

## LETTERS

## An endocannabinoid mechanism for stress-induced analgesia

Andrea G. Hohmann<sup>1</sup>, Richard L. Suplita<sup>1</sup>, Nathan M. Bolton<sup>1</sup>, Mark H. Neely<sup>1</sup>, Darren Fegley<sup>2</sup>, Regina Mangieri<sup>2</sup>, Jocelyn F. Krey<sup>3</sup>, J. Michael Walker<sup>3</sup>, Philip V. Holmes<sup>4</sup>, Jonathon D. Crystal<sup>5</sup>, Andrea Duranti<sup>6</sup>, Andrea Tontini<sup>6</sup>, Marco Mor<sup>6</sup>, Giorgio Tarzia<sup>6</sup> & Daniele Piomelli<sup>2</sup>

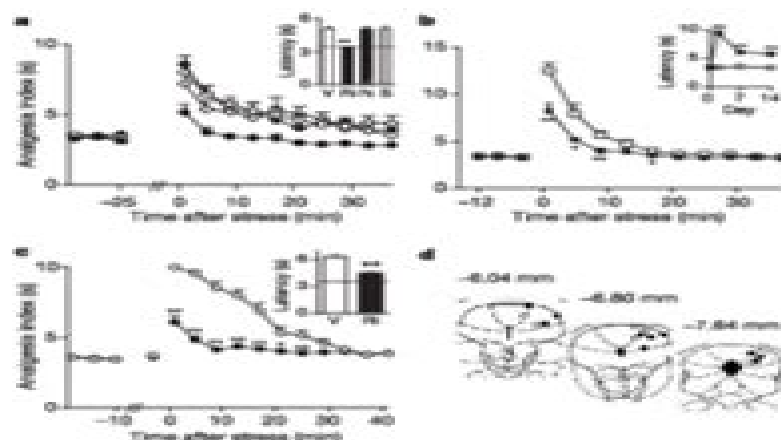
Acute stress suppresses pain by activating brain pathways that engage opioid or non-opioid mechanisms. Here we show that an opioid-independent form of this phenomenon, termed stress-induced analgesia<sup>1</sup>, is mediated by the release of endogenous marijuana-like (cannabinoid) compounds in the brain. Blockade of cannabinoid CB<sub>1</sub> receptors in the periaqueductal grey matter of the midbrain prevents non-opioid stress-induced analgesia. In this region, stress elicits the rapid formation of two endogenous cannabinoids, the lipids 2-arachidonylglycerol<sup>2</sup> (2-AG) and anandamide<sup>3</sup>. A newly developed inhibitor of the 2-AG-deactivating enzyme, monoacylglycerol lipase<sup>4,5</sup>, selectively increases 2-AG concentrations and, when injected into the periaqueductal grey matter, enhances stress-induced analgesia in a CB<sub>1</sub>-dependent manner. Inhibitors of the anandamide-deactivating enzyme fatty-acid amide hydrolase<sup>6</sup>, which selectively elevate anandamide concentrations, exert similar effects. Our results indicate that the coordinated release of 2-AG and anandamide in the periaqueductal grey matter might mediate opioid-independent stress-induced analgesia. These studies also identify monoacylglycerol lipase as a previously unrecognized therapeutic target.

Stress activates neural systems that inhibit pain sensation. This adaptive response, referred to as stress-induced analgesia (SIA), depends on the recruitment of brain pathways that project from the amygdala to the midbrain periaqueductal grey matter (PAG) and descend to the brainstem rostroventromedial medulla and dorsal horn of the spinal cord<sup>7</sup>. Endogenous opioid peptides have key functions in this process<sup>8,9</sup>, but other as yet unidentified neurotransmitters are also known to be involved<sup>7</sup>. We proposed that endocannabinoids might be implicated in stress analgesia for two reasons. First, agonists of CB<sub>1</sub> receptors—the predominant cannabinoid receptor subtype present in the brain<sup>10</sup>—exert profound antinociceptive effects<sup>11</sup> and suppress activity in nociceptive neurons<sup>12–14</sup>. Second, CB<sub>1</sub> antagonists increase the activity of nociceptive rostroventromedial medulla neurons<sup>15</sup> and enhance sensitivity to noxious stimuli<sup>16</sup>, indicating that an intrinsic endocannabinoid tone might regulate descending antinociceptive pathways<sup>17</sup>.

