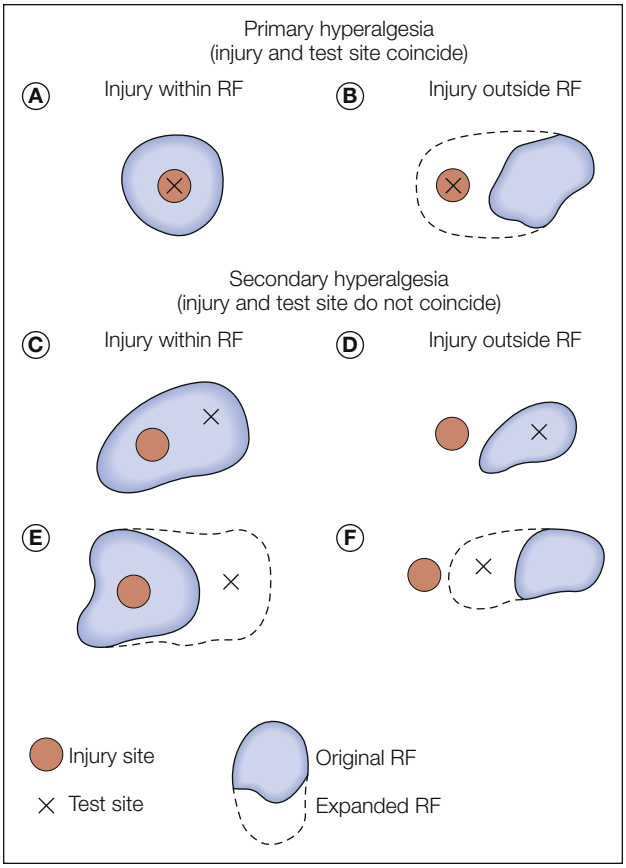

Figure 1-10. Experimental configurations for testing the neural mechanisms of primary and secondary hyperalgesia. To study primary hyperalgesia, the site of injury (indicated by filled circles) and the site of testing (indicated by the X's) must coincide. Alterations in the stimulus–response function from stimuli applied to the original receptive field (RF) (**A**) and expansion of the RF toward the injury site (**B**) are substrates for primary hyperalgesia. To study secondary hyperalgesia, the site of injury and the site of testing must not coincide (**C** and **D**). Sensitization of the stimulus–response function as revealed by testing within the original RF may occur following injuries within (**C**) or outside the RF (**D**). Expansion of the RF to include a test site outside the original RF may occur for injuries within (**E**) or outside (**D**) the RF. *(Reprinted from Treede RD, Meyer RA, Raja SN, et al 1992 Peripheral and central mechanisms of cutaneous hyperalgesia. Progress in Neurobiology 38:397–421. Copyright 1992, with permission from Elsevier.)*

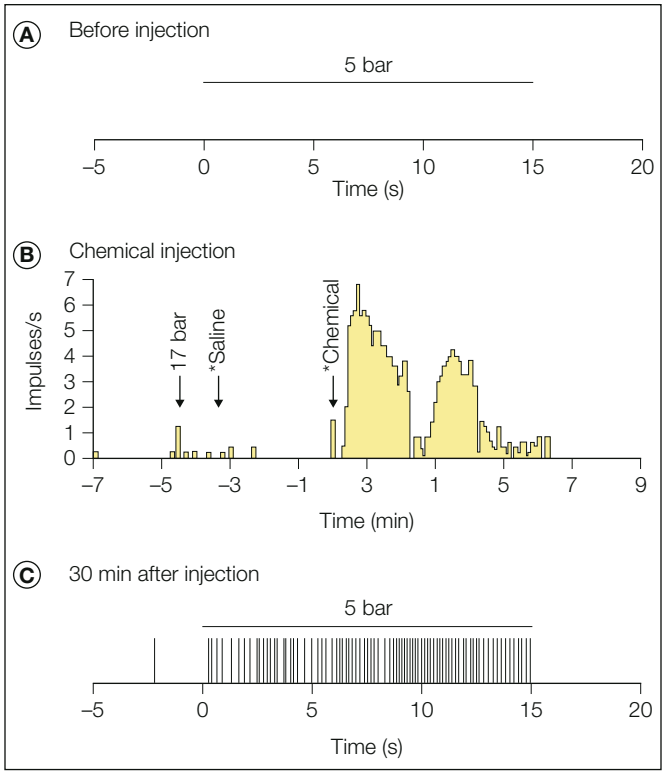

Figure 1-11. Example of sensitization to mechanical stimuli for an Aδ-fiber nociceptor following a chemical injection. **A,** The fiber did not respond to the application of a 5-bar stimulus for 15 seconds to the most sensitive area within its receptive field. The initial mechanical threshold for this fiber was 10 bar, and therefore it was a mechanically insensitive afferent (MIA). **B,** This MIA responded vigorously to a 10-μL intradermal injection of a chemical mixture containing 10 nmol bradykinin, 0.3 nmol prostaglandin E_1, 30 nmol serotonin, and 30 nmol histamine. (Each asterisk indicates the time of needle insertion; bin size = 5 seconds). **C,** Sensitization to mechanical stimuli was demonstrated in this fiber 30 minutes after chemical injection. The fiber now responded to application of the 5-bar stimulus. Each vertical tic corresponds to the time of occurrence of an action potential. The von Frey threshold decreased (from 10 to 4 bar), and the receptive field area increased (from 9 to 88 mm^2). No response to heat was observed either before or after the injection. *(Reproduced with permission from Davis KD, Meyer RA, Campbell JN 1993 Chemosensitivity and sensitization of nociceptive afferents that innervate the hairy skin of monkey. Journal of Neurophysiology 69:1071–1081.)*

Table 1-2 Comparison of Characteristics of Hyperalgesia and Sensitization

HYPERALGESIA (SUBJECT RESPONSE)	SENSITIZATION (FIBER RESPONSE)
Decreased pain threshold	Decreased threshold for response
Increased pain in response to suprathreshold stimuli	Increased response to suprathreshold stimuli
Spontaneous pain	Spontaneous activity

performed (Meyer and Campbell 1981a). Test heat stimuli were applied to the glabrous skin of the hand before and after a 53°C, 30-second burn. The burn led to prominent hyperalgesia in the human subjects (Fig. 1-9A). The CMHs showed a decreased response following the burn (Fig. 1-9C), whereas the type I AMHs were markedly sensitized (Fig. 1-9B). Thus, it is likely that for thermal injuries on the glabrous skin of the hand, AMHs, not CMHs, code for the heat hyperalgesia.

Sensitization is not a uniform property of nociceptors. Tissue type and the nature of the injury are important variables. For example, CMHs that innervate hairy skin become sensitized, whereas as described above, CMHs that innervate the glabrous skin of the hand do not become sensitized to a burn injury (Campbell and Meyer 1983). Thus, CMHs appear to play a role in accounting for hyperalgesia to heat stimuli on hairy skin (LaMotte et al 1983). These data support the conclusion that the hyperalgesia to heat stimuli that occurs at the site of an injury is due to sensitization of primary afferent nociceptors.

Hyperalgesia to Mechanical Stimuli

Distinguishing hyperalgesia to mechanical stimuli in the primary and secondary zones may be incorrect in some respects since the mechanism for hyperalgesia in the two zones may have some common elements. The mechanisms discussed in this section, however, will be limited to those applicable to the primary zone.

Different forms of mechanical hyperalgesia have been characterized. One form is evident when the skin is gently stroked with a cotton swab and is referred to as "stroking hyperalgesia," "dynamic hyperalgesia," or "allodynia." The second form of hyperalgesia is evident when punctate stimuli, such as von Frey probes, are applied and, accordingly, has been termed "punctate hyperalgesia." Hyperalgesia to tonic stimulation with a blunt probe, called "pressure hyperalgesia," and impact hyperalgesia to shooting small bullets against the skin at a controlled velocity have also been described in the primary hyperalgesic zone (Kilo et al 1994). As discussed in the later section on secondary hyperalgesia, the mechanism for these different forms of mechanical hyperalgesia is probably different. Stroking hyperalgesia is thought to be signaled by low-threshold mechanoreceptors, whereas punctate hyperalgesia is mediated at least in part by nociceptors. Pressure hyperalgesia and impact hyperalgesia are probably mediated by sensitized C fibers. Another form of mechanical hyperalgesia termed "progressive tactile hypersensitivity," which may contribute to the allodynia associated with inflammation, has been described (Ma and Woolf 1997).

Nociceptor Sensitization as a Mechanism for Mechanical Hyperalgesia in the Primary Zone

Primary hyperalgesia to mechanical stimuli appears to be due, at least in part, to sensitization of primary afferent nociceptors to mechanical stimuli. This sensitization is manifested in several ways.

Lowered Threshold

Thresholds to mechanical stimulation of either CMHs or AMHs recorded in primates or humans, as measured with von Frey hairs (a punctate stimulus), are not changed by heat and/or mechanical injury (e.g., Thalhammer and LaMotte 1982, Campbell et al 1988a). However, MIAs have been shown to develop mechanical sensitivity after inflammation. Figure 1-11 shows the response of an Aδ-fiber MIA to mechanical stimuli before and after exposure to a mixture of algesic inflammatory mediators (bradykinin, histamine, serotonin, and prostaglandin E_1 [PGE_1]). This MIA was unresponsive to the 5-bar von Frey probe initially, but a robust response to this probe developed after inflammation.

