A Review of Physiology and Pharmacology Related to Acute Perioperative Pain Management

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Objectives:
At the completion of this course, the reader should be able to:
1. Describe the basic physiology involved in pain impulse transmission and pain perception.
2. Identify the role of specific neurotransmitter receptors and their use in transmission and interpretation of acute pain.
3. Identify traditional and contemporary pain management pharmacology.
4. Describe the mechanism of action of specific pharmacology as it relates to the pain impulse transmission and interpretation.
5. Synthesize practical pain management modalities to provide the optimal safety and comfort for perioperative patients.

Introduction
Perioperative pain is a major fear for many patients undergoing simple and complex surgical procedures. With 26.6 million surgeries performed annually in hospitals alone, there are opportunities for anesthesia providers to influence patient experiences and satisfaction. The traditional mainstay of pain management has been opioids. As opioid doses increase, the likelihood of adverse outcomes related to opioids also increases. To avoid these outcomes, practitioners need to give fewer opioids and put greater focus on alternative pain pharmacology and receptor-targeted pharmacotherapy. The purpose of this article is to provide the practicing anesthesia provider with a review of pain transmission physiology and pharmacology and to present new and emerging pain management pharmacologic agents and strategies.

Keywords: Neurotransmitters, nociception, pain, physiology.
tor potential can develop if ion channels open, allowing more cation movement into the nerve terminal than out of the terminal. Closing a channel responsible for hyperpolarization will also generate a generator potential. Once the energy is transduced to electrical energy, an action potential can be transmitted along nerve fibers. Many action potentials traveling down a nerve fiber are referred to as a signal. Intensity of the pain is determined by the number of action potentials traveling along the afferent neuron. More action potentials are perceived by the CNS as greater intensity, whereas fewer action potentials are perceived as less intense pain. The number of action potentials traveling along afferent nerve fibers on the way to cortical areas in the cerebrum can be increased or decreased at the synaptic junction between neurons or by blocking sodium channels along the neuron.

The noxious stimulus leads to an acute inflammatory state at the site of injury. This inflammation dramatically changes the local environment with the release of many inflammatory mediators such as arachidonic acid substrates (prostaglandins, leukotrienes, and thromboxane), bradykinin, serotonin, histamine, substance P, adenosine, adenosine triphosphate, and protons, which have been collectively referred to as a “soup” of inflammatory mediators. These substances can be released from primary neurons or nonneuronal cells such as macrophages, mast cells, and platelets. Apart from histamine, these substances excite and sensitize nociceptors by lowering the threshold for stimulation, increasing the response to suprathreshold stimuli, and by expansion of the receptive field. Serotonin released from platelets and histamine from mast cells enhances the effect of bradykinin. This enhanced sensitivity leads to a greater-than-normal response to a noxious stimulus and innocuous sensations are now perceived as pain. These inflammatory mediators bind with various receptors on transient receptor potential channels, acid-sensitive ion channels, G protein-coupled receptors, and 2-pore potassium chan-

Figure 1. Ascending Pain Pathway
Abbreviations: NSAIDS, nonsteroidal anti-inflammatory drugs; PAG, periaqueductal gray matter; RVM, rostral ventral medulla. (Artwork by Jennifer Vondrak. Used by permission.)
nels on the nerve terminal. Another array of receptors reduces the likelihood of nociceptor activation. Several G protein-coupled receptors such as opioid, cannabinoid, muscarinic cholinergic, adenosine, γ-aminobutyric acid (GABA) B, metabotropic glutamate, and adenosine receptors all inhibit the opening of voltage-gated calcium channels. Generation of an action potential requires cations such as sodium and calcium to move through sodium and calcium channels, respectively, into the nerve terminal. Three sodium channels in particular are highly expressed in nociceptors: Na\textsubscript{v}1.7, Na\textsubscript{v}1.8, and Na\textsubscript{v}1.9.5-7 Other channels once activated also allow calcium and sodium movement into a nerve terminal.