To study non-opioid SIA we delivered brief, continuous electric foot shock to rats and quantified their sensitivity to pain after stress by using the tail-flick test. As demonstrated previously<sup>18,19</sup>, this stimulation protocol caused a profound antinociceptive effect that was not affected by intraperitoneal (i.p.) injection of the opiate antagonist naloxone (14 mg kg<sup>-1</sup>) (Fig. 1a). However, the response was almost abolished by administration of the CB<sub>1</sub> antagonist SR141716A (5 mg kg<sup>-1</sup> i.p.) (Fig. 1a) or its analogue AM251 (5 mg kg<sup>-1</sup> i.p.) (Supplementary Fig. 1), but not by the CB<sub>2</sub>

antagonist SR144528 (5 mg kg<sup>-1</sup> i.p.) (Fig. 1a). The effects of CB<sub>1</sub> antagonists cannot be attributed to changes in basal nociceptive threshold because, in the absence of the stressor, the drugs failed to alter tail-flick latencies (Supplementary Figs 1 and 2).

If CB<sub>1</sub> activation is required for the expression of non-opioid SIA, the latter should be lower in animals rendered tolerant to the



**Figure 1 | CB<sub>1</sub> receptors mediate non-opioid stress-induced analgesia.** **a**, CB<sub>1</sub> antagonist SR141716A (SR, filled circles) blocks stress antinociception. Opiate antagonist naloxone (N, open diamonds) and CB<sub>2</sub> antagonist SR144528 (S, filled diamonds) have no effect. Open circles, vehicle (V). Inset: drug effects ( $P_{0.05} = 3.99$ ,  $P < 0.003$ ). The dashed line indicates the nociceptive threshold. Analgesia index was measured as the tail-flick latency. **b**, Stress antinociception is attenuated in WIN55212-2-tolerant rats (filled squares) compared with controls (open squares) ( $P_{0.05} = 35.11$ ,  $P < 0.0002$ ). Inset: non-stress cannabinoid antinociception is attenuated in WIN55212-2-tolerant rats ( $P_{0.05} = 35.11$ ,  $P < 0.0002$ ). **c**, Naloxone in dorsolateral PAG suppresses stress antinociception ( $P_{0.05} = 25.63$ ,  $P < 0.0002$ ). Inset: drug effects ( $P_{0.05} = 25.63$ ,  $P < 0.0002$ ). **d**, PAG injection sites. Error bars, where visible, indicate s.e.m.;  $n = 4$ –11 per group. Asterisks,  $P < 0.05$ ; two asterisks,  $P < 0.01$  (analysis of variance, Fisher's PLSD test).

<sup>1</sup>Neuroscience and Behavior Program, Department of Psychology, The University of Georgia, Athens, Georgia 30602-3033, USA. <sup>2</sup>Department of Pharmacology and Center for Drug Discovery, University of California, Irvine, California 92697-4260, USA. <sup>3</sup>Behavior Research Laboratory, Departments of Psychology and Neuroscience, Brown University, Providence, Rhode Island 02912, USA. <sup>4</sup>Institute of Medical Chemistry, University of Urbino Carlo Bo, I-61029 Urbino, Italy. <sup>5</sup>Pharmaceutical Department, University of Rome, I-00180 Rome, Italy.