Increased Response to Suprathreshold Stimuli

Although inflammation does not result in a reduction in the mechanical threshold of AMHs and CMHs, responses to suprathreshold stimuli may be augmented (Cooper et al 1991). Inflammation of the rat paw results in an enhanced response to suprathreshold mechanical stimuli, spontaneous activity, and expanded receptor fields for both A- and C-fiber nociceptors (Andrew and Greenspan 1999a).

Expansion of the Receptive Field

The receptive fields of AMH fibers, as well as some CMH fibers, expand modestly into the area of an adjacent heat (Thalhammer and LaMotte 1982) or mechanical (Reeh et al 1987) injury. As a result of this expansion, heat or mechanical stimuli delivered after the injury will activate a greater number of fibers. This spatial summation would be expected to induce more pain.

Loss of Central Inhibition as a Mechanism of Mechanical Hyperalgesia in the Primary Zone

Under usual circumstances, production of pain from activation of nociceptors with mechanical stimuli is inhibited in the CNS by the concurrent activation of low-threshold mechanoreceptors (e.g., Bini et al 1984). There is evidence that injury decreases the responsiveness of low-threshold mechanoreceptors. Hyperalgesia to mechanical stimuli in the primary zone could therefore be due to injury to low-threshold mechanoreceptors, which would lead to central disinhibition of nociceptor input and thus result in enhanced pain (i.e., hyperalgesia).

INFLAMMATORY MEDIATORS AND NOCICEPTORS

Injury results in the local release of numerous chemicals from non-neuronal cells (e.g., fibroblasts, mast cells, neutrophils, monocytes, and platelets), as well as from the sensory terminals of primary afferent fibers that mediate or facilitate the inflammatory process. Inflammatory mediators include prostaglandins, leukotrienes, bradykinin, serotonin, histamine, SP, thromboxanes, platelet-activating factor, purines such as adenosine and ATP, protons, and free radicals (Fig. 1-12, see also Basbaum et al 2009). Cytokines, such as interleukins and tumor necrosis factor, and neurotrophins, especially NGF, are also generated during inflammation. NGF not only is necessary for the survival of nociceptors during development but may also play an important role during inflammatory processes in adult animals. Some of these agents can directly activate nociceptors, whereas others act indirectly via inflammatory cells, which in turn release algogenic agents. Other mediators lead to sensitization of the nociceptor response to natural stimuli and therefore play a role in primary hyperalgesia. The variety of chemical mediators released during inflammation can have a synergistic effect in potentiating nociceptor responses.

A variety of metabotropic and ionotropic receptors, including purinergic and glutamatergic receptors, have been identified on DRG cells and on the peripheral terminals of nociceptive afferent fibers. Activation of these receptors may modulate the sensitivity of peripheral nociceptors to exogenous stimuli (Carlton and Coggeshall 1998).

Arachidonic Acid Metabolites

The prostaglandins, thromboxanes, and leukotrienes are a large family of arachidonic acid metabolites collectively known as eicosanoids. The eicosanoids are generally considered to not activate nociceptors directly but rather enhance the sensation of pain in response to natural stimuli and other endogenous chemicals by increasing the frequency of action potential firing (for reviews see Schaible et al 2002, Cunha and Ferreira 2003, Momin and McNaughton 2009). A sensitizing and direct excitatory effect of PGE_2 and PGI_2, however, has been demonstrated in afferents innervating joints. Prostaglandins are synthesized by the constitutive enzyme cyclooxygenase-1 (Cox-1) and by Cox-2, an enzyme induced in peripheral tissues by inflammation (Ballou et al 2000). Several prostaglandins, PGI_2, PGE_1, PGE_2, and PGD_2, are considered to play a role in inflammatory pain and hyperalgesia. Prostaglandins reduce the threshold for initiation

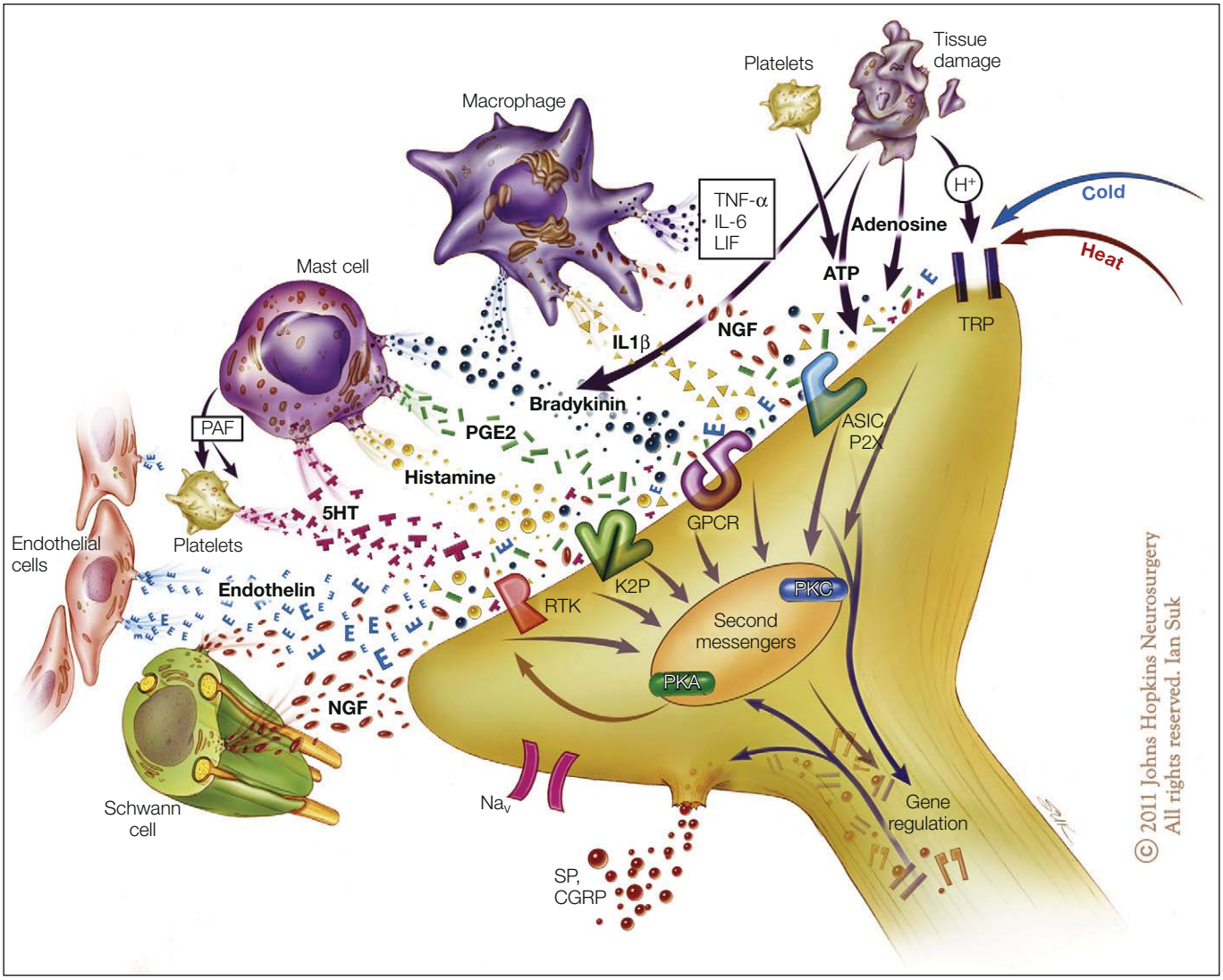

Figure 1-12. Potential mediators of peripheral sensitization after inflammation. Tissue injury and inflammation lead to the release of numerous chemicals from non-neuronal and neuronal cells, such as mast cells, macrophages, platelets, immune and endothelial cells, Schwann cells, keratinocytes, fibroblasts, and peripheral nociceptor terminals. Mediators released include protons (H^+), purines (adenosine, adenosine triphosphate), nerve growth factor (NGF), cytokines such as tumor necrosis factor (TNF-α) and interleukins (IL-1β, IL-6), leukemia inhibitory factor (LIF), prostaglandin E_2 (PGE_2), bradykinin, histamine, serotonin (5-HT), platelet activating factor (PAF), and endothelin. These mediators may act directly to alter the sensitivity of peripheral nociceptors or indirectly via coupling to one or more peripheral membrane-bound receptors, including transient receptor potential (TRP) channels, acid-sensitive ion channels (ASICs), purinergic (P2X) receptors, G protein–coupled receptors (GPCRs), two-pore potassium channels (K_{2P}), and receptor tyrosine kinase (RTK). Binding of the ligands to these receptors can initiate a cascade of events that includes activation of second-messenger systems (protein kinase A [PKA] and C [PKC]) and alteration of gene regulation. *(Artwork by Ian Suk, Johns Hopkins University; adapted from Woolf CJ, Costigan M 1999 Transcriptional and posttranslational plasticity and the generation of inflammatory pain. Proceedings of the National Academy of Sciences of the United States of America 96:7723–7730.)*

of action potentials and increase the excitability of sensory neurons by decreasing the threshold for activation of a nociceptor-specific voltage-activated Na current, $Na_v1.8$, and increasing intracellular cyclic adenosine monophosphate (cAMP) levels (England et al 1996, Gold et al 1996). The prostaglandin-induced increase in firing frequency may also result from an increase in the hyperpolarization-activated current (Ih), which leads to faster depolarization toward the action potential threshold, the consequence of which is a decrease in the time interval between successive action potentials (Momin and McNaughton 2009). Of the leukotrienes (metabolites of the lipoxygenase pathway), LTD_4 and LTB_4 have been suggested to play a role in hyperalgesia (Levine et al 1984) and in sensitization to mechanical stimuli (Martin et al 1987).