**Transmission.** Transmission is the movement of action potentials along afferent neurons, with modulation occurring at the synapse between afferent neurons. As the action potential travels from the periphery to the brain, it is transmitted along 3 afferent sensory fibers identified as first-, second-, and third-order fibers (Figure 1). The second- and third-order fibers have branches along the way to the brain, whereas first-order fibers do not. The first-order fiber does, however, have axon branching in the periphery much like roots of a tree. An axon reflex occurs when the action potential develops and travels down the axon toward the spinal cord and then down a branch of the axon moving back (antidromic) toward the periphery.6 As that signal reaches the peripheral nerve terminal, additional substances such as substance P, calcitonin gene-related peptide, and neurokinin A are released into the tissue. Although pain at the site of the injury is primary hyperalgesia, the release of additional substances beyond the original site causes secondary hyperalgesia. Reducing the number of inflammatory mediators present and minimizing the release of substance P, calcitonin gene-related peptide, and neurokinin A would lessen pain perception.

First-order afferent fibers enter the dorsal horn of the spinal cord and can synapse with second-order fibers, motor fibers, or interneurons. Before entering the dorsal horn and synapsing with another nerve fiber, it will ascend or descend several levels through the tract of Lissauer. The dorsal horn is divided into 5 areas referred to as laminae based on the structure of interneurons (Figure 2). If the first-order fiber is an unmyelinated C fiber, the synapse takes place in lamina I or II, whereas a lightly myelinated A-delta fiber would synapse with a second-order fiber in lamina III, IV, or V. Considerable communication via interneurons exists between C fibers, A-delta fibers, and other fibers in the dorsal horn. Just as the signal could be modulated at the first-order nerve peripheral terminal, it can also be modulated at the synapse of the first- and second-order fibers. The first-order fiber releases excitatory neurotransmitter substances such as glutamate and substance P from its terminal. These bind to N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and neurokinin receptors on the
terminal of the second-order fiber. With ligand binding to these receptors, ion channels open, allowing sodium and calcium to move into the terminal of the second-order fiber. Movement of sodium and calcium ions into the terminal causes the membrane potential to become less negative. Generation of an action potential in the second-order fiber occurs as the threshold is reached. As in the periphery there are receptors that can decrease the signal in the dorsal horn. Inhibition of the signal comes from agonist binding to opioid, presynaptic α7-adrenergic, GABA_A, GABA_B, adenosine, and glycine receptors.

Second-order fibers travel from the dorsal horn to the contralateral side of the spinal cord and on to thalamic nuclei via the spinothalamic path (STT). Paleospinothalamic and neospinothalamic divisions reside in the STT, with each division accommodating C and A-delta fibers respectively. Acute pain signals travel via myelinated A-delta fibers, whereas dull, achy sensations travel via unmyelinated C fibers. Second-order fibers in the STT terminate in ventral posterolateral and ventral posteromedial nuclei of the thalamus, collectively referred to as the ventrobasal complex. Nuclei in the ventrobasal complex receive input from a specific lamina in the dorsal horn of the spinal cord. The thalamus serves as a relay station for sensory information except for olfaction.

Other fibers travel via the spinoreticular tract to the parabrachial region of the brain stem and via the spino-mesencephalic tract to cells in the medulla. Spinobulbar fibers also travel in the STT, projecting to the raphe magnus nuclei in the rostral ventral medulla (RVM), the lateral tegmental nucleus, and the periaqueductal gray matter (PAG) in the midbrain. Other systems are also activated as the signal travels on to the cerebrum, in particular, the endocrine, autonomic, and immune systems.8

Nuclei of the RVM, the lateral tegmental nucleus, and the PAG are involved with descending pathways that modulate pain in the dorsal horn. Nuclei in the RVM project fibers to the dorsal horn, whereas the lateral tegmental nuclei project to both the RVM nuclei and the dorsal horn. Some fibers from the PAG project to the dorsal horn of the spinal cord, but most of the fibers travel from the PAG to the RVM and the lateral pontine tegmental group (locus ceruleus). Further discussion of these descending pain modulating pathways is beyond the scope of this review.