# Stressinduced Analgesia

**SB Merriam**





## **Stressinduced Analgesia:**

**Stress-induced Analgesia** M. D. Tricklebank, Gerald Curzon, 1984      Studies of the Origin of Stress-induced Analgesia Richard Graybell Goldman, 1980      **Stress Induced Analgesia** William D. Brock, 1984      **Handbook of Pain and Palliative Care** Rhonda J. Moore, 2013-10-25 Handbook of Pain and Palliative Care Biobehavioral Approaches for the Life Course Rhonda J Moore editor This book takes both a biobehavioral and a lifespan approach to understanding long term and chronic pain and intervening to optimize patients functioning Rich in clinical diversity chapters explore emerging areas of interest computer based interventions fibromyalgia stress ongoing concerns cancer pain low back pain and special populations pediatric elderly military This coverage provides readers with a knowledge base in assessment treatment and management that is up to date practice strengthening and forward looking Subject areas featured in the Handbook include Patient practitioner communication Assessment tools and strategies Common pain conditions across the lifespan Biobehavioral mechanisms of chronic pain Pharmaceutical neurological and rehabilitative interventions Psychosocial complementary alternative narrative and spiritual approaches Ethical issue and future directions With the rise of integrative perspective and the emphasis on overall quality of life rather than discrete symptoms pain management is gaining importance across medical disciplines Handbook of Pain and Palliative Care stands out as a one stop reference for a range of professionals including health practitioners specializing in pain management or palliative care clinical and health psychologists public health professionals and clinicians and administrators in long term care and hospice      **Molecular Mechanisms of Hormone Actions on Behavior** Anne M. Etgen, Donald W. Pfaff, 2010-03-16 A single volume of 31 articles Mechanisms of Hormone Actions on Behavior is an authoritative selection of relevant chapters from the Hormones Brain and Behavior 2e MRW the most comprehensive source of neuroendocrinological information assembled to date AP June 2009 The study of hormones as they impact the brain and subsequently behavior is a central topic in neuroscience endocrinology and psychiatry This volume offers an overview of neuroendocrinological topics approaching the subject from the perspective of the mechanisms which control hormone actions on behavior Female male and stress hormones are discussed at the cellular behavioral and developmental level and sexual differentiation of the development of hormone dependent neuronal systems neuropeptides neuromodulators and steroid induced neuroplasticity are addressed There is simply no other current single volume reference with such comprehensive coverage and depth Authors selected are the internationally renowned experts for the particular topics on which they write and the volume is richly illustrated with over 175 figures over 50 in color A collection of articles reviewing our fundamental knowledge of the mechanisms of neuroendocrinology the book provides an essential affordable reference for researchers clinicians and graduate students in the area The most comprehensive single volume source of up to date data on the mechanisms behind neuroendocrinology with review articles covering x y z Chapters synthesize information otherwise dispersed across a number of journal articles and book chapters thus saving researchers



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Presents material in most visually useful form for the reader      **Stress Consequences** George Fink,2010-04-06 Stress is a universal phenomenon that impacts adversely on most people This volume provides a readily accessible compendium that focuses on the physical and psychological consequences of stress for individuals and society Clinical attention focuses on disorders of the stress control system e g Cushing s Syndrome Addison s Disease and the adverse impact of stress on human physical and mental health Detailed reviews address disorders such as PTSD anxiety major depression psychoses and related disorders such as combat fatigue and burnout The work covers interactions between stress and neurodegenerative disorders such as Alzheimer s disease and Parkinson s disease as well as stress immune inflammatory interactions in relation to cancer and autoimmune and viral diseases Emphasis is also placed on the role of stress in obesity hypertension diabetes type II and other features of the metabolic syndrome which has now reached epidemic proportions in the USA and other countries Chapters offer impressive scope with topics addressing animal studies disaster diurnal rhythms drug effects and treatments cognition and emotion physical illness psychopathology immunology and inflammation lab studies and tests and psychological biochemical genetic aspects Richly illustrated in full color with over 200 figures Articles carefully selected by one of the world s most preeminent stress researchers and contributors represent the most outstanding scholarship in the field with each chapter providing fully vetted and reliable expert knowledge      *Stressed-Induced Analgesia* Dennis D.

Kelly,NEW YORK ACADEMY OF SCIENCES NY.,1986 Partial Contents The Range of Environmental Triggers of Analgesia Is Stress Necessary Sufficient or Neither The Range of Sensory and Behavioral Changes Accompanying Stress Analgesia Discriminating the Roles of Opioid Peptides and Receptors in the Behavioral Modulation of Pain Relation of Stress Induced Analgesia to Other Stress Induced Behavioral Phenomena Central Nervous System mechanisms of Stress Induced Analgesia Automatic and Humoral Factors in Stress Induced Analgesia and Human Subject and Animal Welfare Issues Relevant to Research on Pain Stress and Analgesia      **Pharmacology of Opioid Peptides** L F Tseong,1995-09-01 This book is being

published at a time when opioid receptors have recently been cloned The structural characteristics of opioid receptors and the recent advances in their molecular cloning and expression are explicated Connecting these cloned opioid receptors with the pharmacology of opioid receptor actions is of particular importance The use of antisense oligodeoxynucleotides to opioid receptors to elucidate the neural mechanisms of opioid action is detailed As analgesia is one of the most important clinical functions for opioids and opioid peptides this book concentrates on the detailed mechanisms of action of opioids and opioid peptides for the production of analgesia The significant pharmacologic actions of opioids and opioid peptides in