Bradykinin

Several lines of evidence suggest that bradykinin may also play a critical role in inflammatory pain and hyperalgesia (see Couture et al 2001, Meini and Maggi 2008 for reviews). Bradykinin is released on tissue injury (e.g., from plasma), is present in inflammatory exudates, and excites and sensitizes unmyelinated and myelinated nociceptors to natural stimuli (Beck and Handwerker 1974, Khan et al 1992). Administration of exogenous bradykinin produces pain and

transient hyperalgesia to heat in humans (Manning et al 1991). Bradykinin acts on B_1 and B_2 receptors to induce nociceptor sensitization by activation of phospholipase C (PLC) and protein kinase C (PKC), production of arachidonic acids, and modulation of the TRPV1 channel (see the section on the vanilloid receptor below) (Reeh and Sauer 1997, Banik et al 2001).

Protons

The low pH levels found in inflamed tissue have led to the hypothesis that local acidosis may contribute to the pain and hyperalgesia associated with inflammation. Continuous administration of low-pH solutions in humans causes pain and hyperalgesia to mechanical stimuli (Steen and Reeh 1993). This correlates with the observation that protons selectively activate nociceptors and produce sensitization of nociceptors to mechanical stimuli. Excitation of nociceptors by protons does not undergo tachyphylaxis or adaptation, and a synergistic excitatory effect of protons and a combination of inflammatory mediators has been reported (Steen et al 1996).

A class of acid-sensing ion channels (ASICs), a subgroup of the degenerin/epithelial sodium channel (DEG/ENaC) family of proteins, has emerged as sensors of low pH (see Holzer 2009, Sluka et al 2009 for review). ASICs signal moderate decreases in extracellular pH, in contrast to TRPV1, which is activated by severe acidosis (pH values below 6). ASIC1A and ASIC3 have been identified in DRG neurons, and their expression is increased by inflammation, nerve injury, and bone cancer, thus suggesting that ASICs may play a role in mediating or modulating pain in these conditions. The observation that a non-selective ASIC inhibitor, amiloride, reduces cutaneous acid-evoked pain in humans suggests that ASICs may be a potential therapeutic target for inflammatory pain (Ugawa et al 2002).

Serotonin

Mast cells, on degranulation, release platelet-activating factor, which in turn leads to the release of serotonin (5-hydroxytryptamine [5-HT]) from platelets. Serotonin causes pain when applied to a human blister base (Richardson and Engel 1986) and can activate nociceptors (Lang et al 1990). Serotonin can also potentiate the pain induced by bradykinin and enhance the response of nociceptors to bradykinin. Additional evidence for a role of 5-HT in nociception stems from observations that 40% of lumbar DRG neurons, mostly small to medium-sized cells, are immunoreactive for the 5-HT_{2A} receptor and many of these cells also express the TRPV1 receptor (Van Steenwinckel et al 2009).

Histamine

Release of SP from nociceptor terminals can cause the release of histamine from mast cells. Histamine can lead to a variety of responses, including vasodilatation and edema. The role of histamine in pain sensation is less clear since application of exogenous histamine to the skin produces itch and not pain sensations (Simone et al 1991a). Histamine excites polymodal visceral nociceptors, especially when applied in high concentrations (Koda et al 1996), and potentiates the responses of nociceptors to bradykinin and heat (Mizumura et al 1995). Mechanosensitive cutaneous nociceptors in rats and humans respond only weakly to histamine (Lang et al 1990), but a subpopulation of mechano-insensitive C fibers was vigorously excited by histamine (Schmelz et al 1997). Activation of histamine H_3 receptors, a ligand-gated ion channel that modulates the influx of Na^+, however, leads to decreased release of inflammatory peptides and reduced pain and inflammation (Cannon et al 2007).

Purines

During inflammation and tissue injury, purines such as adenosine and its mono- or polyphosphate derivatives (AMP, ADP, ATP) may be released or leak into the extracellular space and activate nociceptors (for review see Burnstock 2009). Platelets are a rich source of ATP, and aggregation of platelets or lysis of cells can lead to release of ATP. Adenosine and its phosphates have been reported to induce pain in a human blister base. Intra-arterial or intradermal injection of adenosine also causes pain, and intravenous/intracoronary infusion of adenosine induces angina-like symptoms (Sylvén et al 1986). In animals, adenosine enhances the response to formalin, presumably via the A_2 receptor. Animals lacking the adenosine A_{2a} receptor are hypoalgesic to heat stimuli (Ledent et al 1997).

A number of lines of evidence support the potential role of ATP as a peripheral mediator of pain. ATP is found at increased levels at sites of inflammation and can activate nociceptors. Psychophysical studies in humans indicate that iontophoresis of ATP into normal skin results in dose-related pain. ATP-induced pain is dependent on capsaicin-sensitive neurons; repeated topical application of capsaicin reduces the ATP-induced pain to 25% of normal. In addition, the ATP-induced pain is increased two- to three-fold when iontophoresed into skin made hyperalgesic by acute capsaicin treatment or by ultraviolet inflammation. Thus, in inflammatory conditions ATP may activate nociceptors and serve as an endogenous mediator of pain (Hamilton et al 2000). In human microneurographic studies, injection of ATP activated 60% of mechano-responsive and mechano-insensitive C-nociceptive fibers without sensitizing these fibers to mechanical or heat stimuli (Hilliges et al 2002).

Receptors for ATP have been found on primary sensory neurons both in the DRG and in the periphery. Multiple purinergic (P2) receptors have been suggested to be involved in pain signaling and modulation. ATP presumably activates nociceptive neurons in normal skin via the $P2X_3$ receptor and the heteromeric $P2X_2/P2X_3$ receptor (Chen et al 1995, Lewis et al 1995, Cook et al 1997). Messenger RNA for most of the P2X receptors (1–6) has been found in DRG neurons. In particular, both mRNA for the $P2X_3$ receptor and the receptor protein itself have been found in small-diameter neurons in the DRG. Local intradermal injection of agents activating P2X receptors results in dose-related pain behavior in rodents that is mediated by capsaicin-sensitive neurons (Bland-Ward and Humphrey 1997) and enhanced pain behavior in response to formalin (Sawynok and Reid, 1997). The proportion of C-fiber nociceptors responding and the magnitude of their response are increased by P2X agonists in inflamed skin. Activation of homomeric $P2X_3$ receptors is thought to contribute to acute nociception and

inflammatory pain, whereas activation of heteromeric $P2X_{2/3}$ receptors appears to modulate the longer-lasting nociceptive sensitivity associated with nerve injury or chronic inflammation (Burnstock 2009).

Recently, it has been suggested that peripheral adenosine receptors may also be involved in the modulation of inflammatory pain. A_1 adenosine receptors are expressed in DRG cells, and peripheral activation of these receptors results in a reduction in inflammatory hyperalgesia via interactions with the nitric oxide/cyclic guanosine monophosphate/protein kinase G intracellular signaling pathways (Lima et al 2010).

Cytokines

During inflammation, cytokines (e.g., interleukin-1β [IL-1β], tumor necrosis factor α [TNF-α], IL-6) are released by a variety of cells (e.g., macrophages, Schwann cells) and regulate the inflammatory response (see Miller et al 2009, Schaible 2010). Clinical studies have shown that TNF-α levels in synovial fluid are increased in painful joints (Shafer et al 1994). Treatment with antibodies against TNF-α has been reported to improve the symptoms accompanying rheumatoid arthritis, including pain (Elliott et al 1994). Studies in animals have demonstrated mechanical and thermal hyperalgesia after systemic or local injection of IL-1, IL-6, and TNF-α. Additionally, treatment with antiserum against TNF-α is able to inhibit or delay the onset of hyperalgesia in experimental models of inflammation (Woolf et al 1997).

Cytokines may excite nociceptors either by rapid alterations in the properties of ion channels expressed in sensory neurons; indirectly by stimulating the release of other mediators such as prostaglandins, neurotrophins, and ATP; and by longer-term changes resulting from new gene transcription. Direct excitation and sensitization of nociceptive afferent fibers to thermal and mechanical stimuli have been shown for IL-1β and TNF-α (Fukuoka et al 1994). When applied along a peripheral nerve, TNF-α induces ectopic activity in nociceptive afferent fibers (Sorkin et al 1997).

IL-6 in combination with its soluble IL-6 receptor can sensitize nociceptors to heat as evidenced by increased heat-evoked intradermal release of CGRP (Obreja et al 2002). Other cytokines, IL-1β and TNF-α, also produce transient sensitization of heat-evoked release of CGRP from nociceptors in rat skin (Oprée and Kress 2000). IL-6–deficient mice show reduced mechanical and thermal hyperalgesia following inflammation (Xu et al 1997). These studies provide evidence for a role of cytokines in inflammation-associated hyperalgesia. The sensitization of nociceptors by cytokines may be mediated by p38-induced phosphorylation of TTX-resistant sodium channels, as well as by up-regulation of TRPV1 expression and function (Jin and Gereau 2006; for review see Ma and Quirion 2007).

