PAIN PHARMACOLOGY AND ANALGESIA

Maree T. Smith and Samantha M. South

Centre for Integrated Preclinical Drug Development and School of Pharmacy, The University of Queensland, St Lucia Campus, Brisbane, Queensland, Australia.

Keywords: pain: nociceptive, inflammatory, neuropathic, acute, chronic, nociceptor, analgesia, analgesic, opioids: morphine, Oxycodone, non-steroidal anti-inflammatory drugs, adjuvants: anticonvulsants, tricyclic anti-depressants, anti-arrhythmics, gabapentin, pregabalin.

Contents

1. Pain definitions
1.1 Pain – According to Duration
1.1.1 Acute Pain
1.1.2 Chronic Pain
1.2 Pain – According to Type
1.2.1 Nociceptive Pain
1.2.2 Inflammatory Pain
1.2.3 Neuropathic Pain
1.3 Emotional Response to Pain

2. Pain signaling system
2.1 Pain Detection
2.2 Functional Characteristics of the Pain Signaling Apparatus
2.2.1 Nociceptors
2.2.2 Primary Sensory Neurones
2.2.3 Primary Sensory Neurons and the Spinal Cord
2.2.4 Spinal Cord Neurons
2.3 Pain Characteristics
2.4 Animal Models of Nociception/Pain
2.5 Neurochemical Characteristics of the Nociceptive Signaling System
2.5.1 Transmission of Nociceptive Information from the Periphery to the Spinal Cord
2.6 Nociceptive Neurotransmitters and their Target Receptors
2.6.1 Excitatory Amino Acids and their Receptors
2.6.2 Co-containment of Neurotransmitters in Nerve Terminals
2.7 Descending Modulation of Nociception

3. Neural plasticity and pain
3.1 Inflammation
3.1.1 Inflammation and Peripheral Sensitization
3.1.2 Inflammation and Post-translational Changes
3.1.3 Inflammation-Induced Transcriptional Changes: Effects on Peripheral Sensitization
3.1.4 Inflammation and Central Sensitization
3.2 Peripheral Nerve Injury and Neuropathic Pain
3.3 Central Sensitization and Neuropathic Pain
3.3.1 Dysfunction of Central Inhibition
3. Non-Neuronal Cells in the DRG and the CNS
3.1 Satellite Glia Cells in the DRG
3.2 Activated Microglia and Astrocytes in the CNS
4. Endogenous pain relief system
4.1 Processing of low-intensity stimuli
4.2 Processing of high-intensity stimuli
4.3 Opioids
4.3.1 Heterodimeric Opioid Receptors
4.4 Tolerance to Opioids
4.4.1 Innate Tolerance
4.4.2 Acquired Tolerance
4.4.3 Tolerance to Opioid-Related Side-Effects
4.4.4 Prevention of the Development of Analgesic Tolerance
5. Strategies for producing pain therapeutics
5.1 Modulation of the NMDA Receptor-NOS Cascade
5.1.1 NMDA receptor antagonists
5.1.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
5.1.3 NOS inhibitors
5.1.4 SP antagonists
5.2 Inhibition of Pro-nociceptive Neurotransmitter Release
5.2.1 N-type Calcium Channel Blockers
5.2.2 Gabapentinoids
5.3 Voltage-Gated Sodium Channels as Potential Drug Targets in Persistent Pain States
5.3.1 Na,1.8
5.3.2 Na,1.9
5.3.3 Sodium Channels in Inflammatory Pain
5.3.4 Sodium Channels in Neuropathic Pain
5.4 Transient Receptor Potential Vanilloid Receptor-1 (TRPV1) as a Potential Drug Target
5.5 Purinergic (P2X) Receptors
5.6 Nerve Growth Factor (NGF) and trkA Receptors
5.7 Brain-Derived Neurotropic Factor (BDNF) and trkB Receptors
5.8 Nicotinic Cholinergic Agonists
5.9 Neuronal Nicotinic Cholinergic Antagonists
5.10 Anti-opioid Peptides
5.10.1 CCK-8
5.10.2 Dynorphin A
5.11 Adenosine
5.12 Cannabinoids
6. Pain assessment and pain assessment tools
7. Pharmacological treatment of pain: analgesics and adjuvants
7.1 Treatment of Pain in the Clinical Setting
7.2 Major Aims of the Treatment of Clinical Pain
7.3 Pharmacological management of pain: current treatment guidelines
7.4 Controlled or Sustained Release Oral Formulations
8. Analgesic Agents
8.1 Non-opioid Analgesics
8.1.1 Paracetamol
Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain may be described according to severity (mild, moderate, severe), duration (acute or chronic) or type (nociceptive, inflammatory, neuropathic). In the last two decades, considerable research directed at enhancing our collective understanding of the neurobiology of pain has revealed that persistent ongoing pain secondary to tissue inflammation or peripheral nerve injury is underpinned by considerable complexity and plasticity in the pain signaling system. Following tissue or peripheral nerve injury, there is sensitization of the somatosensory system so that innocuous stimuli are detected as painful (allodynia) or there is a heightened response to painful stimuli (hyperalgesia).

Although a large number of “pain” targets for potential modulation by small molecules or biologics have been identified with several of these molecules now in preclinical or clinical development, these potential new pain medicines are yet to reach the clinic. Hence, pain is currently managed according to the World Health Organisation’s 3-step Analgesic Ladder. For mild pain, non-opioid analgesics such as paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs are recommended, with adjuvants (e.g. antidepressants, anticonvulsants or anti-arrhythmics) added as required if
pain has a neuropathic component. For moderate pain, weak opioids such as codeine and tramadol are added to non-opioids and/or adjuvants, as required. For moderate to severe pain, strong opioids are recommended with morphine as the drug of choice due to its ready availability worldwide at low cost. Strong opioids may be co-administered with non-opioids and with adjuvants, as required. In the next decade, a new generation of pain medicines is likely to reach the market, thereby expanding the armamentarium of drugs available to clinicians for the management of persistent on-going pain.

1. Pain Definitions

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey and Bogduk, 1994). Individuals may describe their pain in terms of its severity, duration and type. As a patient’s emotional response to a painful stimulus contributes significantly to the pain experience, there are often large inter-individual differences in reports of pain severity evoked by apparently similar stimuli. Hence, there are no objective measures that can be used with validity to compare the severity of one person’s pain with that of another. Instead, a number of pain rating scales have been devised and validated for quantifying changes in pain severity within individuals (Melzack and Katz, 2006).

1.1 Pain – According to Duration

1.1.1 Acute Pain

The IASP has defined acute pain as “pain of recent onset and probable limited duration; it usually has an identifiable temporal and causal relationship to injury or disease” (Merskey and Bogduk, 1994). Acute pain such as that which occurs following surgery, trauma, burns or myocardial infarction, may be regarded as an adaptive response with a physiologically important role. Acute pain generally comprises two phases. The first phase (lasting seconds) “alerts” the individual to potentially dangerous stimuli and the second, subchronic phase (lasting hours to days) may be regarded as a “protective” mechanism characterized by “guarding” of the injured tissue as a means of promoting healing and recovery (Merskey and Bogduk, 1994).