gastrointestinal function immune function cardiovascular and respiratory regulation addiction and the cellular mechanisms involved in tolerance and dependence of opioids are also described The book will be of interest both to researchers investigating the neural mechanisms of the pharmacologic and physiologic functions of the endogenous opioid system and to clinicians who are involved in pain management and assessment Cumulated Index Medicus ,1982 *Molecular Aspects of Medicine* H. Baum,J. Gergely,B. L. Fanburg,2013-10-22 *Molecular Aspects of Medicine* Volume 7 discusses diseases such as urolithiasis Another term for this disease is calculosis Urolithiasis occurs when stones are formed in areas such as the biliary salivary or renal systems but it is found more often in the urinary tract The epidemiology and etiology of the disease are extensively covered in the book The second chapter focuses on the cell surface of healthy and disease infected cells Topics such as the plasma membrane the extracellular matrix and cell culture and transformation are also covered in the said chapter The third chapter of the book is about the serum steroid transport proteins This chapter discusses the biochemistry and clinical significance of the steroid binding proteins albumin and different binding globulins The fourth chapter covers the physiology and pharmacology of emesis The book concludes with a discussion on the mechanisms of pain and opioid induced analgesia The text can be a useful tool for doctors medical technologists students and researchers in the field of medicine

Youmans and Winn Neurological Surgery E-Book H. Richard Winn,2022-01-21 Widely regarded as the definitive reference in the field Youmans and Winn Neurological Surgery offers unparalleled multimedia coverage of the entirety of this complex specialty Fully updated to reflect recent advances in the basic and clinical neurosciences the 8th Edition covers everything you need to know about functional and restorative neurosurgery deep brain stimulation stem cell biology radiological and nuclear imaging and neuro oncology as well as minimally invasive surgeries in spine and peripheral nerve surgery and endoscopic and other approaches for cranial procedures and cerebrovascular diseases In four comprehensive volumes Dr H Richard Winn and his expert team of editors and authors provide updated content a significantly expanded video library and hundreds of new video lectures that help you master new procedures new technologies and essential anatomic knowledge in neurosurgery Discusses current topics such as diffusion tensor imaging brain and spine robotic surgery augmented reality as an aid in neurosurgery AI and big data in neurosurgery and neuroimaging in stereotactic functional neurosurgery 55 new chapters provide cutting edge information on Surgical Anatomy of the Spine Precision Medicine in Neurosurgery The Geriatric Patient Neuroanesthesia During Pregnancy Laser Interstitial Thermal Therapy for Epilepsy Fetal Surgery for Myelomeningocele Rehabilitation of Acute Spinal Cord Injury Surgical Considerations for Patients with Polytrauma Endovascular Approaches to Intracranial Aneurysms and much more Hundreds of all new video lectures clarify key concepts in techniques cases and surgical management and evaluation Notable lecture videos include multiple videos on Thalamotomy for Focal Hand Dystonia and a video to accompany a new chapter on the Basic Science of Brain Metastases An extensive video library contains stunning anatomy videos and videos demonstrating intraoperative procedures



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*The Psychobiology of Affective Development (PLE: Emotion)* Nathan A. Fox, Richard Davidson, 2014-11-20 Originally published in 1984 this was the first volume on this topic to appear in an emerging area of study at the time The editors were selective in choosing their contributions to the volume to ensure that both the developmental and neuropsychological domains were well represented One of the major goals was to foster greater contact and cross fertilization between subdisciplines that they firmly believed should be more intimately connected The result is this title which can now be enjoyed in its historical context

**Translational Methods for PTSD Research** Graziano Pinna, 2023-07-02 This volume explores the latest experimental techniques in animal models of PTSD and humans affected by PTSD The methods discussed in this book cover topics such as translational research addressing sex differences highlighting the state of the art of biomarker discovery in the development and maintenance of PTSD and looks at new promising agents to enhance fear extinction retention that may help millions of individuals that suffer from this debilitating disorder worldwide In the Neuromethods series style chapters include the kind of detail and key advice from the specialists needed to get successful results in your laboratory Authoritative and thorough Translational Methods for PTSD Research is a valuable resource that will help researchers understand and learn more about this important disorder

*Advances in Electromagnetic Fields in Living Systems* James C. Lin, 2006-05-28 In spite of the remarkable progress that has been made against cancer the battle is far from over It is estimated that there are 175 000 new female breast cancer cases annually and 40 000 deaths resulting from it in the U S In fact breast cancer incidence rates have shown little change in the 1990s while breast cancer death rates have been declining about 2 percent per year since 1990 Ries et al 1999