Excitatory Amino Acids

A number of excitatory amino acids (EAAs) and peptide receptors are present at post-synaptic sites in the dorsal horn. These receptors have been found on DRG cells and the presynaptic terminals of primary afferents and are considered to play a role in the modulation of nociceptive impulses (see Carlton 2001, Goudet et al 2009). The most studied EAA, glutamate, can act either through ligand-gated ion channels (ionotropic glutamate receptors [iGluRs]) or through G protein–coupled metabotropic receptors (mGluRs). Based on sequence homology and physiological and pharmacological properties, the mGluRs have been further divided into three groups—group I (mGluR 1 and 5), group II (mgluR 2 and 3), and group III (mGluR 4, 6, 7, and 8). iGluR, mGluR1, and mGluR5 receptors have been identified on unmyelinated axons in the skin (Bhave et al 2001, Zhou et al 2001). About 40% of lumbar DRG cells contain mGluR2/3 immunoreactivity, and a majority of these cells are $IB4^+$ small cells.

Several lines of evidence indicate a role of peripheral mGluRs in nociception and inflammatory pain. Peripheral application of glutamate activates nociceptors, and peripheral administration of ligands binding to glutamate receptors induces pain behavior in animals. Involvement of peripheral iGluR, mGluR1, and mGluR5 in formalin-induced pain behavior and glutamate-induced thermal hyperalgesia has been demonstrated (Davidson et al 1997). Intraplantar, but not intrathecal or intracerebroventricular administration of an mGluR5 antagonist reduced inflammatory hyperalgesia. Neurons in the DRG can be double-labeled with antisera for mGluR5 and VR1, thus suggesting that mGluR5 is expressed on the peripheral terminals of nociceptive neurons and contributes to inflammatory hyperalgesia (Walker et al 2001). In particular, mGluR1 activates PLC, which leads to release of Ca^{2+} from intracellular stores and activation of PKC.

Endogenous sources of glutamate in the periphery include plasma, macrophages, epithelial and dendritic cells in the epidermis and dermis, and Schwann cells. In addition, peripheral processes of the primary afferents contain glutamate, and nociceptor stimulation can cause peripheral release of glutamate from the terminals of these afferents.

Peripheral mGluRs are also considered to have antinociceptive effects. Peripheral administration of group II mGluR agonists blocks PGE_2-induced thermal hyperalgesia, and activation of these receptors results in depression of the responses of nociceptors sensitized by exposure to formalin or inflammatory soup (Yang and Gereau 2002, Du 2008). These observations suggest that selective group II agonists may be a therapeutic target for inflammatory pain states.

Nerve Growth Factor

NGF may contribute to inflammatory pain via direct and indirect mechanisms (for review see Pezet and McMahon 2006, Watson et al 2008). Pro-inflammatory cytokines stimulate the release of NGF from various sources, including fibroblasts, keratinocytes, Schwann cells, and inflammatory cells (lymphocytes, macrophages, and mast cells). NGF stimulates mast cells to release histamine and serotonin. NGF can also induce heat hyperalgesia by acting directly on the peripheral terminals of primary afferent fibers (Chuang et al 2001). Transgenic animals modified to overexpress NGF show hyperalgesic pain behavior (Davis et al 1993a). NGF sensitizes nociceptors and may alter the distribution of Aδ fibers such that a greater proportion of fibers have nociceptor properties (Stucky et al 1999). NGF has been implicated in the inflammation-induced changes in nociceptor response properties, such as an increase in the incidence of ongoing activity, increase in the maximum fiber following frequency, and changes in the configuration of the action potential of DRG neurons (Djourhi et al 2001). The inflammation-induced changes in nociceptive neurons are

prevented by sequestration of NGF (Koltzenburg et al 1999). Cultured DRG neurons from inflamed animals exhibit spontaneous activity, and cultured DRG neurons from non-inflamed animals exhibit spontaneous activity when cultivated for 1 day with NGF (Kasai and Mizumura 2001). These studies suggest that in inflamed rats NGF may play a role in inducing spontaneous activity in DRG neurons.

NGF modulates the activity of ligand- and voltage-gated ion channels involved in nociception, such as TRPV1, $P2X_3$, ASIC3, and $Na_v1.8$. NGF potentiates responses of the TRPV1 receptor (see the section on the vanilloid receptors), and NGF-induced hyperalgesia is absent in TRPV1 knockout mice (Chuang et al 2001). NGF-induced hyperalgesia may be mediated via its actions on the TTX-resistant sodium channel $Na_v1.8$. NGF-induced thermal hyperalgesia failed to develop in mice with a mutation in the $Na_v1.8$ gene (Kerr at al 2001). Binding of NGF to TrkA stimulates the mitogen-activated protein kinase (MAPK), phosphatidyl-3′-kinase (PI3K), and PLC-γ intracellular signal transduction pathways (for details see Cheng and Ji 2008). Potential clinical therapeutic approaches being explored include humanized monoclonal antibodies to NGF or its tyrosine kinase receptor TrkA and sequestration of NGF via soluble receptor protein that binds NGF.

Other Receptors

A number of other receptor systems have been reported to play a role in the peripheral modulation of nociceptor responsiveness.

Vanilloid Receptors

The vanilloid receptor TRPV1 (also known as VR1) is present on a subpopulation of primary afferent fibers and is activated by capsaicin, heat, and protons (see Chapter 2). Following inflammation, axonal transport of TRPV1 mRNA is induced, the proportion of TRPV1-labeled unmyelinated axons in the periphery is increased by almost 100% (Carlton and Coggeshall 2001), and the sensitivity of DRG neurons and primary afferent fibers to capsaicin increases (Nicholas et al 1999, Tohda et al 2001). Certain inflammatory mediators, such as bradykinin, lower the threshold of TRPV1-mediated heat-induced currents in DRG neurons and increase the proportion of DRG cells that respond to capsaicin (Stucky et al 1998, Sugiura et al 2002). NGF also potentiates the responses of TRPV1, and NGF-induced thermal hyperalgesia is absent in TRPV1 knockout mice. These observations, along with other experiments performed in mice lacking TRPV1, indicate that this channel protein plays a critical role in inflammation-induced heat hyperalgesia (Caterina et al 2000, Davis et al 2000).

Inflammatory mediators activate or sensitize TRPV1 through a diverse array of second-messenger pathways. For example, the thermal hyperalgesia induced by bradykinin and NGF is thought to be mediated, in part, by PLC-dependent phosphorylation of TRPV1 by PKC. Activation of PLC also leads to hydrolysis of the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) and consequent reversal of TRPV1 disinhibition by that lipid (Chuang et al 2001). A PIP_2 binding site that is critical for the thermal sensitivity of TRPV1 has been identified (Prescott and Julius 2003). Functional coupling between protein kinase A (PKA) and TRPV1 also appears to play an important role in inflammatory hyperalgesia (Rathee et al 2002, Distler et al 2003). Finally, some inflammatory mediators activate TRPV1 indirectly via the production of fatty acid agonists (Shin et al 2002). For instance, bradykinin, acting at B_2 receptors, excites cutaneous nociceptors via production of the 12-lipoxygenase metabolite of arachidonic acid 12-hydroperoxyeicosatetraenoic acid (12-HPETE), which in turn acts as a TRPV1 agonist.

Endothelin Receptors

Endothelins are vasoactive peptides that are widely distributed in somatic and visceral tissue (for reviews see Hans et al 2009, Khodorova et al 2009). Endothelin-1 (ET-1) is synthesized and released by endothelial cells, as well as by leukocytes and macrophages, and acts via GPCRs—ET_A and ET_B. ET_A receptors are found in a large proportion of small cells in DRGs. ET_B receptors are expressed mainly in keratinocytes, DRG satellite cells, and Schwann cells and may induce the synthesis and release of PGE_2. Peripheral administration of ET-1 results in hyperalgesia that is attenuated by ET_A antagonists. ET-1 also potentiates the effects of other algogens such as PGE_2, capsaicin, and formalin. Activation of ET_A receptors on neurons results in enhanced function of TRPV1 and TTX-resistant Na channels and an increase in intracellular Ca^{2+} levels, which in turn activates PKC and other second-messenger systems and leads to enhanced excitability of nociceptors. Endothelins have been implicated in the pain and hyperalgesia associated with inflammation, skin incision, cancer, and sickle cell crisis. ET_B receptors have been reported to mediate both pro- and antinociceptive effects. Activation of ET_B receptors on keratinocytes results in the release of β-endorphins, which inhibit nociceptor activity by binding to opioid receptors on the peripheral terminals of nociceptors (Khodorova et al 2003).

Peripheral Modulators of Nociceptor Activity

GPCRs, present on the plasma membrane and terminals of nociceptive neurons, play an important role in the modulation of pain signaling. GPCRs involved in antinociceptive mechanisms include opioid, cannabinoid, SST, muscarinic acetylcholine, γ-aminobutyric acid ($GABA_B$), mGlu, and α_2-adrenergic receptors (Fig. 1-13, for review see Pan et al 2008). Most GPCR agonists that have antinociceptive action are coupled to $G_{i/o}$ proteins, which modulate voltage-gated Ca^{2+} channels and result in a decrease in presynaptic Ca^{2+} entry and inhibition of neurotransmitter release. GPCRs also modulate an inwardly rectifying K^+ channel, the GIRK channel, which plays a critical role in maintaining resting membrane potential and excitability.

The GPCRs on peripheral nociceptors are attractive potential therapeutic targets for the development of new drugs that may have some benefit, in contrast to the more traditional analgesics, which work at the level of the CNS. Drugs acting at the periphery and inhibiting the generation and signaling of nociceptive input toward the spinal cord and the brain may prevent central plastic changes such as wind-up and central sensitization. In addition, these drugs may provide analgesia without the undesirable adverse effects, such as sedation, dizziness, and cognitive dysfunction, associated with drugs acting on the CNS system (see Stein et al 2009).

