

Summary

Martin Michaelis

Electrophysiological characteristics of injured peripheral nerves

Peripheral nerve injuries render many sensory neurons hyperexcitable. Axons tips of afferent neurons that start to regenerate following injury are one prominent site of ectopic action potential generation. Evoked responses correspond to the original sensory properties of the neuron. It is suggested that axon tips of lesioned afferents express the same or closely related transduction mechanisms that operate under normal conditions at their receptive endings. Cell somata of sensory neurons contribute to the ectopic activity by producing ongoing impulse discharge following nerve injury. Under experimental conditions, such ectopic ongoing activity is produced exclusively by muscle afferents, probably due to a paracrine signal released in the dorsal root ganglion; skin afferents remain silent. The ability to sustain discharges depends on intrinsic resonant properties of the cell membrane. Nerve injury induced ectopic activity is an important causative factor for neuropathic pain and related symptoms. Taking advantage of the specificity of underlying mechanisms will lead to more selective pharmacological treatment of neuropathic pain in the future.

Summary

Joel A. Black, Theodore R. Cummins, Sulayman D. Dib-Hajj, and Stephen G. Waxman
Sodium Channels and the Molecular Basis for Pain

Following peripheral nerve or tissue injury, primary sensory neurons (dorsal root ganglion [DRG] and trigeminal neurons) can exhibit a variety of electrophysiological abnormalities, including hyperexcitability and increased baseline sensitivity. Action potential electrogenesis in most mammalian neurons depends on the depolarization of voltage-gated sodium channels, of which there are at least eight different isoforms present within the nervous system. Distinct voltage-dependence, kinetic and pharmacological properties are associated with the differing sodium channel isoforms. Notably, three sensory neuron-specific sodium channels -- PN1, SNS and NaN -- are preferentially expressed in DRG and trigeminal neurons, in addition to several sodium channels more widely expressed throughout the nervous system. Dramatic alterations in the expression of differing sodium channels, and the currents produced by these channels, in DRG neurons are associated with nerve or tissue injury. This chapter reviews recent advances in the expression of sodium channels in small DRG neurons, which are predominantly nociceptive, in relation to neuropathic and inflammatory pain, and discusses implications of these advances for the development of new strategies for pain management.

Key Words: DRG neuron, hyperexcitability; ion channels; nerve injury; neuropathic pain.

Summary

Valerie M.K. Verge, Tracy D. Wilson-Gerwing, Laurie A. Karchewski and Kelly A. Gratto

Changes in DRG neurons after injury: possible involvement in the development and maintenance of neuropathic pain

The cell body response of sensory neurons to peripheral nerve injury is an important aspect of effective repair and is most often thought of as being protective to the neuron. However, increased plasticity, alterations in signaling molecules, and enhanced synthesis of growth factors and cytokines may also contribute to the development of neuropathic pain states. This

chapter will summarize aspects of the cell body response to injury of sensory neurons and the putative mechanisms believed to underlie these changes as they relate to the acquisition of neuropathic pain syndromes following complete or partial nerve lesions.

Key Words: Neuropathic pain, injury, neuropeptides, neurotrophins, cytokines, IL-6, PACAP, Galanin, NPY, P2X3, NGF, BDNF, NT-3, GDNF, nitric oxide synthase.

Summary

Neuroinflammation, Cytokines and Neuropathic Pain

Linda S. Sorkin

Inflammation contributes to neuropathic pain. This chapter looks at the inflammatory components of several animal models of neuropathic pain. The relationship among neuropathic pain, Wallerian degeneration and macrophage infiltration is explored. Relationships between the proinflammatory cytokines and the development of neuropathic pain are also discussed.

Key Words: Neuroimmune, tumor necrosis factor, interleukin-1, interleukin-6, neuritis, allodynia.

Summary

Victoria Chapman and Anthony H. Dickenson

Pharmacological plasticity associated with neuropathic pain states

The management of neuropathic pain states remains a clinical problem. Basic studies of animal models of neuropathy are greatly advancing our understanding of the neurobiological changes associated with peripheral nerve damage. In many instances the relevance of these changes to the pharmacological plasticity associated with neuropathy remains obscure. Here we discuss some of the potential analgesic targets for neuropathic pain states and their mechanisms of action. Interventions that reduce excitability, such as sodium and calcium channel blockers, are important potential analgesic candidates for these pain states. Conversely, increasing systems that inhibit somatosensory processing is a viable alternative approach. Recent studies have provided evidence that cannabinoid drugs are antinociceptive. Here, the potential of cannabinoids as novel analgesics for persistent pain states is discussed.

Key Words: Animal models of neuropathy; plasticity; sodium channels; calcium channels; gabapentin; cannabinoid drugs.