Third-order fibers travel from the ventral posterolateral nucleus of the thalamus to cortical and subcortical structures throughout the cerebrum.

**Perception.** Perception occurs as various cerebral cortical areas communicate with each other, including the primary and secondary somatosensory, prefrontal, cingulate, and insular cortices. Collectively these structures are referred to as the pain matrix9 and were originally identified as the neuromatrix by Melzack.10 Other regions of the brain such as cerebellum, amygdala, hippocampus, and basal ganglia are involved in pain perception as well depending on the unique circumstance for each individual.9 These structures in the brain are all involved with how the individual will perceive pain and respond to the pain (nocifensive behavior) and in activation of descending pain modulation from the PAG.11

**Modulation.** Along this pain pathway, numerous ion channels such as sodium, calcium, and potassium have the potential to favor or inhibit the action potential. Opioid binding to µ-opioid receptors inhibits opening of calcium channels, facilitates potassium efflux leading to hyperpolarization of the nerve terminal, and inhibits adenylyl cyclase leading to decreased cyclic adenosine monophosphate production.12 All the outcomes from opioid binding to the µ receptor would inhibit the release of excitatory neurotransmitters. Some drugs block N-type voltage-gated calcium channels, and others such as gabapentin bind to the α2-δ, calcium channel subunit, preventing the channel from opening.13 In both cases, release of a neurotransmitter substance that would favor continuation of the action potential is reduced. Cannabinoid receptors are found in the brain, in the spinal cord, and on peripheral sensory fibers.3 Ligand binding to the cannabinoid-1 receptor causes hyperpolarization of the cell, decreasing the amount of neurotransmitter released. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the amount of prostaglandin synthesis both peripherally and centrally, which would reduce the number of inflammatory mediators.

The Table defines key terms used in this article.

**Pharmacology**

**• Opioids.** There are 4 G protein-coupled opioid receptors: µ, δ, κ, and nociceptin. The nociceptin receptor does not have high affinity for opioid ligands, leaving the first 3 receptors as the most likely to be involved with opioid ligand binding. The µ receptors are found in the periphery, the dorsal horn of the spinal cord, and in the brain stem. These µ receptors are the most plentiful in laminae I and II (substantia gelatinosa) and account for 70% of the opioid ligand binding in laminae I and II, with the δ and κ receptors accountable for 24% and 6%, respectively.3

The first-order fiber has its cell body in the dorsal root ganglion. In this cell body, opioid receptors are synthesized and transported to peripheral nerve terminals as well as centrally to the dorsal horn. Opioids commonly used in clinical practice such as morphine, fentanyl, sufentanil, remifentanil, levorphanol, and hydromorphone have an effect by binding to these µ receptors.14 Binding to the µ receptor activates an α subunit (GI), which ultimately causes hyperpolarization of the cell, leading to decreased calcium movement into the cell and reduced release of neurotransmitters such as substance P, glutamate, and calcitonin gene-related peptide.
hyperpolarization of the cell is taking place, β-arrestins are also engaged. β-Arrestins promote adverse effects related to opioid binding. Currently under study is a biased ligand that would activate the α subunit of the G protein-coupled receptor but minimize β-arrestin activity. The ligand is biased in the sense that it activates only a select cell response. 

κ-Receptor agonism in preclinical studies has shown a consistent analgesic effect, but central effects such as sedation and dysphoria have limited the use of these drugs. There is, however, continued research on peripherally acting κ receptor agonists. 

Although opioids have been the mainstay of pain management, they are not without adverse effects, which are more likely to occur as the dose increases. These effects include nausea, vomiting, constipation, urinary retention, chest wall rigidity, and bronchoconstriction. Remifentanil has in some cases led to opioid-induced hyperalgesia. Because of these adverse effects, there has been a trend toward reducing the opioid dose and adding other drugs as part of a multimodal approach to pain management.