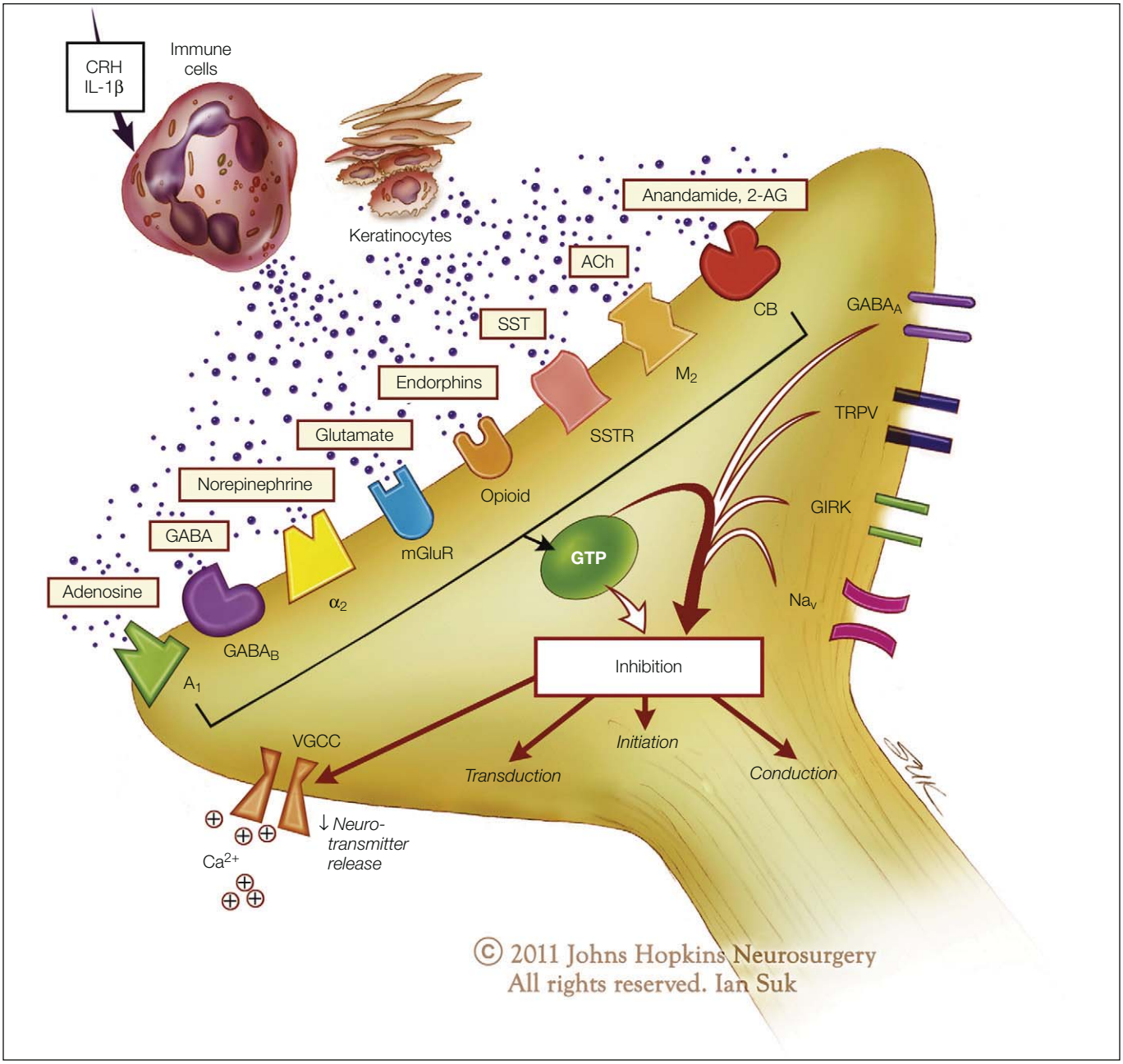

Figure 1-13. Potential peripheral modulatory mechanisms of nociceptor activity. Several metabotropic G protein–coupled receptors (GPCRs) may play a role in inhibition of the initiation, transduction, or conduction of pain signals from peripheral nociceptive terminals. These GCPRs include opioid, cannabinoid (CB), somatostatin (SSTR), muscarinic acetylcholine (M_2), γ-aminobutyric acid B ($GABA_B$), metabotropic glutamate (mGluR), adenosine 1 (A_1), and α_2-adrenergic (α_2) receptors. Activation of these GCPRs by their endogenous ligands leads to inhibition of voltage-gated Ca^{2+} channels (VGCCs), which results in a decrease in presynaptic Ca^{2+} entry and inhibition of neurotransmitter release. GPCRs also modulate an inwardly rectifying K^+ channel, the GIRK channel, which plays an important role in maintenance of the duration and excitability of the resting membrane potential. GPCRs also regulate the function and kinetics of ion channels involved in sensory transduction, such as the transient receptor potential vanilloid (TRPV) channels and sodium channels (Na_v). *(Artwork by Ian Suk, Johns Hopkins University.)*

Opioids

Besides their central analgesic action, morphine and other opioids produce analgesia in inflamed tissues by a peripheral mechanism (see Stein et al 2009). Opioid receptors have been demonstrated on the peripheral terminals of afferent fibers, and axonal transport of these receptors is enhanced during inflammation. Peripheral analgesia by opioids appears to be part of a physiological antinociceptive system since increased amounts of endogenous opioids have been found in inflamed tissues. Inflammatory cells such as macrophages, monocytes, and lymphocytes contain opioid peptides. Release of endogenous opioids and antinociception can be induced by IL-1β and corticotropin-releasing hormone (CRH) originating from the inflamed tissue.

An alternative mechanism for activation of endogenous opioid analgesia at the site of tissue injury has been described (see Khodorova et al 2009 for review). ET-1, a potent vasoactive peptide, is synthesized and released by epithelia after

tissue injury. Although ET-1 can trigger pain by activating ET_A receptors on nociceptors, it also has an analgesic effect through its actions on ET_B receptors. Activation of ET_B receptors on keratinocytes by ET-1 results in the release of β-endorphins and analgesia mediated via peripheral μ- and κ-opioid receptors linked to GIRKs (see Fig. 1-13).

Cannabinoids

Cannabinoids have recently emerged as a potential therapy for chronic pain. Clinical use of non-selective cannabinoids is, however, limited by their CNS actions, which lead to psychotropic effects, temporary memory impairment, and dependence. The endocannabinoid system includes the two cloned metabotropic receptors CB1 and CB2, possibly the orphan receptor GPR55, and the endogenous ligands anandamide and 2-arachidonoylglycerol. CB1 and CB2 receptors are GPCRs expressed in neural and non-neural immune cells. They are distributed at many key sites in the pain-signaling pathway, including the peripheral and central terminals of primary afferent fibers, spinal dorsal horn neurons, and the brain stem and brain. CB1 and CB2 mRNA and protein are widely expressed in the majority of DRG nociceptive neurons (Agarwal et al 2007), and their expression has been shown to be up-regulated following inflammation (Amaya et al 2006) and nerve injury (Beltramo et al 2006, Mitrirattaanakul et al 2006). Multiple lines of evidence suggest that the analgesic effects of CB1 and CB2 agonists may be mediated via their actions on nociceptive primary afferents. Cannabinoids regulate the function and kinetics of ion channels involved in sensory transduction, such as the TRP channels (e.g., TRPV1, TRPA1, TRPM8) and purinergic ion channels ($P2X_2$, $P2X_{2/3}$), as well as channels that directly affect neuronal excitability (various K^+ and Ca^{2+} channels). Studies in animal models suggest that peripheral CB1 and CB2 receptors may be important targets in controlling the pain associated with inflammation, neuropathy, and bone cancer (see Anand et al 2009, Kress and Kuner 2009 for reviews). CB receptor agonists also enhance the analgesic effects of opioid agonists and non-steroidal anti-inflammatory drugs in experimental pain models.

Somatostatin

SST is a regulatory peptide that is widely distributed in neural and non-neural cells such as immune cells, fibroblasts, and neuroendocrine cells. Found in a subpopulation of capsaicin-sensitive peptidergic DRG neurons, SST binds to G protein–coupled membrane receptors. Activation of SST receptors opens various K^+ channels and inhibits voltage-gated Ca^{2+} channels, which results in its anti-inflammatory and analgesic effects. SST decreases the release of peptides such as SP and CGRP from sensory nerve endings in the periphery and reduces neurogenic inflammation (for review see Pinter et al 2006). The analgesic effects of SST are thought to result from inhibition of the TRPV1 ion channel (Carlton et al 2004) and possibly via an interaction with opioid receptors. Intraplantar administration of the SST receptor agonist octreotide reduces the phase II response after formalin injection, decreases the response of CMHs to heat stimuli, and attenuates the thermal responses of nociceptors sensitized by bradykinin. Endogenous release of SST from nociceptive afferents is considered to play a modulatory role in inflammatory and neuropathic pain. Intra-articular injection of SST into the knee resulted in pain relief in patients with osteoarthritis and rheumatoid arthritis. Synthetic SST agonists may have potential as anti-inflammatory and analgesic drugs.