1.1.2 Chronic Pain

Chronic pain is defined as “pain lasting for long periods of time. It commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause” (Merskey and Bogduk, 1994). Persistent pain is often regarded as a maladaptive response that confers no physiological advantage, such that the pain state itself has become the “disease”, requiring treatment (Cousins, 2007). Persistent pain may have multiple components including nociceptive pain, inflammatory pain and neuropathic pain, which are variously defined as follows (Devor and Seltzer, 1999):

1.2 Pain – According to Type

1.2.1 Nociceptive Pain

Nociceptive pain refers to the normal, acute pain sensation evoked by activation of...
specialized primary afferent nerve fibres (nociceptors) located in undamaged or previously undamaged skin, viscera and other organs in the absence of sensitization.

1.2.2 Inflammatory Pain

Inflammatory pain such as arthritis may be defined as hypersensitivity that arises in inflamed tissue following sensitization of peripheral nerve terminals.

1.2.3 Neuropathic Pain

Neuropathic pain is defined by the IASP as pain due to a dysfunction of, or damage to, a nerve or group of nerves, primarily peripheral nerves, although pain due to central nervous system (CNS) damage (“central pain”) may share these characteristics. Examples of peripheral neuropathic pain are painful diabetic neuropathy, post-herpetic neuralgia (post-shingles pain), HIV-AIDS (human immunodeficiency virus-acquired immunodeficiency syndrome) neuropathy and chemotherapy-induced neuropathic pain. The most common types of central neuropathic pain are post-stroke pain, pain in multiple sclerosis and spinal cord injury pain.

At present, persistent inflammatory and neuropathic pains present great challenges to general practitioners and pain specialists alike, because the currently available drugs used to treat these conditions have significant limitations. Moreover, opioids that are effective for the relief of moderate to severe nociceptive pain are often considerably less effective for the relief of neuropathic pain, particularly when administered by systemic routes.

1.3 Emotional Response to Pain

Although the IASP definition of pain recognizes its multi-dimensional nature, incorporating a patient’s emotional response to a noxious stimulus, it is only relatively recently that brain imaging techniques have begun to explore this latter aspect in humans, and most research attention has focused on brain imaging of acute pain (Kupers and Kehlet, 2006). By contrast, in the last two decades, there have been considerable advances in our collective understanding of the neurobiology of pain, particularly persistent pain, which has revealed many novel potentially “druggable” targets for the development of new pain therapeutics for human use (Pace et al., 2006; Schaible, 2007). Hence, this chapter has been structured in two parts, with the first providing an overview of the pain signaling system, highlighting recent advances in our understanding of the neurobiology of pain with emphasis on potential targets for the development of new pain therapeutics. The second provides an overview of medications currently used for managing acute and chronic pain.

2. Pain Signaling System

2.1 Pain Detection

Put simply, pain signals from peripheral tissue exposed to damaging or potentially damaging stimuli are detected by nociceptors located in the affected tissue and whose
cell bodies are located in the dorsal root ganglia (Sherrington, 1906). Nociceptive (pain) signals are transmitted via nociceptive primary afferent nerve fibres (so-called first-order neurones) to the outer layers (laminae I and II) of the dorsal aspect of the spinal cord (dorsal horn) (Sherrington, 1906). Nociceptive signals are then relayed from the dorsal horn by second-order neurones via spinothalamic tracts to higher centres in the brain, which may in turn activate descending inhibitory mechanisms to reduce the severity of the perceived pain to tolerable levels (Figure 1) (Sherrington, 1906; Dubner, 2004; Yaksh, 2006).

2.2 Functional Characteristics of the Pain Signaling Apparatus

2.2.1 Nociceptors

Nociceptors (Figure 1) in the skin (cutaneous), muscle, joints, viscera and dura that detect noxious (damaging or potentially damaging) stimuli (Sherrington, 1906), respond in aggregate to a broad range of physical (heat, cold, pressure) or chemical (acid, irritants, inflammatory mediators) stimuli, but only at intensities capable of causing tissue damage (Millan, 1999; Caterina et al., 2000). Nociceptive information is relayed from the nociceptors to the CNS via axons that are either small (2-6 \( \mu \)m) myelinated A\( \delta \)-fibres with a conduction velocity in the range 4-30 m/s, or thin (0.4-1.2 \( \mu \)m), unmyelinated C-fibres with conduction velocities < 2.5 m/s. Additionally, cutaneous mechanoreceptors are often supplied by large (> 10 \( \mu \)m), fast (30-100 m/s) myelinated A\( \beta \) fibres that, in the absence of tissue or nerve injury, are responsive only to touch, vibration, pressure and other modes of non-noxious, low intensity mechanical stimuli (Woolf et al., 1994; Millan, 1999; Willis and Coggeshall, 2004). Generally, a single discharge of an individual nociceptor is not perceived as noxious and many nociceptors need to be recruited for “pain” to be perceived (Millan, 1999; Willis and Coggeshall, 2004). However, in the presence of persistent inflammation or nerve injury, A\( \beta \) fibres undergo phenotypic change such that non-noxious stimuli may become encoded as noxious stimuli (Dubner, 2004).

2.2.2 Primary Sensory Neurones

The cell bodies of primary afferent sensory neurons that innervate the limbs and trunk are located in sensory ganglia associated with spinal nerves (dorsal root ganglia). The axons of these primary afferent sensory neurones give rise to a peripheral branch that innervates various tissue types and a central branch that travels through a dorsal root to enter the spinal cord and synapse with second-order neurones (Todd and Koerber, 2006). Fibres that innervate skin are referred to as cutaneous sensory neurons, whereas afferent fibres innervating abdominal or pelvic viscera are termed visceral afferents (Todd and Koerber, 2006). Together, these primary sensory neurones are a means for providing ongoing surveillance of the external environment as well as the ongoing state of the body itself (Todd and Koerber, 2006).
Figure 1. Nociceptive signals are detected by specialized primary afferent nerve fibres (nociceptors) located in the injured peripheral tissue from where they are transmitted to the dorsal horn of the spinal cord. Nociceptive signals are then relayed to higher centres in the brain, which may result in activation of the descending inhibitory system to reduce the severity of the perceived pain. (See also Figure 6)

2.2.3 Primary Sensory Neurons and the Spinal Cord

The central terminals of nociceptive primary afferents mainly terminate in the superficial layers (laminae I and II) of the dorsal horn, the site of the first synapse in ascending pathways that convey sensory information to the brain (Todd and Koerber, 2006). However, it should be noted that myelinated and unmyelinated fibres that signal the presence of innocuous mechanical and thermal stimuli also project to these same laminae (Todd and Koerber, 2006). Low-threshold Aβ mechanoreceptors terminate in deeper laminae (Willis and Coggeshall, 2004). The rostrocaudal and mediolateral location of the central terminals of primary afferents in the dorsal horn encodes the location of the afferents’ peripheral receptive field, generating a somatotopic map of the body surface in the horizontal plane of the dorsal horn (Woolf and Salter, 2006). At the level of individual nerve territories, the map is organized such that neighbouring peripheral fields occupy contiguous parts of the spinal cord (Woolf and Salter, 2006).

2.2.4 Spinal Cord Neurons

Dorsal horn neurones can be classified as (i) projection neurons, (ii) local interneurons, or (iii) propriospinal neurons (Willis and Coggeshall, 2004). Although projection neurons are the primary output from the spinal cord, transferring sensory information
from the spinal cord to the brain, they represent a small minority of the total number of cells in the dorsal horn (Woolf and Salter, 2006).