- **Nonsteroidal Anti-Inflammatory Drugs.** Nonsteroidal anti-inflammatory drugs can be nonselective in which both the cyclooxygenase 1 (COX-1) enzyme and the cyclooxygenase 2 (COX-2) enzyme are affected or the NSAID can be selective for the COX-2 enzyme. Nonselective NSAIDs such as ketorolac inhibit the synthesis of COX-1 and COX-2, leading to decreased production of several prostaglandins (PGE₂, PGD₂, PGFα, PGI₁, and thromboxane). When used with an opioid, ketorolac can reduce the opioid requirement by 25% to 50%. However, all nonselective NSAIDs inhibit platelet aggregation and are capable of adverse effects on the gastrointestinal system, leading to gastric ulcers, interference with autoregulation of renal blood flow, hepatotoxicity, and hypertension. Therefore, a nonselective NSAID such as ketorolac should be used for no more than 5 days. Selective COX-2 inhibitors may also increase the likelihood of edema, hypertension, and possibly myocardial infarction.

Anti-inflammatory drugs are an important part of multimodal analgesia. The newer COX-2 inhibitors demonstrate similar efficacy to their traditional NSAID counterparts, with several advantages. These compounds inhibit COX-2. Without inhibition, COX-2 would lead to increased synthesis of prostaglandin E₂, which in turn sensitizes peripheral nociceptors. The use of “coxibs” in addition to opioids after laparoscopic surgery showed a reduction in required opioid doses by 29% and a reduction in pain severity by about 33%. Selective COX-2 NSAIDs lack the gastrointestinal impact of traditional NSAIDs and decrease the risk of postoperative bleeding, renal dysfuncion, and bronchospasm in sensitive patients.

The adverse event profile is generally safe for COX-2 inhibitors. Although these drugs are well tolerated, there is some concern about their cardiovascular safety profile. There may be an increase in the risk of thromboembolic events after coronary artery bypass grafting. However, a meta-analysis showed an identical incidence of cardiovascular events in both placebo and COX-2 inhibitor groups. This supports the idea that short-term coxib use in the perioperative period does not increase the risk of thromboembolic adverse events.

- **Acetaminophen.** The exact mechanism of pain management properties of acetaminophen is unknown but is believed to involve central actions. According to the drug manufacturer, intravenous (IV) acetaminophen is indicated for the management of mild to moderate pain and the management of moderate to severe pain with adjunctive opioid analgesics. A large randomized controlled trial regarding major orthopedic surgery showed that groups receiving perioperative administration of IV acetaminophen had significantly less pain intensity on the visual analog scale and less consumption of opioids over a
24-hour period compared with those receiving placebo. Other studies have shown similar results, including a large, multicenter, randomized controlled trial for treatment of pain after abdominal laparoscopic surgery. Understanding the pain management benefits and low risk profile of acetaminophen is of specific usefulness in bariatric surgical patients. Because patients undergoing bariatric surgery have a risk of apnea leading to hypoxemia, opioid-sparing methods should be emphasized. Looking specifically at IV acetaminophen in bariatric surgery, Gonzalez et al found that, as expected, the use of IV acetaminophen decreased opioid use by 39.5%.

Acetaminophen is primarily metabolized in the liver through first-order kinetics. Because of this, there remains a risk of hepatotoxicity in cases of medication dosing errors or preexisting liver impairment. Benzodiazepines. Anxiolytics such as midazolam are frequently used in the perioperative period for treating anxiety. Although traditional thinking rationalizes that anxiolytics are used only in the treatment of anxiety, recent studies have suggested that preemptive treatment with midazolam can decrease the perioperative pain response and opioid requirements. The literature shows that in a recent, randomized, double-blind study, diclofenac was given with and without midazolam and effects were compared. The results of this study indicated that the group that received the midazolam-diclofenac combination reported significantly less postoperative pain than did the group receiving diclofenac alone (P < .05). The group receiving the midazolam also had a reduced requirement for postoperative analgesics in the early postoperative period. Another randomized, double-blind study found that the use of midazolam as an adjunct to patient-controlled analgesia (PCA) with morphine found that patients receiving adjunctive midazolam used significantly less PCA-administered morphine than did the control group.

