Pharmacology of Pain Transmission and Modulation

I. General issues

A. Pain can only be studied fully in integrated systems. Pain is a conscious experience that emerges from brain activity. The word “pain” does not equate with nociception, which is a preconscious neural activity that is normally necessary, but not sufficient, for pain. When we speak of “pain transmission,” we are referring to nociceptive transmission, since pain per se cannot be communicated by animals.

B. Drug actions may be highly selective, but rarely specific, and effects may be seen in animals at doses that are not possible in patients.

C. Be aware that animal studies, although extremely valuable in modeling clinical conditions, generally provide information on efficacy and may not affect cognitive and affective aspects of human pain.

D. Know that behavioral studies in animals generally study threshold responses but can reveal secondary effects of drugs, whereas electrophysiological studies can provide information on suprathreshold responses yet often not side effects.

E. Molecular approaches have been valuable in the identification of channels and receptors in pain pathways, and approaches such as the use of knockout mice are a very powerful means of identifying function. However, the interpretation of data may be complicated by the effects of changes other than those to the receptor/channel that was deleted.

F. Many of the transmitter and receptor systems in the central nervous system undergo developmental changes, and therefore infants should not be viewed simply as small adults (Alvares and Fitzgerald 1999; Hunt and Mantyh 2001; Carpenter and Dickenson 2002).

II. Peripheral mechanisms

A. Know that the nociceptor is composed of a number of sensory and chemical receptors that result in the polymodal nature of nociceptive sensory neurons (Besson and Chaouch 1987; Dray and Perkins 1993; Eglen et al. 1999; Millan 1999).

B. Be aware that a large number of chemical mediators such as ATP, prostanoids, bradykinin, serotonin, histamine, and hydrogen ions (acid pH) can activate nociceptors (Eglen et al. 1999; Millan 1999). Heat responses involve the capsaicin-activated vanilloid receptor family and the transient receptor potential V (TRPV) receptors. ATP acts on a large family of PX receptors, hydrogen ions act on acid-sensing ion channels (ASICs) and TRPV1, and the receptors for all these chemicals are invariably multiple (Dray and Perkins 1993; Dray et al. 1994; Dray 1997; Hill 1999; Julius and Basbaum 2001).

C. Know that these chemicals and also neuropeptides (e.g., substance P and calcitonin gene related peptide [CGRP] through the axon reflex) and prostaglandins participate in peripheral events leading to hyperalgesia and edema in inflammation, including increased blood flow (Besson and Chaouch 1987; Dray and Perkins 1993; Millan 1999).

D. Be aware of the difference between activation and sensitization of the peripheral terminals of primary afferent nociceptors. Be aware that some compounds do both (e.g., bradykinin), whereas others are primarily sensitizing (e.g., prostaglandins). Sensitization leads to a drop in the threshold for activation of nociceptors.
E. Be aware that there are several classes of anti-inflammatory agents. Be aware that cyclooxygenase (COX), the key enzyme for the production of prostaglandins in inflammatory exudates, exists in at least two forms, so that inhibitors of the inducible COX-2 have similar efficacy to other NSAIDs but have reduced gastrointestinal side effects, although there is an increased risk of cardiovascular and renal side effects (Appleton 1997; Fitzgerald 2003; Kiefer and Dannhardt 2004).

F. Know that populations of silent nociceptors may become active during inflammation (Millan 1999).

G. Neuropathic pain involves changes in the peripheral and central nervous systems (Suzuki and Dickenson 2000). The former changes involve clustering and other changes in sodium channels that promote ectopic activity (Waxman 1999). The effects of local anesthetics and anticonvulsants such as carbamazepine in neuropathic pain are probably partly due to their blocking of these sodium channels. Novel sodium channels in C fibers have been described that may provide novel drug targets. Cross-talk between damaged fibers can also occur, as can changes in expression and redistribution of channels and other proteins (Suzuki and Dickenson 2000).

H. Be aware that there are growth factors, for example nerve growth factor (NGF), which are produced by neural and non-neural tissue, that may influence the responsiveness, phenotype, and regrowth of sensory neurons in states of both inflammation and nerve injury (McMahon et al. 1993; Millan 1999).