### 2.2.4.1 Projection Neurons and the Spinal Cord

Neurons with axons that project to the brain are present in relatively large numbers in lamina I and are scattered through the deeper part of the dorsal horn (laminae III-VI) and the ventral horn. Those in lamina I and many of those from deeper laminae have axons that cross the midline and ascend to a variety of supraspinal targets including the thalamus, midbrain periaqueductal grey matter, lateral parabrachial area of the pons and various parts of the medullary reticular formation (Todd and Koerber, 2006). Projection neurons are also involved in the activation of descending control systems, which in turn modulate dorsal horn neurons through both excitatory and inhibitory mechanisms (Woolf and Salter, 2006).

### 2.2.4.2 Spinal Interneurons

The majority of the dorsal horn neuronal population is comprised of interneurons that arborize in the same segment generally close to the cell body, although it is also quite common for cells to give rise to axons that extend into other laminae (Todd and Koerber, 2006; Woolf and Salter, 2006). Dorsal horn inter-neurones may be inhibitory cells that use gamma-aminobutyric acid (GABA) and/or glycine as their principal neurotransmitter, and excitatory glutamatergic cells (Todd and Spike, 1993). GABAergic cells comprise ∼25-30% of neurones in lamina I/II and ∼40% of those in lamina III (Todd and Sullivan, 1990). Many inhibitory interneurons are spontaneously active, and in this way maintain an ongoing tonic inhibitory control over dorsal horn nociceptive processing (Woolf and Salter, 2006). Excitatory glutamatergic interneurons identified by the presence of vesicular glutamate transporters (VGLUTs), are present in large numbers of axons in the spinal cord (Todd et al., 2003). Within the dorsal horn, VGLUT1-expressing neurons are largely restricted to the deeper laminae (III-VI) with VGLUT present mainly on the central terminals of myelinated primary afferents (Todd et al., 2003) whereas VGLUT2 is present on numerous axon terminals that are more evenly distributed throughout the dorsal horn (Todd et al., 2003).

### Bibliography

Abbadie C., Trafton J., Liu J., Mantyl P.W., Basbaum A.I. (1997) Inflammation increases the distribution of dorsal horn neurons that internalize the neurokinin-1 receptor in response to noxious and non-noxious stimulation. *J Neurosci* 17, 8049-8060. [Study showing that after inflammation, dorsal horn circuits are reorganized compared with the non-inflamed state and that this reorganization demonstrates a critical]
contribution of SP.]

Akkari R., Burbiel J.C., Hockemeyer J., Muller C.E. (2006) Recent progress in the development of adenosine receptor ligands as antiinflammatory drugs. *Curr Top Med Chem* 6, 1375-1399. [Review focuses on adenosine ligands or adenosine signalling modulators published or patented in the last 3 years.]


Babul N., Darke A.C., Hagen N. (1995) Hydromorphone metabolite accumulation in renal failure. *J Pain Symptom Manage* 10, 184-186. [First case report demonstrating that hydromorphone-3-glucuronide (H3G) plasma levels accumulate in renal failure such that H3G levels exceed those of hydromorphone by ~100-fold in a patient with renal failure compared with only ~30-fold in patients with normal renal function.]

Backlund M., Lindgren L., Kajimoto Y., Rosenberg P.H. (1997) Comparison of epidural morphine and oxycodone for pain after abdominal surgery. *J Clin Anesth* 9, 30-35. [Clinical study showing that the potency of epidural oxycodone for the relief of post-operative pain is ~10% that of epidural morphine.]

Bartlett S.E., Cramond T., Smith M.T. (1994) The excitatory effects of morphine-3-glucuronide are attenuated by LY274614, a competitive NMDA receptor antagonist, and by midazolam, an agonist at the benzodiazepine site on the GABAA receptor complex. *Life Sci* 54, 687-694. [Study describing the dose-dependent neuro-excitatory effects of the major morphine metabolite, morphine-3-glucuronide in the rat following intracerebroventricular injection with these effects being attenuated by an agonist at the GABAA-benzodiazepine receptor complex and an antagonist at the NMDA receptor.]

Basbaum A.I. (1999) Distinct neurochemical features of acute and persistent pain. *Proc Natl Acad Sci USA* 96, 7739-7743. [Used preprotachykinin knockout mice and protein kinase C gamma knockout mice to emphasize that acute and persistent pain are underpinned by distinctly different neurochemical profiles.]


Bitner R.S., Nikkel A.L., Curzon P., Arneric S.P., Bannon A.W., Decker M.W. (1998) Role of the nucleus raphe magnus in antinociception produced by ABT-594: immediate early gene responses possibly linked to neuronal nicotinic acetylcholine receptors on serotonergic neurons. *J Neurosci* 18, 5426-5432. [Study showing that the antinociceptive effects of the novel cholinergic channel modulator, (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594), may in part involve the activation of the nucleus raphe...
magnus, a site where alpha4-containing nAChRs are expressed by serotonergic neurons.]


Cao Y.Q., Mantyh P.W., Carlson E.J., Gillespie A.-M., Epstein C.H., Basbaum A.I. (1998) Primary afferent tachykinins are required to experience moderate to intense pain. Nature (London) 392, 390-394. [Study undertaken in the preprotachykinin A gene (PPT-A) knockout mouse showing that the release of tachykinins such as substance P and neurokinin A from primary afferent pain-sensing receptors (nociceptors) is required to produce moderate to intense pain.]

Cardenas C.G., Del Mar L.P., Cooper B.Y., Scroggs R.S. (1997) SHT4 receptors couple positively to tetrodotoxin-insensitive sodium channels in a subpopulation of capsaicin-sensitive rat sensory neurons. J Neurosci 17, 7181-7189. [Electrophysiological study suggesting that SHT- and PGE2-mediated increases in Na⁺ current may be involved in hyperesthesia in different but overlapping subpopulations of nociceptors.]

Caterina M.J., Leffler A., Malmberg A.B., Martin W.H., Trafton J., Petersen-Zeitz K.R., Koltzenburg M., Basbaum A.I., Julius D. (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288 (5464), 306-313. [First study to show that sensory neurons from TRPV1/VR-1 knockout mice are severely deficient in their responses to noxious mechanical stimuli, vanilloid-evoked pain behaviour, detection of painful heat, and thermal hypersensitivity in inflammation.]


Chabal C., Jacobson L., Russell L.C., Burchiel K.J. (1992) Pain response to perineuronal injection of normal saline, epinephrine, and lidocaine in humans. Pain 49, 9-12. [Clinical study assessing sensitivity of neurona to epinephrine that demonstrates that alpha-adrenergic sensitivity is only one of many components sustaining or exacerbating pain after nerve injury.]

Chang G., Chen L., Mao J. (2007) Opioid tolerance and hyperalgesia. Med Clin North Am 91, 100-211. [Review of clinical implications of the phenomena of opioid-induced hyperalgesia, tolerance and dependence that have been documented in both clinical and preclinical studies.]


Coderre T.J. (1993) The role of excitatory amino acid receptors and intracellular messengers in persistent nociception after tissue injury in rats. Mol Neurobiol 7, 329-346. [Review evidence that central sensitization, and the persistent nociception it leads to, are dependent on an action of glutamate and aspartate at excitatory amino acid (EAA) receptors and influenced by various intracellular second messengers that are coupled to EAA receptors (nitric oxide, arachidonic acid, and protein kinase C, immediate early genes).]