Cholinergic Receptors

Non-neuronally released acetylcholine, acting on peripheral cholinergic receptors, may have a modulatory role on nociception. Nicotine has a weak excitatory effect on C-fiber nociceptors and induces mild sensitization to heat, but no alterations in mechanical responsiveness. In contrast, muscarine desensitizes C nociceptors to mechanical and heat stimuli (Bernardini et al 2001). Thus, nicotinic and muscarinic receptors may have opposing effects on cutaneous nociceptors. Studies in mice with targeted deletions of the M_2 receptor gene suggest that M_2 receptors on cutaneous nerve endings depress the responsiveness of nociceptive fibers to noxious stimuli (see Wess et al 2003 for review). High levels of expression of M_2 mRNA and considerably lower levels of M_3 and M_4 mRNA are detected in medium-sized and small DRG neurons in the rat (Tata et al 2000). M_2, M_3, and M_4 muscarinic receptor subtypes may be involved in the modulation of nociceptive transduction.

γ-Aminobutyric Acid Receptors

The inhibitory neurotransmitter GABA activates both ionotropic ($GABA_A$ and $GABA_C$) and metabotropic ($GABA_B$) receptors. $GABA_A$ receptors have been found in DRG cells and on their central terminals in the dorsal horn. $GABA_A$ receptors have been reported to be present in 10–14% of the unmyelinated primary afferent axons in the glabrous skin of the cat (Carlton et al 1999). Behavioral studies suggest a bimodal effect of $GABA_A$ receptors on the modulation of peripheral nociceptive transmission; a low concentration of $GABA_A$ agonists attenuates and a high concentration enhances formalin-induced pain behavior. $GABA_B$ receptors are also present in primary afferents, and $GABA_B$ mRNA is expressed in DRG cells (Towers et al 2000). Degeneration of primary afferent fibers by administration of capsaicin to neonatal rats decreases $GABA_B$ receptor density by 50%, thus indicating that these receptors are localized in TRPV1-expressing nociceptive afferents (Price et al 1987). Activation of the $GABA_B$ receptor by agonists such as baclofen inhibits neuronal excitability by inhibition of N-type Ca^{2+} currents and potentiation of voltage-dependent K^+ currents (Takeda et al 2004).

α_2-Adrenoceptors

Traditionally, the analgesic effects of α_2-adrenergic agonists, such as clonidine and dexmedetomidine, are thought to be secondary to their actions in the CNS (for review see Pertovaara 2006). However, peripheral α_2-adrenoceptors may also be involved in modulation of nociceptor activity. Studies using selective α_2-subtype knockout mice have shown that the α_{2A}-adrenergic receptors are primarily involved in the analgesic effect of α_2-adrenoceptor agonists (Stone et al 1997). Selective removal of TRPV1-expressing sensory neurons induces a large decrease in α_{2A}- but not in α_{2C}-adrenoceptors in the spinal dorsal horn, which suggests that α_{2A}-adrenoceptors are located on the central terminals of primary afferent neurons whereas the α_{2C} subtype is located primarily on spinal dorsal horn neurons (Stone et al 1998, Chen et al 2007). α_2-Adrenergic agonists may inhibit the depolarization-induced Ca^{2+} influx and induce a GIRK current in nociceptors.

SECOND MESSENGERS AND SIGNAL TRANSDUCTION PATHWAYS

As described above, inflammation is associated with the release of a host of chemical mediators (Fig. 1-12). Although some of these agents may directly activate nociceptors, most of the inflammatory mediators lead to changes in the sensory neuron rather than directly activating it. Such changes in sensory neurons include early post-translational alterations in the peripheral terminals of nociceptors (peripheral sensitization) and a delayed transcription-dependent alteration (see Woolf and Costigan 1999, Kidd and Urban 2001). Peripheral sensitization can be the result of changes in the transducer molecule (e.g., TRPV1 receptor) or in voltage-gated ion channels (e.g., sodium channels) secondary to the phosphorylation of membrane-bound proteins. Inflammation can also induce delayed and longer-lasting transcription-dependent changes in effector genes in DRG cells as a result of electrical activity and retrograde transport of specific signal molecules such as NGF. An increase in intracellular calcium induced by electrical activity activates a host of intracellular transcription factors such as the cAMP-response element–binding protein (CREB; Ji and Rupp 1997).

Considerable attention has been focused on the signal transduction mechanisms of primary afferent neurons and their alteration by inflammation. Two principal signaling pathways have been postulated to mediate inflammation-induced hyperalgesia. Inflammatory mediators such as PGE_2, serotonin, and adenosine activate PKA (Gold et al 1998), whereas NGF, bradykinin, and epinephrine induce hyperalgesia in part by activating PKA but also through an ε isozyme of PKC (Khasar et al 1999). PKA and PKC sensitize nociceptors to heat by modulating the activity of TTX-resistant sodium currents. As described above, these signaling pathways also interact with the heat transducer TRPV1, which results in sensitization of the receptor to heat.

MAPKs are also reported to be involved in the transduction of extracellular stimuli (e.g., signals from extracellular growth factors such as NGF) into diverse intracellular responses and neuronal plasticity. Three subfamilies of MAPKs have been well characterized—the extracellular signal–regulated kinases (ERKs), the c-Jun amino-terminal kinases (JNKs), and the p38 enzymes. ERK is present in primary afferent neurons, is phosphorylated by nociceptive stimuli, and is thought to play a role in inflammatory hyperalgesia (Dai et al 2002). Inflammation also activates p38 in the soma of C-fiber nociceptive cells in the DRG (Ji et al 2002). Inhibiting the activation of p38 in the DRG reduces the inflammation-induced increase in TRPV1 receptors in the DRG and attenuates heat hyperalgesia. Activation of p38 in the DRG is dependent on peripheral production of NGF during inflammation. Thus, MAPKs and NGF play important regulatory roles in TRPV1 receptor expression and maintenance of heat hyperalgesia after inflammation.

POSTOPERATIVE PAIN AND HYPERALGESIA

The pain resulting from different tissue injuries may differ in its characteristics and mechanisms. Postoperative, incisional pain is a unique but common form of acute pain. Studies in rodents have characterized the primary hyperalgesia to mechanical and thermal stimuli caused by a surgical incision (Brennan et al 1996, Pogatzki and Raja 2003). Primary hyperalgesia to mechanical stimuli lasts for 2–3 days, whereas hyperalgesia to heat lasts longer—6–7 days after plantar incision. As with other types of tissue injury, secondary hyperalgesia after incision injury is present only to mechanical, not thermal, stimuli (Pogatzki et al 2000). The incision-induced primary and secondary hyperalgesia results from characteristic peripheral, spinal, and supraspinal mechanisms (Zahn and Brennan 1999, Pogatzki et al 2002). The conversion of mechanically insensitive "silent nociceptors" to mechanically responsive fibers may play an important role in the maintenance of primary mechanical hyperalgesia (Pogatzki et al 2002). Release of ATP from injured cells is considered to play an important role in the induction of mechanical allodynia after a skin incision (Tsuda et al 2001).

The incision-induced spontaneous activity in primary afferent fibers plays a critical role in maintaining wide–dynamic range neurons in the dorsal horn in a sensitized state. In contrast to the central mechanisms of hyperalgesia following other forms of cutaneous injury where *N*-methyl-D-aspartate (NMDA) receptors play a critical role, the hyperalgesia that results from an incision is characterized by distinct pharmacological mechanisms that are not dependent on NMDA receptors.

ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN INFLAMMATION

Nociceptors normally do not respond to sympathetic stimulation. In addition, sympathectomy plus depletion of catecholamine stores with reserpine has no effect on acute inflammation. In contrast, sympathectomy reduces the severity of injury in chronic adjuvant-induced arthritis (see Raja 1995, Jänig et al 1996 for reviews). Inflammation may lead to catechol sensitization of cutaneous nociceptors. Sympathetic stimulation and close arterial injection of norepinephrine (NE) also excite 35–40% of C-polymodal nociceptors in chronically inflamed rats (Sato et al 1993). This adrenergic activation of nociceptors was blocked by α_2- but not by α_1-adrenergic antagonists. Sympathetic efferent fibers are also thought to play a role in neurogenic inflammation.

In human skin sensitized by the topical application of capsaicin, hyperalgesia persists longer at sites where exogenous NE was administered, and this α-adrenoceptor–mediated effect was independent of the vasoconstrictor response (Drummond 1995, 1996). Additionally, local administration of an α-adrenergic antagonist reduced the spontaneous pain and hyperalgesia resulting from the intradermal injection of capsaicin (Kinnman et al 1997). However, physiological modulation of sympathetic vasoconstrictor activity by whole-body warming or cooling does not alter the intensity or spatial distribution of capsaicin-evoked spontaneous pain and mechanical hyperalgesia (Baron et al 1999). Anatomical studies indicate that SP and NMDA receptor mRNA is up-regulated in preganglionic sympathetic neurons after paw inflammation in rats (Ohtori et al 2002). These changes are postulated to possibly be evidence of a role of the sympathetic nervous system in inflammatory hyperalgesia.

SECONDARY HYPERALGESIA

An understanding of secondary hyperalgesia is important not only with regard to understanding the neural mechanisms of acute pain but also with regard to understanding many aspects of chronic pain. In this section we consider the nature

of secondary hyperalgesia and its possible peripheral and central mechanisms.