Modern mammography is relied upon most often for breast cancer screening Mammograms can detect most breast cancers but they miss some Its accuracy and sensitivity are age and breast density dependent For example the false negative rate is about 25% for women under age 50 with invasive breast cancer Kerlikowske et al 1996 1997 It reduces to 10% for women more than 50 years of age Although the amount of radiation exposure during mammography is minimal about the same as receiving a dental x ray the radiation from mammograms can cause additional breast cancer deaths Feig 1996 NIH 1997 It has been estimated that if 10 000 women have yearly mammograms for ten years the radiation from mammograms will cause one additional breast cancer death Because the absolute benefit of screening women aged 40 to 49 years is small and there is concern that the harm may be substantial there have been suggestions that these women should be informed about the potential benefits and risks of screening mammography Kerlikowske 1997

**Pain** Chas Bountra, Rajesh Munglani, William K. Schmidt, 2003-05-13 This reference presents a detailed overview of approaches and techniques in the management of pain



caused by tissue nerve and central nervous system injuries categorizing pain into a variety of syndromes and underlying mechanisms to aid the development of interventional pharmacologic measures     [Hormones, Brain and Behavior Online](#) ,2002-06-18 Hormones Brain and Behavior Second Edition is a comprehensive work discussing the effect of hormones on the brain and subsequently behavior This major reference work has 109 chapters covering a broad range of topics with an extensive discussion of the effects of hormones on insects fish amphibians birds rodents and humans To truly understand all aspects of our behavior we must take every influence including the hormonal influences into consideration Donald Pfaff and a number of well qualified editors examine and discuss how we are influenced by hormonal factors offering insight and information on the lives of a variety of species Hormones Brain and Behavior offers the reader comprehensive coverage of growing field of research with a state of the art overview of hormonally mediated behaviors This reference provides unique treatment of all major vertebrate and invertebrate model systems with excellent opportunities for relating behavior to molecular genetics The topics cover an unusual breadth from molecules to ecophysiology ranging from basic science to clinical research making this reference of interest to a broad range of scientists in a variety of fields Available online exclusively via ScienceDirect A limited edition print version is also available Comprehensive coverage of a growing field of research Unique treatment of all major vertebrate and invertebrate model systems with excellent opportunities for relating behavior to molecular genetics Covers an unusual breadth ranging from molecules to ecophysiology and from basic science to clinical research     [Psychoneuroimmunology](#) Robert Ader,2014-06-28 Psychoneuroimmunology Second Edition presents reports on the relationship between the nervous and immune systems The book is divided into four sections The first section details the role of neural structures and neurotransmitter signals in communication with the immune system It documents the extensive neural connections with organs of the immune system the dynamics of noradrenergic sympathetic innervation of spleen and thymus and the evidence for immune signaling of the CNS Part II elaborates the role of hormones in the modulation of immune functions the basis for bidirectional communication between the neuroendocrine and immune systems and the potential physiological implications of these neuroendocrine immune system interactions The third part addresses behavioral influences on immune response the effects of conditioning stress and social interactions in modulating immune responses and the behavioral consequences of experimentally altered or genetically determined immunologic states The final section presents the effects of psychosocial factors on immune responses and the potential impact of behavioral interventions in modulating immunity in healthy human subjects and in patients with AIDS Neuroscientists endocrinologists and immunologists will find the book interesting     [Psychopharmacology Abstracts](#) ,1979     [Endocannabinoids](#) ,2015-11-27 Endocannabinoids the latest volume in the International Review of Neurobiology series is a comprehensive overview of the state of the art research into the neurobiology of migraines It reviews the current knowledge and understanding in the field and provides a starting point for researchers and practitioners entering the field Contains the expertise of contributors in the



field of the neurobiology of migraines The endocannabinoid system is the biological system in the body which mediates the effects of cannabis Provides an up to date comprehensive overview of the biological functions of endocannabinoid signaling in the brain and how it regulates an array of processes such as brain development reward emotion and pain Progress in Tryptophan and Serotonin Research 1986 David A. Bender, Michael H. Joseph, Walter Kochen, Hans Steinhart, 2019-07-22 No detailed description available for Progress in Tryptophan and Serotonin Research 1986



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