Coggeshall R.E., Carlton S.M. (1998) Ultrastructural analysis of NMDA, AMPA, and kainate receptors on unmyelinated and myelinated axons in the periphery. J Comp Neurool 391, 78-86. [Study to determine the proportions of unmyelinated cutaneous axons at the dermal-epidermal junction in glabrous skin and of myelinated and unmyelinated axons in the sural and medial plantar nerves that immunolabel for subunits of the ionotropic glutamate receptors.]

Coggeshall R.E., Tate S., Carlton S.M. (2004) Differential expression of tetrodotoxin-resistant sodium channels Nav1.8 and Nav1.9 in normal and inflamed rats. Neurosci Lett 355, 45-48. [Study shows that tetrodotoxin-resistant Na+ channel subunits Nav1.8 (SNS) and Nav1.9 (SNS2) are transported to the periphery in normal animals and are differentially regulated during inflammation. An increase in Nav1.8 expression in myelinated axons suggests that these may contribute to peripheral sensitization and
inflammatory.]


Cousins M.J. (2007) Persistent Pain: A Disease Entity. *J Pain Symptom Manage* **33**, S4-S10. [Review presenting evidence of independent, pain-perpetuating pathophysiologic changes that occur after, or in the absence of, acute painful events or concomitant painful conditions in the central nervous system.]


Daniels D.J., Lenard N.R., Etienne C.L., Law P.Y., Roerig S.C., Portoghese P.S. (2005) Opioid-induced tolerance and dependence in mice is modulated by the distance between pharmacophores in a bivalent ligand series. *Proc Natl Acad Sci USA* **102**, 19208-19213. [A study investigating the possible physical interaction between mu and delta opioid receptors using bivalent ligands that contain different length spacers shows that physical interaction between the mu and delta opioid receptors modulates mu-mediated tolerance and dependence.]


De Biasi S., Rustioni A. (1988) Glutamate and substance P coexist in primary afferent terminals in the superficial laminae of spinal cord. *Proc Natl Acad Sci USA* **85**, 8720-8724. [Immunocytochemical assessment of the superficial dorsal horn demonstrated that substance P and glutamate were co-localized, indicating the possibility of co-release of these neuromediators from the same primary afferent terminal.]


Devor M. (2006) Sodium channels and mechanisms of neuropathic pain. *J Pain* 7 (Suppl 1), S3-S12. [Review on sodium channels and neuropathic pain within the context of the pain system.]


Dib-Hajj S.D., Tyrrell L., Black J.A., Waxman S.G. (1998) NaN, a novel voltage-gated Na channel, is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy *Proc Natl Acad Sci USA* 95, 8963-8968. [Study demonstrating a preferential expression of NaN in DRG and trigeminal ganglia and the reduction of NaN mRNA levels in DRG after axonal injury, suggesting that NaN, together with SNS/PN3, may influence the generation of electrical activity in peripheral sensory neurons.]


Dougherty P.M., Palecek J., Paleckova V., Sorkin L.S., Willis W.D. (1992) The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *J Neurosci* 12, 3025-3041. [Study showing a role for excitatory amino acids in the transmission of sensory information from primary afferent fibers to dorsal horn neurons and a role for NMDA receptors in the generation of hyperalgesia.]


Duggan A.W., Riley R.C., Mark M.A., MacMillan S.J.A., Schaible H.G. (1995) Afferent volley patterns and the spinal release of immunoreactive substance P in the dorsal horn of the anaesthetised spinal cat. *Neurosci* 65, 849-858. [Using microprobes bearing immobilized SP antibodies, paper shows maximal SP release from central terminals of primary afferent fibres occurs with relatively few impulses and at low frequencies in a manner similar to that from peripheral terminals of these fibres.]


Dunbar P.J., Chapman C.R., Buckley F.P., Gavrin J.R. (1996) Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. *Pain* 68, 265-270. [Clinical study showing that the analgesic equivalency ratio of hydromorphone to morphine is 3:1 for the treatment of oral mucositis in bone marrow transplant patients contrary to the widely accepted ratio of 7:1 determined from single dose studies.]

Dunlop J. (2006) Glutamate-based therapeutic approaches: targeting the glutamate transport system. *Curr Opin Pharmacol* 6, 103-107. [Review of development of EAAT transporter inhibitors with improved subtype selectivity as tools for elucidating the contribution of each transporter subtype to the regulation of extracellular glutamate homeostasis and for the discovery of compounds capable of upregulating the activity of EAAT2.]

phenomena of tolerance and hyperalgesia and their clinical implications.]


Fitzgerald E.M., Okuse K., Wood J.N., Dolphin A.C., Moss S.J. (1999) cAMP-dependent phosphorylation of the tetrodotoxin-resistant voltage-dependent sodium channel SNS. J Physiol (London) 516, 433-446. [Paper examining PKA phosphorylation of the cloned α-subunit of the rat sensory neurone-specific TTX-r channel SNS using site-directed mutagenesis, demonstrates that the removal of five PKA consensus sites strongly reduces the degree to which SNS is modulated by cAMP-dependent phosphorylation.]

Food and Drug Administration (1999) Over-the-counter drug products containing analgesic/antipyretic active ingredients for internal use; required alcohol warning; final rule; compliance date. Food and Drug Administration, HHS, Fed Regist 64, 13066-13067.

Fundytus M.E., Fisher K., Dray A., Henry J.L., Coderre T.J. (1998) In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats. Neuroreport 9, 731-735. [Study involving intrathecal administration of antibodies raised against the C-terminals of mGluR1 and mGluR5 in various rat pain models, demonstrated that mGluRs are involved in nociceptive processing in persistent pain states but not acute pain signaling.]

Furuyama T., Kiyama H., Sato K., Park H.T., Maeno H., Takagi H., Tohyama M. (1993) Region-specific expression of subunits of ionotropic glutamate receptors (AMPA-type, KA-type and NMDA receptors) in the rat spinal cord with special reference to nociception. Brain Res Mol Brain Res 18, 141-151. [Study in the rat showing that the subunit composition of AMPA-type receptors regulating motor neurons is different from that of AMPA-type receptors in the spinal sensory neurons, and that there are at least two types of glutamergic systems which regulate motor neurons: via AMPA-type receptors and via NMDA receptors.]


Chem 271, 5768-5776. [First study to provide evidence that the mechanism of action of gabapentin is via interaction with alpha2delta subunit of a calcium channel.]


Gillen C., Haurand M., Kobelt D.J., Wnendt S. (2000) Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. Nauyn Schmiedebergs Arch Pharmacol 362, 116-121. [First study to define the binding of tramadol hydrochloride [(1RS,2RS)-2-[(dimethyl-amino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride] and its metabolites M1, M2, M3, M4 and M5 at the cloned human mu-opioid receptor and to show that the metabolite (+)-M1 is responsible for the mu-opioid-derived analgesic effect.]