Alpha-2-Adrenergic Agonists. The α2 agonists have been synthesized and used since the 1960s for blood pressure treatment, sedation, and drug detoxification. Recent use of α2 agonists has been shown to modify the pain response. The effects of this drug class in the management of pain perception seem to take place both centrally and peripherally. Presynaptic and postsynaptic α2-adrenergic receptors are found on primary afferent nerves, dorsal horn neurons, and brain-stem nuclei. α2-Adrenergic receptors in the dorsal horn of the spinal cord cause hyperpolarization and a decrease in spontaneous activity of dorsal horn neurons. This decreases the nociception transmission. Peripherally, it is suggested that α2 agonists have their effect via the Gi protein. The introduction of dexmedetomidine as an IV agent has increased the usefulness of these drugs in the operating room setting.

The research regarding the pain management strategies involving α2 agonists is varied. Many studies have shown a significant decrease in the perioperative use of opioids in groups receiving dexmedetomidine. Dexmedetomidine causes minimal respiratory depression; however, other side effects may include hypotension and severe bradycardia.

Anticonvulsants (Pregabalin and Gabapentin). Pregabalin and gabapentin are commonly used for treatment of seizures and neuropathic pain. Both drugs bind to the αδ subunit of voltage-gated calcium channels in the spinal cord and brain. This results in reduced calcium influx in the presynaptic terminal, reducing the presynaptic excitatory neurotransmitter release. Numerous studies show that anticonvulsants given preoperatively reduce the use of postoperative opioids. Recent studies show lower use of PCA opioids and lower anxiety in the immediate postoperative period when pregabalin is given preoperatively. Anticonvulsants can be an attractive strategy in those patients who benefit from opioid reduction or are at risk of development of chronic postsurgical pain.

The literature shows that pregabalin and gabapentin are safe, with mostly mild to moderate side effects. The most commonly reported side effects are dizziness, somnolence, and peripheral edema. The most serious adverse reactions reported include angioedema and hypersensitivity reactions. Additionally, the risk of increased suicidal ideation or behavior may be a concern, although this is a concern with antiepileptic drugs as a class. Reduced dosing should be used in those patients with renal insufficiency. Elderly patients may have a higher frequency of the already-mentioned side effects.

N-Methyl-D-Aspartate Receptor Antagonists. Recent research into NMDA receptor links to nociceptive pain transmission and central sensitization necessitate a review of NMDA receptor antagonists. Antagonists such as ketamine and magnesium noncompetitively bind to this receptor, modulating central sensory processing by preventing calcium movement through the NMDA receptor channel into the cell and thus have potential as anti-hyperalgesic agents. Ketamine in low doses has demonstrated analgesic efficacy without causing psychomimetic effects typically associated with larger doses. Low-dose ketamine has not been associated with adverse effects on respirations, cardiovascular function, or gastrointestinal function. Ketamine is thought to potentiate the effects of opioid analgesic effects, theoretically leading to decreased opioid consumption. However, research results remain divided. In one large study of orthopedic surgeries, ketamine reduced neither postoperative pain nor postoperative PCA use. However, a large study of...
thoracic surgical patients showed the combination of ketamine and morphine to be more efficacious in lowering pain scores than morphine by itself. Continuous infusion of ketamine in the perioperative period has been associated with significantly lower morphine use and better tolerance of early mobilization.

Magnesium was the first discovered NMDA antagonist. At very high doses, it has been shown to decrease postoperative pain. Initial doses of 50 mg/kg administered intravenously preoperatively followed by an infusion (15 mg/kg/h) postoperatively resulted in a decrease in PCA morphine use for the next 48 hours. Additionally, pain scores were lower following magnesium sulfate use. As with ketamine, research findings remain divided on the efficacy of magnesium sulfate in pain management. A systematic review of NMDA antagonists found no evidence to support preemptive analgesia with magnesium sulfate.

