PAIN PHARMACOLOGY AND ANALGESIA

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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 μm) myelinated Aδ-fibres with a conduction velocity in the range 4-30 m/s, or thin (0.4-1.2 μm), unmyelinated C-fibres with conduction velocities < 2.5 m/s. Additionally, cutaneous mechanoreceptors are often supplied by large (> 10 μm), fast (30-100 m/s) myelinated Aβ 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, Aβ 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).

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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(v)1.3 and Na(v) 1.7 and decreases in the expression of Na(v) 1.6 and Na(v)1.8 in DRG neurones from streptozotocin-induced diabetic rats and increased phosphorylation of Na(v)1.6 and Na(v)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.]


and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 27, 499-505. [Study undertaken in healthy volunteers of the oral and buccal bioavailability of morphine tablets showed route dependent differences in the morphine to morphine-6-glucuronide AUC ratios.]

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.]


Jonker J.W., Wagenaar E., van Deemter L., Gottschlich R., Bender J.M., Dassenbrock J., Schinkel A.H. (1999) Role of blood-brain barrier P-glycoprotein in limiting brain accumulation and sedative side-effects of asimadoline, a peripherally acting analgesic drug. *Br J Pharmacol* 127, 43-50. [Study in mdr1a/1b double knockout mice showing the absence of P-gp leads to a 9 fold increase in brain asimadoline accumulation without impairing the oral uptake of asimadoline.]


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 chemotherapy-induced neuropathic pain model or a skin-incision model of post-operative pain.]


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., Aunapuu 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.]


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.


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.]


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.]


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.]

[Review of studies on the localization of kainate receptors in dorsal root ganglia and spinal dorsal horn and their physiological and pathophysiological importance particularly with regard to nociceptive pathways including a brief overview of the agonist and antagonist pharmacology].


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.]

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.]


Stubhaug A., Breivik J., Eide P.K., Kreunen M., Foss A. (1997) Mapping of punctate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 41, 1124-1132. [Clinical study in patients showing that NMDA receptor blockade prevents central sensitization induced by nociceptive input during and after surgery.]

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.]

Tao F., Liaw W.J., Zhang B., Yaster M., Rothstein J.D., Johns R.A., Tao Y.X. (2004) Evidence of neuronal excitatory amino acid carrier 1 expression in rat dorsal root ganglion neurons and their central terminals. Neuroscience 123, 1045-1051. [Immunohistochemical study indicating the presence of EAAC1 in dorsal root ganglion neurons and their central terminals, thereby suggesting that EAAC1 might play an important role in nociceptive neurotransmission via the regulation of pre-synaptically released glutamate.]


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., Ziegglänsberger 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.]


Urban M.O., Zahn P.K., Gebhart G.F. (1999) Descending facilitatory influences from the rostral medial medulla mediate secondary, but not primary hyperalgesia in the rat. *Neuroscience* 90, 349-352. [Study undertaken in rat models of primary and secondary hyperalgesia showing that descending nociceptive facilitatory influences from the rostral medial medulla significantly contribute to the development of secondary, but not primary, hyperalgesia.]


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.]


Watkins L.R., Hutchinson M.R., Ledeboer A., Wieseler-Frank I., Milligan E.D., Maier S.F. (2007) Norman Cousins Lecture. Glia as the “bad guys”: implications for improving clinical pain control and the clinical utility of opioids. *Brain Behav Immun* 21, 131-146. [Review of the role of glia in the development and maintenance of persistent pain states as well as the development of tolerance to the pain-relieving effects of opioid analogues such as morphine and the possibility of developing new treatments targeted to activated glia as a means of improving pain management.]


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.]


Woollf C.J., King A.E. (1987) Physiology and morphology of multireceptive neurons with C-afferent fiber inputs in the deep dorsal horn of the rat lumbar spinal cord. *J Neurophysiol* 58, 460-479. [Electrophysiological study defining the physiological properties and morphology of neurons that respond
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.]


Yakovlev Y., 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.