Gold M.S., Levine J.D., Correa A.M. (1998) Modulation of TTX-R INa by PKC and PKA and their role in PGE2-induced sensitization of rat sensory neurons in vitro. J Neurosci 18, 1108-1112. [Study showing that agents that produce hyperalgesia, i.e. prostaglandin E2, adenosine, and serotonin, can modulate tetrodotoxin (TTX)-resistant sodium current suggesting that modulation of TTX-resistant sodium current may be a mechanism for sensitization of nociceptors.]

Gold M.S., Weinreich D.B., Schuster M.J., Levine J.D. (1996) Hyperalgesic agents increase a tetrodotoxin-resistant Na+ current in nociceptors. Proc Natl Acad Sci USA 93, 1108-1112. [Study showing that agents that produce hyperalgesia, i.e. prostaglandin E2, adenosine, and serotonin, can modulate tetrodotoxin (TTX)-resistant sodium current suggesting that modulation of TTX-resistant sodium current may be a mechanism for sensitization of nociceptors.]

Gold M.S. (1999) Tetrodotoxin-resistant Na+ currents and inflammatory hyperalgesia. Proc Natl Acad Sci USA 96, 7645-7649. [Review of evidence supporting a role for tetrodotoxin (TTX)-resistant Na+ currents in the sensitization of primary afferent neurons and inflammatory-induced hyperalgesia.]

Gold M.S., Weinreich D., Kim C.S., Wang R., Trecanor J., Porreca F., Lai J. (2003) Redistribution of Na(V)1.8 in uninjured axons enables neuropathic pain. J Neurosci 23, 158-166. [Study demonstrating that Na(V)1.8 expression increases in unmyelinated axons along the sciatic nerve and that attenuation of Na(V)1.8 expression prevented the redistribution of Na(V)1.8 in the sciatic nerve and reversed sciatic nerve ligation-induced neuropathic pain.]


Guo W., Zou S., Tal M., Ren K. (2002) Activation of spinal kainate receptors after inflammation: behavioral hyperalgesia and subunit gene expression. Eur J Pharmacol 452, 309-318. [Study showing that the neural response to CFA-induced inflammation and hyperalgesia involves the activation of GluR5 and GluR6 subunits of kainate receptors.]


approaches to pain management, the analgesic "ladder", and opioids.]
Harris D.S., Mendelson J.E., Lin E.T., Upton R.A., Jones R.T. (2004) Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. *Clin Pharmacokinet* 43, 329-340. [In opioid-experienced volunteers, there were less than dose-proportional increases in plasma buprenorphine concentrations were proposed to contribute to the observed plateau for most pharmacodynamic effects as the dose is increased.]
Heiskanen T., Kalso E. (1997) Controlled-release oxycodone and morphine in cancer related pain. *Pain* 73, 37-45. [In a randomized controlled study in patients with cancer pain, the total opioid consumption ratio of oxycodone to morphine was 2:3 when oxycodone was administered first, and 3:4 when oxycodone was administered after morphine. Significantly more vomiting occurred with morphine, whereas constipation was more common with oxycodone.]
Heiskanen T., Olkkola K.T., Kalso E. (1998) Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* 64, 603-611. [A randomized, double-blind crossover study in healthy human CYP2D6 extensive metabolizers pre-treated with quinidine on one occasion or placebo on another showed that a quinidine-induced significant reduction in plasma oxymorphone levels did not significantly alter the pharmacodynamic effects of oxycodone.]
Heppenstall P.A., Lewin G.R. (2001) BDNF but not NT-4 is required for normal flexion reflex plasticity and function. *Proc Natl Acad Sci USA* 98, 8107-8112. [Study utilising a spinal cord preparation from BDNF and NT-4 knockout mice demonstrating a direct role for presynaptic BDNF release from sensory neurons in the modulation of pain-related neurotransmission.]
Hill D.R., Shaw T.M., Graham W., Woodruff G.N. (1990) Autoradiographical detection of cholecystokinin A receptors in primate brain using 125I Bolton Hunter CCK 8 and 3H MK329. *J Neurosci* 10, 1070-1081. [Study using in vitro autoradiography to show that CCK-A receptors in primate brain may be involved in the processing of sensory information from the gut, the regulation of hormone secretion, and the activity of dopamine cell activity.]
Hogg R.C., Bertrand D. (2007) Partial agonists as therapeutic agents at neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol* 73, 459-468. [This review discusses the pharmacological properties of partial agonists and recent research developments in the field of partial agonists acting at nicotinic receptors.]
Hokfelt T. (1991) Neuropeptides in perspective – The last 10 years. *Neuron* 7, 867-879. [Review of the scientific investigation of neuropeptides, including synthesis, localisation, role in neuronal plasticity and potential for development as therapeutic compounds.]
Hollmann M., Heinemann S. (1994) Cloned glutamate receptors. *Ann Rev Neurosci* 17, 31-108. [Comprehensive review of the cloned glutamate receptors, including ligands, function and location.]
Hong S., Morrow T.J., Paulson P.E., Isom L.L., Wiley J.W. (2004) Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons in the rat. *J Biol Chem* 279, 29341-29350. [Study showing significant increases in the expression of Na(+)1.3 and Na(+) 1.7 and decreases in the expression of Na(+) 1.6 and Na(+)1.8 in DRG neurones from streptozotocin-induced diabetic rats and increased phosphorylation of Na(+)1.6 and Na(+)1.8. These results suggest that both TTX-S and TTX-R sodium channels play important roles and that differential phosphorylation of sodium channels contributes to painful diabetic neuropathy.]
Honig S., Murray K.A. (1984) An appraisal of codeine as an analgesic: single-dose analysis. *J Clin Pharmacol* 24, 96-102. [Clinical study of single dose, codeine versus acetaminophen in the post-operative setting. This paper also provides a review the literature highlighting the difficulty in unequivocally establishing the value of codeine as an analgesic, in acceptable oral doses, in the single dose setting.]
Hoskin P.J., Hanks G.W., Aherne G.W., Chapman D., Littleton P., Filshie J. (1989) The bioavailability...

Hur C., Chan A.T., Tramontano A.C., Gazelle G.S. (2006) Coxibs versus combination NSAID and PPI therapy for chronic pain: an exploration of the risks, benefits, and costs. *Ann Pharmacother* **40**, 1052-1063. [Systematic review comparing combination therapy with a nonselective NSAID and PPI relative to coxibs reported that both treatment paradigms provided equivalent pain control but coxibs have a lower GI tract complication profile but at an unknown increased risk of cardiovascular events and a greater financial cost.]


Inturrisi C.E. (2002) Clinical pharmacology of opioids for pain. *Clin J Pain* **18** (Suppl), S3-13. [Comprehensive review of the clinical pharmacology of opioids for the management of pain; topics covered include opioid receptors, opioids (endogenous and exogenous), pharmacokinetics, issues related to opioid rotation, tolerance and dependence, as well as advantages and disadvantages of opioids for the management of pain.]


states. *Pain* **123**, 75-82. [Study in rats showing antisense oligodeoxynucleotides targeting the Nav 1.8 sodium channel decreased mechanical allodynia following CFA-induced inflammation and chronic constriction injury of the sciatic nerve but did not alter mechanical allodynia in a vincristine chemotheraphy-induced neuropathic pain model or a skin-incision model of post-operative pain.]

Kalso E., Poyhia R., Onnela P., Linko K., Tigerstedt I., Tammisto T. (1991) Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Scand* **35**, 642-646. [A clinical study showing that in post-surgical patients, intravenous oxycodone was more potent, had a faster onset and longer duration of analgesic action than intravenous morphine.]