Summary

Susan M. Carlton and Richard E. Coggeshall

Sprouting/reorganization in the spinal cord after nerve injury

The morphological, neurochemical and receptor reorganizations observed in the spinal cord following various experimental nerve injuries (i.e. chronic constriction, partial nerve ligation or spinal nerve ligation) are summarized. The relationship of these changes to the development and maintenance of neuropathic pain are discussed.

Key Words: Nerve injury models; sprouting, myelinated fibers; Fos, plasticity after nerve lesions; peptides, plasticity after nerve lesions; amino acids, plasticity after nerve lesions;

biogenic amines, plasticity after nerve lesions; enzymes; plasticity after nerve lesions; receptors, plasticity after nerve lesions; dorsal horn, plasticity; neuropathic pain.

Summary

Jin Mo Chung and Kyungsoon Chung

Pre-clinical nerve ligation models: behavior and electrophysiology

This chapter discusses behavioral and electrophysiological aspects of animal models for neuropathic pain. Comparisons of different models are made while discussing several important aspects of neuropathic pain behaviors, such as appropriate behavioral tests and factors influencing neuropathic pain behaviors. A major point is that behavioral tests in animal models should be most relevant to human neuropathic pain. Since neuropathic pain patients suffer from various types of pain including mechanical allodynia, spontaneous burning pain, cold allodynia, and heat hyperalgesia, a good neuropathic pain model should therefore show behaviors representing one or hopefully all of these characteristics. However, we have to keep in mind that behavioral tests rely on animals' reactions, which depend not only on animals' perception (pain) but also expression (motor). Therefore, results of behavioral tests should always be interpreted cautiously.

In the second part of the chapter, electrophysiological evidence for abnormal activity of both axotomized and intact afferent neurons is discussed. Abnormal activity generated by sensory neurons seems to play an important role in initiating and maintaining neuropathic pain behaviors. These abnormal activities are generated not only from axotomized but also from intact afferent neurons after peripheral nerve injury, and both of them are important. However, the relative contribution of these two sources (axotomized and intact fibers) to pain behaviors is not clear. Furthermore, the detailed generation mechanisms of these the two components are not known and these should be a major focus of future research.

Key Words: Adrenergic receptors, animal model, causalgia, cold allodynia, CRPS, ectopic discharges, mechanical allodynia, neuropathic pain, purinergic receptors, spinal nerve ligation, sympathetically maintained pain.

Summary

Nigel A. Calcutt and Jason D. Freshwater

Animal models of toxic and metabolic sensory neuropathies

This chapter examines animal models of sensory neuropathies other than those induced by physical trauma. Clinical manifestations of peripheral sensory neuropathies range from sensory loss to spontaneous pain and tend to first occur in the longest nerves of the body. Studies of toxic and metabolic neuropathies in animals have largely used rodents to allow structural, functional, biochemical and behavioral investigations. Development of these models, particularly the behavioral assays used to assess pain perception, has been hindered by issues of systemic toxicity, concurrent motor neuropathy, the relatively short life-span of rodents and the shortness of their peripheral nerves. Nevertheless, there has been substantial progress in defining sensory dysfunction in a variety of animal models of peripheral neuropathies that has allowed investigation of underlying mechanisms of neurotoxicity and the efficacy of potential therapeutic agents. The validity of animal models of peripheral neuropathy will only be confirmed when they successfully mediate translation of mechanistically designed therapeutics from the laboratory to the clinic.

Key Words: Peripheral neuropathy, pain, diabetes, neurotrophins, aldose reductase, neurotoxins, cisplatin, taxol, vincristine, thalidomide.

Summary

Ralf Baron and Srinivasa N. Raja

Role of adrenergic transmitters and receptors in nerve and tissue injury related pain

Several studies in experimental animals and humans support the hypothesis that adrenergic receptors may play a role in the mechanisms of inflammatory and neuropathic pain. Clinical pain syndromes in which sympathetically maintained pain (SMP) might be a symptom are, e.g., complex regional pain syndroms (CRPS) and post-traumatic neuralgia. In these patients sympathetic blocks may relieve pain. The specific sites of interaction and the receptor subtype(s) that may be involved are controversial and need to be confirmed with additional studies. Several aspects of the pathophysiology of CRPS and SMP continues to puzzle investigators and hopefully future studies will shed light on these issues.

Key Words: Neuropathic, sympathetic, pain, afferent, nociceptor, norepinephrine, inflammation, CRPS, SMP, RSD, causalgia.