I. Be aware that cytokines and changes in the peptide content of sensory neurons have an impact upon inflammation and neuropathy (Sommer 2001).

J. Know the basis for the involvement of the sympathetic nervous system in certain pain states including nerve injury (Jänig and Baron 2001).

III. Synaptic transmission in the dorsal horn

A. Understand the importance of N- and P-type calcium channels in the mechanisms of transmitter release from nerve terminals. Agents that block these voltage-dependent calcium channels (VDCCs) may include gabapentin (Vanegas and Schaible 2000; Matthews and Dickenson 2001). Other means of modulation of release can occur through activation of receptors that reduce Ca$^{2+}$ influx or cause hyperpolarization, such as opioid receptors. Realize that the expression and function of VDCCs can change in different pain models (Dickenson 1994b; Price et al. 1994).

B. Be aware that C fibers contain and release glutamate, and whereas a proportion also contain substance P and CGRP, others are nonpeptide (the isolectin B$_4$ population). The peptide content and phenotype are altered by tissue and nerve damage.

C. Know that glutamate, the excitatory amino acid (EAA) implicated in transmission from primary afferent nociceptors to dorsal horn neurons, has a number of receptors (AMPA, kainate, N methyl d aspartate [NMDA], and metabotropic), and that various combinations of these receptors exist on neurons in various laminae of the dorsal horn. The activation of these receptors determines the time course of the responses of dorsal horn cells to noxious stimuli and their different susceptibilities to pharmacological agents (Dickenson 1995; Millan 1999).

D. Know that some neuropeptides present in primary afferent nociceptors are excitatory (e.g., including substance P and CGRP; Hunt and Mantyh 2001), while others are inhibitory (e.g., somatostatin) to dorsal horn neurons.

E. Understand the processes that underlie wind-up and central hyperalgesia. Be aware of the pivotal role of the NMDA-type of EAA receptor in these processes (Dickenson 1994b). Understand how central mechanisms can change in pathological events such as neuropathy (Dickenson et al. 2001).

F. Understand the importance of postsynaptic modulation of transmission by drugs that block the receptors for the peptides and glutamate (Fields et al. 1991). Know that ketamine, memantine, and dextromethorphan block the NMDA-receptor complex (Dickenson 1994b; Price et al. 1994). Know
that there are many sites for modulation of the NMDA receptor (glycine site, polyamine site, channel) and that drugs that antagonize subtypes of the receptor may have fewer side effects than existing drugs (Chizh et al. 2001).

G. Be aware that prostaglandins, generated by spinal COX, affect synaptic transmission in the spinal cord as well as contributing to inflammatory pain in peripheral tissues; therefore, cyclooxygenase inhibitors such as aspirin and NSAIDs may have both peripheral and central nervous system actions relevant to analgesia (Yaksh and Malmberg 1994). COX-2 now appears to be constitutive in the spinal cord.

IV. Central sensitization

A. Know that prolonged firing of unmyelinated primary afferents can initiate glutamate-receptor mediated, prolonged enhancement of excitatory synaptic transmission to dorsal horn nociceptive neurons and in the brainstem rostroventral medulla.

B. Be aware that NMDA-mediated wind-up like mechanisms underlie this central hypersensitivity, but that intracellular changes, the generation of nitric oxide and prostanoids, highly diffusible mediators, and other mediators are all important downstream mechanisms (Meller and Gebhart 1993). Know the broad classes of agents capable of blocking the development of central sensitization, which include VDCC blockers, NMDA-receptor antagonists, nitric oxide synthase inhibitors, and agents that increase inhibitions (McQuay and Dickenson 1990; McMahon et al. 1993; Dickenson 1994b; Dickenson et al. 2001).

C. Be aware that central sensitization is more susceptible to inhibitory or analgesic agents when they are administered before, rather than after, the initiating afferent barrage. Know that this is the rationale used to justify preemptive analgesia, but that this is difficult to study in clinical settings (McQuay and Dickenson 1990; Coderre et al. 1993; Dickenson 1994b; Woolf 1994).