King T., Ossipov M.H., Vanderah T.W., Porreca F., Lai J. (2005) Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? *Neurosignals* **14**, 194-205. [Review of the evidence that prolonged opioid exposure enhances a descending pain facilitatory pathway from the RVM that is mediated at least in part by CCK activity and is essential for the maintenance of antinociceptive tolerance.]


Ko S., Zhao M.G., Toyoda H., Qiu C.S., Zhuo M. (2005) Altered behavioral responses to noxious stimuli and fear in glutamate receptor 5 (GluR5)- or GluR6-deficient mice. *J Neurosci* **25**, 977-984. [Study that used GluR5 and GluR6 subunit knockout mice to show that GluR5 is the kainate subunit involved in capsaicin-evoked or inflammatory pain but GluR6 is the kainate subunit involved in fear-memory and lateral amygdala synaptic potentiation.]


Kovelowski C.J., Ossipov M.H., Sun H., Lai T.P., Malan T.P., Porreca F. (2000) Supraspinal cholecystokinin may drive tonic descending facilitation mechanisms to maintain neuropathic pain in the rat. *Pain* **87**, 265-273. [Study in rats implicating descending nociceptive facilitatory pathways in the maintenance of neuropathic pain that appears to be dependent on CCK release, and that may be driven by sustained afferent input from injured peripheral nerves to brainstem sites.]


possible psychological adverse effects.


Kurrikoff K., Koks S., Matsui T., Bourin M., Arend A., Unapuu M., Vasar E. (2004) Deletion of the CCK2 receptor gene reduces mechanical sensitivity and abolishes the development of hyperalgesia in mononeuropathic mice. *Eur J Neurosci* 20, 1577-1586. [Study showing that CCK2 knockout mice (i) have increased expression of CCK1, delta and kappa opioid receptor, (ii) are hyposensitive to mechanical stimulation and (ii) don’t develop allodynia after peripheral nerve injury but have increased spinal POMC expression. Together these data suggest that mechanical sensitivity and development of neuropathic pain are regulated by antagonistic interactions between CCK and opioid systems.]


Lai J., Gold M.S., Kim C.S., Bian D., Ossipov M.H., Hunter J.C., Porreca F. (2002) Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8. *Pain* 95, 143-152. [Rat study showing administration of specific antisense oligodeoxynucleotide to NaV1.8 reversed spinal nerve injury-induced neuropathic pain suggesting that NaV1.8 may be a suitable target for novel anti-neuropathic drugs due to its restricted distribution to sensory nerves.]

Lai J., Luo M.C., Chen Q., Ma S., Gardell L.R., Ossipov M.H., Porreca F. (2006) Dynorphin A activates bradykinin receptors to maintain neuropathic pain. *Nat Neurosci* 9, 1534-1540. [First study to show that dynorphin promotes pronociceptive signalling through agonist action at bradykinin receptors and suggest new avenues for therapeutic intervention.]


Lalovic B., Phillips B., Risler L.L., Howald W., Shen D.D. (2004) Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. *Drug Metab Dispos* 32, 447-454. [Study used expressed human CYP’s, human liver microsomes and intestinal mucosal microsomes to show that the total intrinsic clearance for noroxycodone formation was 8 times greater than that for oxymorphone formation with liver microsomal N-demethylation being 4-5 times greater than that of intestinal microsomes.]


dynorphin. *J Pharmacol Exp Ther* **299**, 6-11. [Review of the potential mechanisms through which dynorphin contributes to spinally mediated antinociception, as well its interaction with multiple sites on the NMDA receptor complex to produce nociception and potential toxicity.]


Luo Z.D., Calcutt N.A., Higuera E.S., Valder C.R., Song Y.-H., Svensson C.I., Myers R.R. (2002) Injury type-specific calcium channel α2δ-1 subunit up-regulation in rat neuropathic pain models correlates with anti-allodynic effects of gabapentin. *J Pharm Exp Ther* **303**, 1199-1205. [Study demonstrating that gabapentin-sensitivity of mechanical allodynia secondary to peripheral nerve injury induced by chronic constriction injury of the sciatic nerve, spinal nerve transection or ligation, diabetes-induced neuropathy but not vincristine-induced chemical neuropathy, was correlated in rats with upregulation of alpha2delta-1 subunit expression in the DRG and/or spinal cord.]


Ma Q.-P., Allehone A.J., Woolf C.J. (1998) Morphine, the NMDA receptor antagonist MK801 and the tachykinin NK1 receptor antagonist RP67580 attenuate the development of inflammation-induced
progressive tactile hypersensitivity. *Pain* **77**, 49-57. [Study showing intermittent tactile stimulation of the CFA-induced inflamed hindpaw to induce inflammatory progressive tactile hypersensitivity is sensitive to morphine, and to a lesser extent NMDA and NK1 receptor antagonists.]

Malmberg A.B., Yaksh T.L. (1995) Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behavior and antinociception in the formalin and hot-plate tests in rats. *Pain* **60**, 83-90. [Study in rats showing that chronic intrathecal infusion of omega-conopeptides that block N-type voltage-sensitive calcium channels produce significant antinociception with minimal development of tolerance.]


that the CCK 2 antagonist L-365,260 does not augment the analgesic effect of morphine in subjects with chronic neuropathic pain.


McCleane G. (2007) Topic analgesics. Med Clin North Am 91, 125-139. [Review of agents that have been used topically for pain management.]


Meller S.T., Dykstra C., Gebhart G.F. (1996) Acute thermal hyperalgesia in the rat is produced by activation of N-methyl-D-aspartate receptors and protein kinase C and production of nitric oxide. Neuroscience 71, 327-335. [Study showing that N-methyl-D-aspartate induced thermal hyperalgesia is mediated by activation of nitric oxide synthase and protein kinase C, but not by phospholipase C, phospholipase A2, cyclo-oxygenase or lipoxygenase.]


Melzack R., Katz J. (2006) Pain assessment in adult patients. In: Wall and Melzack’s Textbook of Pain McMahon S.B., Koltzenburg M. (eds). 5th ed. Elsevier Limited. pp. 291-304. [Due to the subjectivity of the pain experience, patient self-report is the most valid measure. This chapter reviews the various pain measurement scales that have been devised and validated.]


Nassar M.A., Stirling L.C., Forlani G., Baker M.D., Matthew E.A., Dickenson A.H., Wood J.N. (2004) Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc Natl Acad Sci USA* **101**, 12706-12711. [Study used the Cre (Na(v)1.8) recombinase-loxP (Na(v)1.7) conditional knockout technique to produce nociceptor-specific Na(v)1.7 knockout mice that exhibited increased mechanical and thermal pain thresholds but with a decrease in all inflammatory pain responses evoked by a range of stimuli, such as formalin, carrageenan, complete Freund’s adjuvant, or nerve growth factor.]

Nassar M.A., Levato A., Stirling L.C., Wood J.N. (2005) Neuropathic pain develops normally in mice lacking both Nav1.7 and Nav1.8. *Mol Pain* **1**, 24-32. [Study using sodium channel Na(v)1.7 knockout mice or Na(v)1.7 and Na1.8 double knockout mice to demonstrate that the development of neuropathic pain does not require the presence of either Nav1.7 or Nav1.8 alone or in combination whereas Nav1.7 is highly significant in determining inflammatory pain thresholds.]