Summary

Karen M. Park and Richard H. Gracely

Evaluation of neuropathic pain

Many clinicians diagnose neuropathic pain after a patient's pain has not been relieved by routine analgesics. This chapter describes tests that can be used to diagnose neuropathic pain before a trial of routine analgesics. The time and resources necessary to complete testing can be varied according to the situation, from patient bedside in a busy clinic setting to research facility. Psychophysical constructs in the measurement of pain and clinical terminology are also described.

Key Words: Neuropathic pain, hyperalgesia, allodynia.

Summary

Per Kristian Eide

Glutamate Receptor Antagonists and Neuropathic Pain

During the last decade, major attention has been given to the role of glutamate receptors in neuropathic pain. Glutamate receptors play an important role in central sensitization, which represents an important pathophysiological mechanism of neuropathic pain. In animal models of neuropathic pain, N-methyl-D-aspartate (NMDA) receptor antagonists inhibit various behavioral responses such as allodynia-like responses. Several clinical trials in patients with peripheral or central neuropathic pain demonstrate that NMDA receptor antagonists modulate various characteristics of neuropathic pain, such as spontaneous ongoing pain, mechanical allodynia and abnormal temporal summation of pain. The clinical use of these drugs presently is restricted by their side-effect profile. However, the trials of NMDA receptor antagonists represent a step towards mechanism-based treatment of neuropathic pain.

Key Words: Neuropathic pain; central sensitization; glutamate; NMDA receptor antagonists; pain relief.

Summary

Charles P. Taylor

Antiepileptic Drugs for Treatment of Neuropathic Pain

Beginning with two controlled studies of carbamazepine for the treatment of trigeminal neuralgia in the early 1960's, it has become clear that several medications used mostly for preventing seizures also reduce neuropathic pain originating from injury to the peripheral or central nervous system. One drug mechanism thought to reduce neuropathic pain is a voltage-dependent blockade of the sodium channels that underlie action potentials generated in peripheral and central sensory neurons. In addition, several of the newer anticonvulsant medications, including the amino acid derivative, gabapentin, have less clearly defined mechanisms of action. Nevertheless, both types of drugs prevent allodynia in animal models of neuropathic pain, and reduce pain scores in controlled clinical trials. This brief review summarizes clinical evidence that several antiepileptic medications reduce pain caused by neuropathies, and also summarizes data in animal models that seek to clarify the cellular and molecular mechanisms involved.

Key Words: Carbamazepine, lamotrigine, gabapentin, phenytoin, felbamate, diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, allodynia, hyperalgesia.

Summary

Mark S. Wallace

Calcium Channel Antagonists for the Treatment of Pain

Several lines of evidence developed in preclinical models suggest that both spontaneous pain and evoked pain are mediated in part by voltage-dependent calcium channels (VDCC). There are six distinguishable types of VDCC presently described, designated L, N, P/Q, R and T; these are expressed throughout the nervous system. Preclinical studies suggest that N-type calcium channel antagonists are mainly effective in reducing pain associated with inflammation and tissue/nerve injury, although some effect has been shown in acute models of pain. Antinociceptive effects of L- and P/Q-type VDCC antagonists have also been reported; however, these effects appear to be moderate at best. This article will summarize the animal and human studies on the effects of the calcium channel antagonists on nociceptive processing.

Key Words: Calcium, channel, antagonist, blockers, pain, nociception, animal, human.

Summary

Hartmut Buerkle and Stuart A. Dunbar

Cholinergic, adenosinergic and α_2 adrenergic mechanisms in chronic neuropathic pain

The use of acetylcholinesterase inhibitors, adenosine and α_2 -adrenergic agonists in the management of chronic neuropathic pain is discussed in this section. The published experience with chronic neuraxial administration of these compounds is limited to a few studies of chronic epidural administration in cancer patients, and some case reports of chronic intrathecal administration in non-cancer pain patients. Preclinical data suggest that spinal delivery of adenosine and α_2 agonists may be an alternative to spinal opioids where tolerance has developed. There is a relative lack of cross tolerance between these three agent types. Among drugs in these three distinct classes, clonidine is as yet the only drug to receive

approval for epidural administration in cancer patients with intractable pain. While neostigmine and adenosine also appear safe given a lack of reported toxicity in animals and in human bolus dose studies, there is still a lack of clinical data to confirm that they lack neurotoxicity during chronic intrathecal infusion. Despite this, the potential advantages of the spinal delivery of these compounds includes enhanced efficacy in neuropathic pain states, a differential side effect profile that can be exploited, and a lack of cross tolerance with opioids. Further clinical studies are required to explore these and to establish a lack of toxicity during chronic intrathecal administration.

Key Words: α_2 -adrenergic agonist, acetylcholinesterase inhibitors, adenosine, clonidine, dexmedetomidine, muscarinic receptors, neostigmine, purinergic.



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