- **Glucocorticoids.** Corticosteroids have been used to reduce postoperative pain and reduce inflammation for many years. These drugs act by inhibiting phospholipase, resulting in decreased production of prostaglandins, leukotrienes, and cytokines, which play a role in inflammatory pain. Despite the long history of corticosteroid use and the evidence for analgesic actions, few studies have been conducted involving corticosteroid use postoperatively for pain relief, and no widespread use has been seen. This may be due to the adverse effects associated with repeated corticosteroid administration. A double-blind study compared the efficacy of methylprednisone with that of single-dose ketorolac. The pain intensity up to 6 hours postoperatively was similar to that seen with ketorolac and significantly lower than scores in the placebo group. That study reported no serious adverse effects. Glucocorticoids have long-term analgesic effects after surgery, but more studies with adequate power need to be conducted.

**Discussion**

As with many aspects of anesthesia care, pain management must be strategized based on the individual patient’s needs, risks, and circumstances. Many factors must be taken into consideration during the perioperative period to safely and adequately manage the surgical patient’s pain. Pharmacologic strategies alone may not be sufficient for all circumstances. In such instances, multimodal, regional, neuraxial, and psychological strategies should be strongly considered. A detailed risk-benefit analysis is always prudent when one is planning pain management strategies.

As noted in the Pharmacology section, any given drug may show significant effect in pain management in one study but not in another study. There are several reasons why this might be the case, such as methodologic differences in the studies, statistical issues, or different procedures. Attempting to overcome these limitations, an international panel of anesthesia providers and surgeons came together to form the PROSPECT (PROcedure-SPEcific Postoperative Pain ManagementT) group. The intent is to provide procedure-specific pain management.
recommendations using the methods of the Cochrane Collaboration to evaluate published pain management research studies. Procedures with information currently available on the website (http://www.postoppain.org) include abdominal hysterectomy, cesarean delivery, colonic resection, hernia repair, hemorrhoidectomy, laparoscopic cholecystectomy, noncosmetic breast surgery, radical prostatectomy, thoracotomy, total hip arthroplasty, and total knee arthroplasty. As more studies are completed and reviewed, the findings on the website are updated. PROSPECT reviews include what is recommended and what is not recommended for a particular procedure (Figure 3).

The American Pain Society with input from the American Society of Anesthesiologists recently convened a panel to develop guidelines on the management of postoperative pain.38 As was the case with the PROSPECT group, multimodal analgesia was strongly recommended. For postoperative pain management, strong recommendations from the panel supported the use of IV opioids, use of PCA, acetaminophen and/or NSAIDs for adults and children, use of a preoperative dose of oral celecoxib in adults if not contraindicated, and use of gabapentin or pregabalin as a component of multimodal analgesia. The panel made more than 30 recommendations.

Conclusion

Based on the physiology and pharmacology reviewed in this article, some points are of special note:

• Minimizing the number of substances contributing to the “inflammatory soup” would decrease the likelihood or time to a generator potential.

• Substances that contribute to the “inflammatory soup” come from both neuronal and nonneuronal sources.

• Giving a drug that blocks the effect of any one of the inflammatory substances will not lead to significant reductions in pain intensity.

• The intensity of the pain signal can be decreased by reducing the amount of excitatory neurotransmitters released at synaptic junctions or by decreasing sodium influx along the nerve.

• The emotional component of pain can be negatively influenced by increases in pain intensity.

• Opioids in high enough doses will lower pain intensity but will also have undesirable side effects.

As a way to best deal with the complexity of pain, multimodal analgesia is recommended for all procedures. Multimodal analgesia allows for lower doses of drugs, which can act synergistically to achieve the desired outcome with minimal side effects.

The quest for the most comfortable surgical experience continues and perhaps may continue for ages to come. Why some analgesics work in some procedures but not in others is not always clear. Those answers will come from ongoing studies. Until then, the PROSPECT group and the American Pain Society are giving practitioners some evidence-based direction.

REFERENCES


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