Neumann S., Doubell T.P., Leslie T., Woolf C.J. (1996) Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature (London)* **384**, 360-364. [Study showing that inflammation results in A(beta) fibres acquiring the capacity to increase the excitability of spinal cord neurons due to a phenotypic switch in a subpopulation of these fibres so that they, like C-fibres, now express substance P.]


Okuse K., Chaplan S.R., McMahon S.B., Luo Z.D., Calcutt N.A., Scott B.P., Akopian A.N., Wood J.N. (1997) Regulation of expression of the sensory neuron-specific sodium channel SNS in inflammatory and neuropathic pain. *Mol Cell Biol* **10**, 196-207. [Study in rat models of inflammatory and neuropathic pain indicating that the SNS (PN1) sodium channel is unlikely to underlie sensory neuron hyperexcitability associated with inflammation whereas reduced SNS (PN1) transcript levels were shown to be associated with peripheral nerve damage.]

©Encyclopedia of Life Support Systems (EOLSS)


Pick C.G., Peter Y., Schreiber S., Weizman R. (1997) Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with kappa 3 analgesia. *Brain Res* **744**, 41-46. [Behavioural study in rats suggesting that buprenorphine produces antinociception as a partial mu receptor agonist as well as through an interaction with kappa-3 opioid receptors and to a lesser extent with kappa 1 opioid receptors.]

©Encyclopedia of Life Support Systems (EOLSS)
Plummer J.L., Gourlay G.K., Cmielewski P.L., Odontiadis J., Harvey I. (1995) Behavioural effects of norpethidine, a metabolite of pethidine, in rats. *Toxicology* 95, 37-44. [Behavioural study in rats of the pethidine metabolite, norpethidine, indicates that its neurotoxic effects are unlikely to involve dopaminergic or cholinergic pathways.]


Ross F.B., Wallis S.C., Smith M.T. (2000) Co-administration of sub-antinociceptive doses of oxycodone and morphine produces marked antinociceptive synergy with reduced CNS side-effects in rats *Pain* 84, 421-428. [First study in rats to show that co-administration of sub-antinociceptive doses of oxycodone with morphine by intracerebroventricular or systemic routes, results in markedly increased (synergistic) levels of antinociception.]


Schaefer M., Zhou L., Stein C. (1998) Cholecystokinin inhibits peripheral opioid analgesia in inflamed tissue. *Neuroscience* 82, 603-611. [Study in rats showing that activation of peripheral cholecystokinin B (CCK B) but not CCK A receptors attenuates the peripheral antinociceptive effects of µ-opioid agonists in inflamed tissue, possibly via a protein kinase C-dependent mechanism in sensory nerve terminals.]


Schulte G., Robertson B., Fredholm B.B., DeLander G.E., Shortland P., Molander C. (2003) Distribution of antinociceptive adenosine A1 receptors in the spinal cord dorsal horn, and relationship to primary afferents and neuronal subpopulations. *Neuroscience* 121, 907-916. [Study using immunohistochemistry, in situ hybridization, radioligand binding and confocal microscopy to show that adenosine A1 receptors are localised in the postsynaptic neuronal cell bodies and processes of inner lamina II of the dorsal horn of the spinal cord, in close contact with structures important for modulation of nociceptive information.]

Scott D.A., Wright C.E., Angus J.A. (2002) Actions of intrathecal omega-conotoxins CVID, GVIA, MVIIA, and morphine in acute and neuropathic pain in the rat. *Eur J Pharmacol* 451, 279-286. [Study undertaken a spinal nerve ligation model of neuropathic pain in the rat showing that the therapeutic window of spinally administered CVID, was superior to that of either MVIIA or GVIA.]

Sherrington C.S. (1906) The integrative action of the nervous system. Scribner, New York. [Seminal text written as a series of 10 lectures that changed the subsequent course of neurophysiology; re-published 3 times in 1920, 1947 & 1961.]


©Encyclopedia of Life Support Systems (EOLSS)
Silverman J.D., Kruger L. (1988) Acid phosphatase as a selective marker for a class of small sensory ganglion cells in several mammals: spinal cord distribution, histochemical properties, and relation to fluoride-resistant acid phosphatase (FRAP) of rodents. Somatosens Res 5, 219-246. [Review of the visualization of FRAP-like activity in several nonrodent species, with reference to previous work indicating its presence only in mouse and rat, with the inclusion of technical factors, limitations and alternative interpretations.]


Slack S.E., Pezet S., McMahon S.B., Thompson S.W., Malcangio M. (2004) Brain-derived neurotrophic factor induces NMDA receptor subunit one phosphorylation via ERK and PKC in the rat spinal cord. Eur J Neurosci 20, 1769-1778. [Paper provides evidence to suggest that BDNF modulates the activity of the NMDA receptor by phosphorylation via the kinases ERK and PKC.]


Smith H.S. (2006) Arachidonic acid pathways in nociception; J Support Oncol 4, 277-287. [Review of the mechanisms contributing to various pain and inflammatory states, the metabolic fates of arachidonic acid, the functions of its many metabolites, and the interrelatedness of the various metabolic pathways involved in nociception with a view to optimising future pain treatments.]


immunomodulatory effects of codeine and codeine 6-glucuronide. *Pharm Res* **13**, 296-300. [Study showing intracerebroventricular codeine-6-glucuronide, the major metabolite of systemically administered codeine, is a potent antinociceptive agent, suggesting that codeine-6-glucuronide may contribute to the analgesic effects of codeine.]


Subrahmanyam V., Renwick A.B., Walters D.G., Price R.J., Tonelli A.P., Lake B.G. (2001) Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. *Drug Metab Dispos* **29**, 1146-1155. [Study used human liver microsomes to show that cis-tramadol is metabolized to the tramadol metabolites, M1, M2, M3, and M5 via multiple CYP isoforms with hepatic CYP2D6 being primarily responsible for metabolism to M1 whereas M2 formation is catalyzed by both CYP2B6 and CYP3A4.]

Szekely J.I., Torok K., Mate G. (2002) The role of ionotropic glutamate receptors in nociception with special regard to the AMPA binding sites. *Curr Pharm Des* **8**, 887-912. [Review of the antinociceptive effects of ionotropic glutamate receptor antagonists, with emphasis on clinical potential.]

Taiwo Y.O., Goetzl E.J., Levine J.D. (1987) Hyperalgesia onset latency suggests a hierarchy of action. *Brain Res* **423**, 333-337. [Study assessing the temporal onset of hyperalgesia following intradermal administration of various inflammatory mediators in rats, showed that inflammatory mediators known to produce hyperalgesia via indirect mechanisms resulted in a significant delay in onset of hyperalgesia after intradermal administration.]

Tao R., Auerbach S.B. (1995) Involvement of the dorsal raphe but not median raphe nucleus in morphine-induced increases in serotonin release in the rat forebrain. *Neuroscience* **68**, 553-561. [In vivo microdialysis study showing that systemic morphine acting in the dorsal raphe nucleus, but not the median raphe nucleus, enhances serotonin release in specific forebrain sites, and that increases in serotonin release in dorsal raphe nucleus projection sites do not occur secondary to changes in behavioral state or body temperature.]


calcium channel alpha(2)-delta subunit as a target for antiepileptic drug discovery. *Epilepsy Res* **73**, 137-150. [Review summarizing the preclinical pharmacology of pregabalin, the biology of the high affinity binding site on the alpha(2)-delta subunit of calcium channels and pregabalin’s presumed mechanism of action.]