D. Be aware that central sensitization has been observed in laboratory models of inflammation and neuropathic pain and can be demonstrated in human psychophysical studies (Woolf and Doubell 1994).

E. Know that pain signaling transmitters can activate the expression of certain intracellular agents and genes that may contribute to central sensitization (Dubner and Ruda 1992; Meller and Gebhart 1993; Dray et al. 1994; Petersen-Zeitz and Basbaum 1999).

F. Be aware that anticonvulsants and excitability blockers may have actions at both central and peripheral sites (Dray et al. 1994).

G. Know that there is increasing evidence for roles of non-neuronal cells such as glia in spinal events that lead to persistent pain (Watkins and Maier 2003).

V. Neurotransmitters in pain modulation

A. Know that a number of receptor systems can be activated by transmitters and drugs to produce analgesic effects. These include opioid receptors, alpha-2 adrenoceptors, some of the 5-HT receptors (5-HT, in particular), the adenosine A1 receptor, and cannabinoids (Yaksh and Malmberg 1994; Dickenson 1994a, 1995; Millan 1999; Chapman and Iversen 2002).

B. Know the four main types of opioid receptors (mu, delta, kappa, and ORL-1) and the various opioid peptides and, in the case of the mu receptor, the major classes of clinically used drugs acting on this receptor (Yaksh and Noueihehd 1985; Dickenson 1994a). Be aware that molecular studies of the opioid receptors have led to detailed knowledge of their structure, their mechanism, and their precise location in the nervous system (Dickenson 1994a; Uhl et al. 1994; Darland et al. 1998).

C. Subtypes, interactions, and changes in expression of the opioid receptors have been shown in neurons, but as yet, the basic findings are difficult to relate to the clinical use of opioids (Dickenson and Suzuki 1999).
D. Understand that numerous factors, such as nerve injury and inflammation, can reduce and enhance opioid analgesia (Dickenson 1994; Rowbotham 2001). Be aware of proposed mechanisms of opioid tolerance that include NMDA receptors, cholecystokinin, and dynorphin (Basbaum 1995). Also realize that opioid analgesia will depend on various factors that include route of administration, formulation, type of opioid, type of pain state, and symptoms (Dickenson and Suzuki 1999; Rowbotham 2001).

E. Know that opioid agonists act in the central nervous system at both spinal and supraspinal sites involved in pain transmission and modulation (Yaksh and Noueihed 1985; Besson and Chaouch 1987; Meller and Gebhart 1993). After inflammation, peripheral sites of action of opioids can contribute (Machelska et al. 1999, Stein et al. 2003).

F. Know that at the spinal cord level, opioids act predominantly presynaptically to inhibit transmitter release from nociceptive sensory neurons and postsynaptically to inhibit activity of dorsal horn neurons (Dickenson 1994a).

G. Be aware that several neurotransmitters are involved in descending pain modulation and facilitation from brainstem and midbrain centers (e.g., norepinephrine, serotonin, glutamate, NMDA, and gamma-aminobutyric acid) (Yaksh and Noueihed 1985; Besson and Chaouch 1987; Fields et al. 1991; Dickenson 1994a; Hunt and Mantyh 2001). Understand that these neurotransmitters bind to different receptor classes so that some will mediate inhibition and others, facilitation, of pain. Some systems can interact synergistically, and others will interact antagonistically (Dickenson and Sullivan 1993). The role of descending facilitations in spinal cord function is gaining prominence, whereas many previous studies have concentrated on inhibitions.

H. Realize that the supraspinal monoamine systems are also modulated by opioid receptors, and that this mechanism forms an important component of opioid analgesia (Millan 1999). Antidepressants, alpha-2 adrenoceptor agonists such as clonidine, and the triptans all interact in some way with norepinephrine and serotonin transmission.

I. Understand the use of adjuncts to enhance opioid analgesia based on the principle that drugs can either increase inhibitions or decrease excitations; thus, combinations of appropriate agents are logical when single agents are insufficient (Dickenson and Sullivan 1993; Dickenson 1994a; Yaksh and Malmberg 1994).

**REFERENCES**