Secondary Hyperalgesia to Mechanical but Not Heat Stimuli

Primary hyperalgesia is characterized by the presence of enhanced pain in response to heat and mechanical stimuli, whereas secondary hyperalgesia is characterized by enhanced pain in response to only mechanical stimuli (e.g., Ali et al 1996). In one study in which the sensory changes that occur in the zones of primary and secondary hyperalgesia were compared (Raja et al 1984), burn injuries were induced in two locations on the glabrous skin of the hand in human subjects (Fig. 1-14). Within minutes of the injury, lightly touching the skin at the site of the two burns, as well as in a large area surrounding the burns, caused pain. The decrease in the pain threshold to von Frey hairs in the primary (injured) zone was similar to that in the area of secondary hyperalgesia (Fig. 1-14B). Marked hyperalgesia to heat was observed in the area of primary hyperalgesia (site A, the injury site, Fig. 1-14C). In the uninjured region between the two burns, however, the painfulness of the heat stimuli actually decreased (Fig. 1-14D). Notably, the area between the burns was hypo-algesic to heat while being hyperalgesic to mechanical stimuli.

Spreading Sensitization of Nociceptors Does Not Occur

Activation of nociceptors leads to a flare response (discussed in more detail below). This response is neurogenic in the sense that it depends on intact innervation of the skin by nociceptors. The flare response extends well outside the area of initial injury. One explanation for the flare response is that it involves spreading activation of nociceptors. Activation of one nociceptor leads to the release of chemicals that activate neighboring nociceptors, which leads to further release of chemicals and activation of additional nociceptors. Lewis (1942) believed that a similar mechanism, which he termed *spreading sensitization*, accounted for secondary hyperalgesia. Activation and sensitization of one nociceptor lead to spread of this sensitization to another nociceptor, possibly because of the effects of a sensitizing substance released from the nociceptor initially activated. Another theoretical possibility is that coupling between nociceptors increases after injury.

Several lines of evidence indicate that spreading sensitization does not occur:

- A heat injury to half the receptive field of nociceptors does not alter the sensitivity of the other half to heat stimuli (Thalhammer and LaMotte 1983).
- A mechanical injury adjacent to the receptive field of nociceptors fails to alter the responses of CMHs in the monkey (Campbell et al 1988a) and rat (Reeh et al 1986).
- Antidromic stimulation of nociceptive fibers in the monkey (Meyer et al 1988) and rat (Reeh et al 1986) does not cause sensitization.
- Application of mustard oil to one part of the receptive field of C-fiber nociceptors in humans does not lead to sensitization of other parts of the receptive field (Schmelz et al 1996).

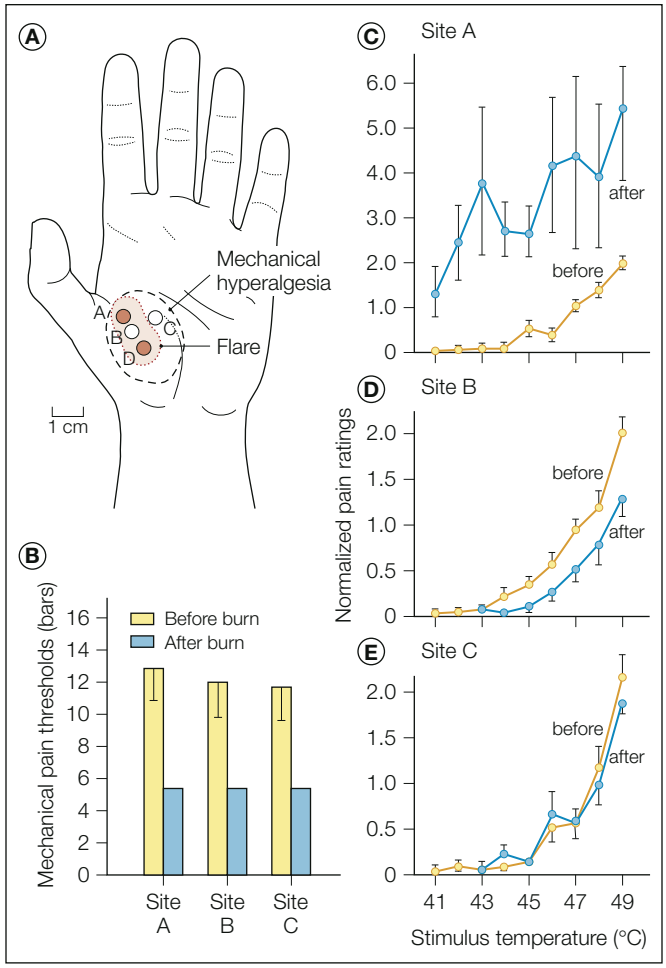

Figure 1-14. Hyperalgesia to mechanical and heat stimuli develops at the site of injury (zone of primary hyperalgesia), whereas hyperalgesia to mechanical but not heat stimuli develops in the uninjured area surrounding an injury (zone of secondary hyperalgesia). A, Two burns (53°C, 30 seconds) were applied to the glabrous skin of the hand (sites A and D). Mechanical thresholds for pain and ratings of pain in response to heat stimuli were recorded before and after the burns at one of the injury sites (site A), in the uninjured skin between the two burns (site B), and at an adjacent site (site C). The areas of flare and mechanical hyperalgesia following the burns in one subject are also shown. In all subjects, the area of mechanical hyperalgesia was larger than the area of flare. Mechanical hyperalgesia was present even after the flare disappeared. **B,** Mean mechanical thresholds for pain before and after burns. The mechanical threshold for pain was significantly decreased following the burn. The mechanical hyperalgesia was of similar magnitude at each of the three test spots (A, B, C). **C–E,** Mean normalized ratings of the painfulness of heat stimuli (same as described in Fig. 1-5) before and after burns. **C,** At burn site A, all the characteristics of heat hyperalgesia (i.e., decrease in pain threshold, increased pain in response to suprathreshold stimuli, and spontaneous pain) were observed after the burns. **D,** In the uninjured area between the two burns (site B), pain ratings decreased after the burns. Thus, heat hypalgesia was observed. **E,** At site C, pain ratings before and after the burns were not significantly different. (Note that a different scale is used in **C.**) *(Reproduced with permission from Raja SN, Campbell JN, Meyer RA 1984 Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. Brain 107:1179–1188.)*

Other differences exist between flare and secondary hyperalgesia (LaMotte et al 1991):

- The zone of secondary hyperalgesia is generally larger than the zone of flare.
- Flare can be induced without causing secondary hyperalgesia (for example, with histamine), and secondary hyperalgesia can be induced without a flare response.

- Secondary hyperalgesia does not spread beyond the body's midline, whereas the flare response does.

Central Mechanisms of Secondary Hyperalgesia

If peripheral sensitization does not account for secondary hyperalgesia, the mechanisms noted in Figure 1-10C–F should be examined in the CNS. Indeed, it has been relatively easy to demonstrate enhanced responsiveness of CNS neurons to mechanical stimuli after cutaneous injury (e.g., Simone et al 1991b). Substantial evidence favors the following important tenet: the peripheral signal for pain does not reside exclusively with nociceptors. Under pathological circumstances, other receptor types, which are normally associated with the sensation of touch, acquire the capacity to evoke pain. This principle applies not only to secondary hyperalgesia but also to neuropathic pain states in general. This condition arises in part through augmentation of the responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors, a phenomenon often termed *central sensitization*.

Many of the insights acquired about secondary hyperalgesia have been gained from studies with capsaicin. Investigators have been drawn to the use of capsaicin as the "injury" stimulus for several reasons:

- Capsaicin selectively activates nociceptors (Szolcsányi 1990).
- Capsaicin causes intense pain and a large zone of secondary hyperalgesia when applied topically or intradermally to the skin (Simone et al 1989).
- Injection of capsaicin into the skin does not produce any apparent tissue injury.
- The characteristics of hyperalgesia resemble those for heat or cut injuries. Immediately around the injection site, heat and mechanical hyperalgesia is present. Outside this area of primary hyperalgesia is a large zone of secondary hyperalgesia characterized by mechanical hyperalgesia but not heat hyperalgesia (Ali et al 1996).

LaMotte and colleagues performed a number of pivotal experiments to determine the relative importance of peripheral and central sensitization in secondary hyperalgesia (LaMotte et al 1991). To test whether peripheral nerve fibers are sensitized, capsaicin was administered under conditions of a proximal nerve block, and the magnitude of hyperalgesia was determined after the effects of the anesthetic dissipated. When the relevant nerve is blocked proximal to the capsaicin injection site, the CNS is spared the nociceptive input generated at the time of injection. The effects of capsaicin on the peripheral nervous system are not affected (e.g., a flare develops) since the nerve block is proximal to the area of capsaicin application. Figure 1-15 shows the results of this experiment in one subject. No hyperalgesia was present after the block had worn off. Thus, when the CNS is spared the input of nociceptors at the time of the acute insult, hyperalgesia does not develop (LaMotte et al 1991, Pedersen et al 1996).

Additional evidence that central sensitization, not peripheral sensitization, plays a major role in secondary hyperalgesia includes the following:

- Electrical stimulation of the skin can be used to produce a large zone of secondary hyperalgesia (Koppert et al 2001). Electrical stimulation directly activates the axon and therefore bypasses a peripheral receptor mechanism.