Thompson S.W., Bennett D.L., Kerr B.J., Bradbury E.J., McMahon S.B. (1999) Brain-derived neurotrophic factor is an endogenous modulator of nociceptive responses in the spinal cord. *Proc Natl Acad Sci USA* **96**, 7714-7718. [Review summarizing how BDNF satisfies many of the criteria necessary to be regarded as a neurotransmitter/neuromodulator in small-diameter nociceptive neurons and implicating BDNF in sensory abnormalities associated with persistent inflammation.]


Tölle T.R., Berthele A., Zieglgänsberger W., Seeburg P.H., Wisden W. (1993) The differential expression of 16 NMDA and non-NMDA receptor subunits in the rat spinal cord and in periaqueductal gray. *J Neurosci* **13**, 5009-5028. [Study that used in situ hybridization in rat lumbar spinal cord and the periaqueductal gray to assess the differential expression of 16 genes, encoding all known subunits for the NMDA receptor, AMPA/low-affinity kainate, high-affinity kainate ionotropic receptors and two orphan receptor subunits.]


Vulchanova L., Riedl M.S., Shuster S.J., Buell G., Suprenant A., North R.A. Elde R. (1997) Immunohistochemical study of the P2X2 and P2X3 receptor subunits in rat and monkey sensory neurons and their central terminals. *Neuropharmacology* **36**, 1229-1242. [Study showing species differences in P2X2 and P2X3 localisation between rats and monkey and that these receptors are expressed differentially on sensory neurons in the dorsal root and nodose ganglia as well as the dorsal horn of the spinal cord.]


Whitcomb D., Block G. (1994) Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* **272**, 1845-1850. [Retrospective case series studied to determine that acetaminophen hepatotoxicity after an overdose appears to be enhanced by fasting in addition to alcohol ingestion.]


Wiffen P.J., McQuay H.J., Moore R.A. (2005) Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev* **Jul** **20**(3), CD005451. [Meta-analysis of clinical trials indicating that there is evidence to show that carbamazepine is effective even though the clinical trials are small.]


to low- and to high-intensity mechanical stimulation of the skin of the rat hindpaw.]

Woolf C.J., Safieh-Garabedian B., Ma Q.-P., Crilly P., Winter J. (1994) Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience 62, 327-331. [Study showing that elevation in levels of the neurotrophin, NGF, in the periphery is a major contributor to CFA-induced inflammatory pain.]


Wotherspoon G., Fox A., McIntyre P., Colley S., Bevan S., Winter J. (2005) Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience 135, 235-245. [Study showing marked upregulation of cannabinoid CB2 receptor immunoreactivity in dorsal root ganglia and in laminae 1/2 of the dorsal horn of the spinal cord in mouse models of neuropathic pain, suggesting that the CB2 receptor may be a useful target for the development of novel anti-neuropathic pain medications.]

Wright A.W., Mather L.E., Smith M.T. (2001) Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. Life Sci 69, 409-420. [Comparative study of the neuro-excitatory pharmacology of hydromorphone-3-glucuronide (H3G) relative to morphine-3-glucuronide (M3G) in rats showing that following intracerebroventricular administration, H3G is approximately 2.5-fold more potent than M3G.]


Xu X.-J., Alster P., Wu W.-P., Hao J.-X., Wiesenfeld-Hallin Z. (2001) Increased level of cholecystokinin in cerebrospinal fluid is associated with chronic pain-like behaviour in spinally injured rats. Peptides 22, 1305-1308. [Study showed that spinaly injured rats which exhibit pain-like behaviours have elevated CSF levels of the anti-opioid peptide, cholecystokinin, relative to non-injured rats and spinally injured rats that don’t exhibit pain-like behaviours.]


Yeung J.C., Rudy T.A. (1980) Multiplicative interaction between narcotic agonisms expressed at spinal and supraspinal sites of antinociceptive action as revealed by concurrent intrathecal and intracerebroventricular injections of morphine. J Pharmacol Exp Ther 215, 633-642. [Study showing that the analgetic potency of intrathecal morphine is potentiated by concurrent administration of intracerebroventricular morphine and vice versa.]

Yu X.-M., Salter M.W. (1999) Src, a molecular switch governing gain control of synaptic transmission mediated by N-methyl-D-aspartate receptors. Proc Natl Acad Sci USA 96, 7697-7704. [Paper provides evidence to support view that increased NMDA receptor function secondary to Src activation and raised
intracellular sodium may underpin physiological and pathophysiological enhancement of excitatory transmission in the dorsal horn of the spinal cord and elsewhere in the central nervous system.


Biographical Sketches

**Professor Maree T. Smith** was born in Brisbane and educated at The University of Queensland, Brisbane, Queensland, Australia. Professor Smith graduated with a Bachelor of Pharmacy in 1975 followed by B Pharm (Hons) in 1976 and PhD in Medicine in 1983.

Since 2005, she has been employed as the Director of the Centre for Integrated Preclinical Drug Development and she has a joint appointment (20%) as Professor of Pharmacy at The University of Queensland, Brisbane, Queensland, Australia. Her previous appointments include Professor of Pharmacy (2004), Reader in Pharmacy (1999-2003), Senior Lecturer in Pharmacy (1995-1998) and Lecturer in Pharmacy (mid 1989-1994) at The University of Queensland, Brisbane, Queensland, Australia. Prior to that (1984-mid-1989), she undertook postdoctoral training in pain medicine with Professor Tess Cramond in the Division of Anaesthetics, The University of Queensland, and in bioanalytical methods, pharmacokinetics and pharmacokinetic modeling in the Department of Medicine, The University of Queensland. She is a member of the editorial board for Pain: Clinical Updates.

Professor Smith is a member of the International Association for the Study of Pain, Pharmaceutical Society of Australia, Australian Pain Society, Australian Society for Medical Research, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Australasian Pharmaceutical Sciences Association, Women in Biotechnology and AusBiotech.

**Dr Samantha South** was born in Brisbane and educated at The University of Western Australia, Perth, Western Australia and The University of Queensland, Brisbane, Queensland, Australia. Dr South graduated with a Bachelor of Pharmacology from The University of Western Australia in 1994, moved to Queensland the following year and completed a Postgraduate Honours degree in Pharmacology in 1995 followed by a PhD in Pharmacy in 2000.

Since 2005, Dr South has been employed as the Technical and Quality Control Manager for the Efficacy laboratory of the Centre for Integrated Preclinical Drug Development and she has a joint appointment (10%) as a Senior Research Officer within the School of Pharmacy at The University of Queensland, Brisbane, Queensland, Australia. Her previous appointments include Senior Research Officer, School of Pharmacy at The University of Queensland (2004-2005), Senior Research Fellow, The Garvan Institute, Sydney, New South Wales, Australia (2003-2004) and Senior Research Officer, The Weill Medical College of Cornell University, New York, New York, USA (1999-2003).
Dr South is a member of the International Association for the Study of Pain, the Australian Pain Society, Australian Society for Medical Research and Women in Biotechnology.