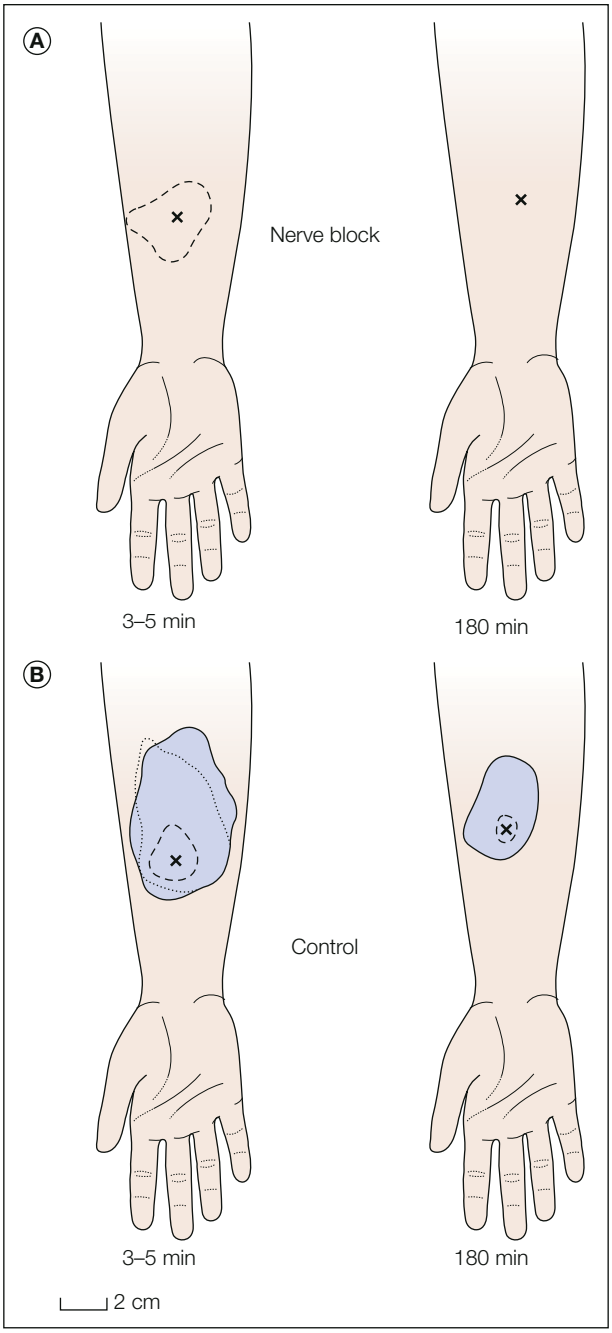

Figure 1-15. A proximal nerve block prevents the development of secondary hyperalgesia. **A,** After blockade of the lateral antebrachial nerve with 1% Xylocaine, capsaicin (100 μg in 10 μL) was injected into the anesthetic skin. A flare (dashed line) developed within 5 minutes. No hyperalgesia was present 180 minutes after the capsaicin injection when the local anesthetic block had dissipated. **B,** On the control arm, normal flare and hyperalgesia in response to stroking (dotted line) and punctate (solid line) stimuli developed within 5 minutes. Hyperalgesia to punctate stimuli was still present 180 minutes after the capsaicin injection. *(Adapted from LaMotte RH, Shain CN, Simone DA, et al 1991 Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. Journal of Neurophysiology 66:190–211.)*

- When an anesthetic strip is produced in the skin, electrical stimulation on one side of the anesthetic strip produces a flare only on that side of the strip, thus indicating that the strip has blocked the axon reflexive flare; secondary hyperalgesia develops symmetrically around the stimulation site

and extends well beyond the anesthetic strip (Klede et al 2003).
- Secondary hyperalgesia following injection of capsaicin within the territory of a given nerve spreads into the territory of an adjacent nerve (Sang et al 1996).

Different Mechanisms for Stroking and Punctate Hyperalgesia

Two distinct forms of mechanical hyperalgesia are observed in the zone of secondary hyperalgesia: punctate hyperalgesia and stroking hyperalgesia. Hyperalgesia to blunt pressure is not observed in the secondary zone (Koltzenburg et al 1992). We will first consider stroking hyperalgesia (also called allodynia). Stroking hyperalgesia appears to be mediated by activity in low-threshold mechanoreceptors. When a pressure cuff was used to selectively block myelinated fibers, the pain in response to stroking disappeared at a time when touch sensation was lost but heat and cold sensations were still present (LaMotte et al 1991, Koltzenburg et al 1992). This is also true in patients with stroking hyperalgesia from neuropathic pain (Campbell et al 1988b). In another series of experiments, Torebjörk and colleagues (1992) performed intraneural microstimulation in awake human subjects. As shown in Figure 1-16, stimulation of primary afferent fibers normally concerned with tactile sensibility evoked pain when (but not before) secondary hyperalgesia was produced.

Punctate hyperalgesia is manifested by heightened pain associated with the application of small, stiff, or sharp probes to the skin (e.g., von Frey monofilaments). Several lines of evidence indicate that punctate hyperalgesia has a different neural mechanism than stroking hyperalgesia does and is mediated by central sensitization to activity in nociceptors:
- The area of punctate hyperalgesia is consistently larger than that of stroking hyperalgesia.
- Stroking hyperalgesia after capsaicin injection lasts 1–2 hours, whereas punctate hyperalgesia lasts more than 12 hours (LaMotte et al 1991).
- Punctate hyperalgesia, not stroking hyperalgesia, developed after intradermal capsaicin injection into the arm of a patient with a severe large-fiber neuropathy (Treede and Cole 1993). This evidence suggests that punctate hyperalgesia is mediated by small-diameter (presumably nociceptive) fibers.
- The pain produced by touching the skin with different wool fabrics was greatly increased in the region of secondary hyperalgesia (Cervero et al 1994). The pain was proportional to the prickliness of the fabrics. Since nociceptors and not low-threshold mechanoreceptors exhibit a differential response to different wool fabrics (Garnsworthy et al 1988), activity in nociceptors probably contributes to this form of secondary hyperalgesia to wool fabrics.
- When the area of primary hyperalgesia is anesthetized or cooled, stroking hyperalgesia is eliminated but punctate hyperalgesia persists (LaMotte et al 1991). Therefore, stroking hyperalgesia has an ongoing dependence on input from the sensitized area, whereas punctate hyperalgesia is more enduring and less dependent on ongoing discharge from the sensitized area.

The pain in response to a controlled punctate stimulus does not vary significantly across the zone of secondary hyperalgesia but decreases precipitously at the border (Huang et al 2000). This suggests that the sensitization responsible for secondary hyperalgesia is an all-or-nothing phenomenon. In addition, subjects were able to grade the magnitude of pain from stimuli of different intensity. Interestingly, although the threshold for pain in response to punctate stimuli decreases in the zone of secondary hyperalgesia (Magerl et al 1998), the threshold for touch detection increases (Magerl and Treede 2004).

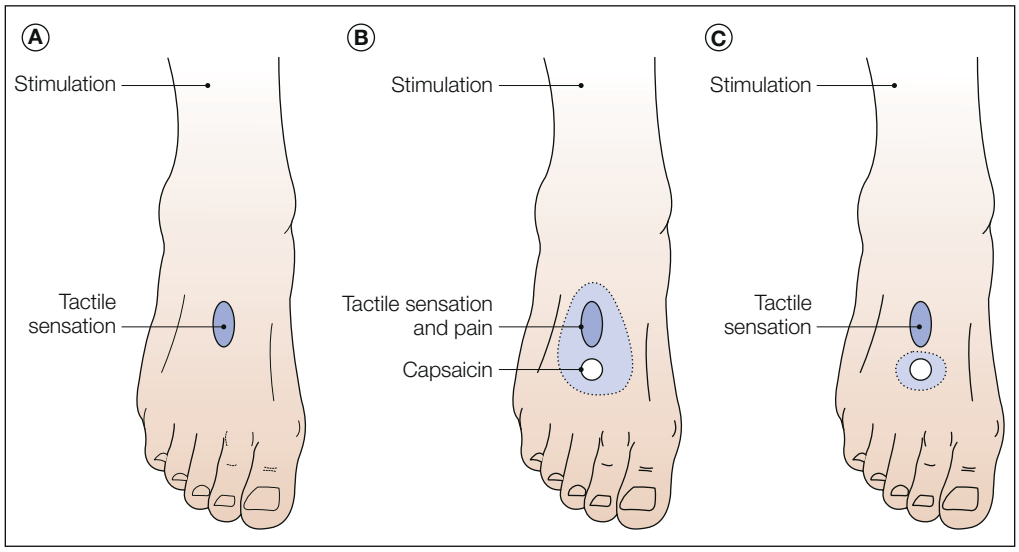

Figure 1-16. Microneurographic evidence that large-diameter myelinated fibers are involved in the pain observed in the zone of secondary hyperalgesia. **A,** Intraneural electrical stimulation of the superficial peroneal nerve at a fixed intensity and frequency evoked a purely tactile (non-painful) sensation projected to a small area of skin on the dorsum of the foot (dark blue area). **B,** After intradermal injection of capsaicin (100 μg in 10 μL) adjacent to the projected zone (at the site indicated by the open circle), a zone of secondary hyperalgesia (indicated by light blue area) developed that overlapped the sensory projection field. Now, intraneural stimulation at the same intensity and frequency as in **A** was perceived as a tactile sensation accompanied by pain. **C,** When the zone of secondary hyperalgesia no longer overlapped the sensory projection field, the intraneural stimulation was again perceived as purely tactile, without any pain component. *(Adapted from Torebjörk HE, Lundberg LER, LaMotte RH 1992 Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. Journal of Physiology [London] 448:765–780.)*