

Chapter 2

Understanding the Agent, Part I: Opioid Biology and Basic Pharmacology

A Canadian mother was prescribed codeine for post-episiotomy pain in April 2005; the pregnancy and delivery were otherwise uncomplicated, and the infant was born at 90th percentile for weight. One week later, he developed lethargy and difficulty breastfeeding, and on day of life 11, he was brought to a pediatrician for evaluation; he was found to have regained his birthweight and sent home. On day 13, the infant was found cyanotic, apneic, and pulseless, and both field and emergency department resuscitations were unsuccessful. Postmortem analysis included extensive evaluation for inborn errors of metabolism, none of which were found. Toxicologic analysis revealed morphine plasma levels of 70 ng/mL. The mother had been taking acetaminophen 500 mg/codeine 30 mg twice daily, titrating down from the prescribed dose, due to her own sedation and constipation [1].

Opioids, which have enjoyed centuries of therapeutic use and for the most part an unchallenged reign in treating severe pain, are conceptualized in this book as the etiologic *agent* in what has come to be known as the opioid epidemic in America.

Understanding all that we can about any agent in an epidemic is essential to ending its upper hand in the conflict, and this section of the book seeks to invest the practitioner with the essentials of the agent.

In order to understand opioids, however, a solid understanding of the host system that exogenous opioids mimic and affect is fundamental. Knowledge of a bacterium or virus' anatomy and physiology is not enough; understanding its biologic/chemical substrates and tissue "preferences," virulence mechanisms, and transmission is critical to designing strategies for host protection. We also live in the era of elucidating host (and agent) genetic factors that affect pathogenicity, and this may ultimately inform and direct the most rational and effective treatments—and prophylaxis. While much of these concepts are explored in more detail in subsequent sections focusing on vector and host, it is essential to first explore the native

systems which opioids are designed to both mimic and affect in order to understand how they exert their influence both therapeutically and pathologically. As such, we begin our examination of the agent with an examination of ourselves.

Opioid Biology

The opioid system exists throughout the animal kingdom, even within invertebrates [2]. This complex system is apparently designed not only to provide relief of pain but is intimately involved with numerous physiologic functions including neuroimmunoendocrine homeostasis, and in higher organisms both cognitive and emotional processes.

Endogenous Opioids: The Body's Natural Analgesics

Opioids by definition are chemical agents that exert their effects via interaction with opioid receptors located primarily within the central nervous system but to some extent within the periphery as well. Three opioid receptor classes are currently described: the *mu-opioid receptor (MOR)*, *delta-opioid receptor (DOR)*, and *kappa-opioid receptor (KOR)*. The biochemistry and activities of these receptors will be described in more detail in a subsequent section. Endogenous opioids are polypeptides currently classified within four major families: the *endorphins*, *enkephalins*, *dynorphins*, and *enkephalins*. These peptides are cleaved from precursor peptides: pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin, respectively. (Each of these precursors is in turn derived from a longer sequence indicated by the prefix “pre-,” e.g., pre-pro-opiomelanocortin [pre-POMC] rendered during the post-ribosomal translation process).

β-Endorphin is the most well studied of the endogenous opioids. POMC (the precursor to *β-endorphin*) is known to be produced primarily within the pituitary, hypothalamus (arcuate nucleus), and medulla (nucleus tractus solitarius) as well as extraneural sites such as the pancreas, and melanocytes. This widespread distribution mirrors the diverse activity of POMC derivatives, with complex roles in energy homeostasis, stress response, immune function, and also melanocyte stimulation. As POMC travels through the cell's endomembrane system, it is cleaved (primarily within the trans-Golgi network) to various active molecules including *β-endorphin*, adrenocorticotrophic hormone (ACTH), lipotropins, and melanotropins. Discussion of these latter hormones is outside the scope of this work, but is referenced here briefly to bring attention to the fact that the body's natural pain—modulating system—is intricately connected with the neuroimmunoendocrine system as a whole. As a point of interest, the well-known anecdotal observation that redheaded individuals apparently have decreased responsiveness to exogenous opioids and sedatives and/or decreased tolerance to pain may have some biologic possibility in the

fact that mutations within the POMC production process are associated with the redhead phenotype [3]. However, the few studies done in this area are contradictory, with some studies showing increased and others showing decreased tolerance to both pain and analgesics/anesthetics [4–6].

β -Endorphins act within both central and peripheral nervous systems to produce analgesia via multiple modes of action, primarily by interaction with the mu-opioid receptor (MOR). In the 1970s and 1980s, most research on endorphin and MOR ligand activity within the brain focused on the *periaqueductal gray* (PAG) region of the tegmentum of the midbrain. It was shown that endorphins/MOR ligands block the release of gamma-aminobutyric acid (GABA) within the PAG which normally acts tonically via projection fibers to inhibit serotonergic activity in the nucleus raphe magnus and other areas of the *rostromedullary* (RVM). These medullary areas provide powerful analgesic activity via “descending modulation” effects upon the dorsal horn of the spinal cord and also within the trigeminal nucleus caudalis and are tonically inhibited by PAG GABA activity (Fig. 2.1).

More recent research, beginning with the work of Fields [7, 8] has focused on direct activity of MOR ligands upon cell populations within the RVM itself, labeled “ON” and “OFF” cells. “OFF” cells are antinociceptive neurons within the RVM that are tonically inhibited by GABA, but upon activation by endorphin (or exogenous MOR ligand) activity work at the level of the dorsal horn of the spinal cord via serotonin to downmodulate ascending pain signals. MOR ligands conversely demonstrate a direct inhibitory effect upon RVM “ON” cells, which tonically act to facilitate ascending pain signals within the spinothalamic and pathway [9].

Inhibition of substance P activity within the RVM may be another mechanism of endorphin/MOR ligand-facilitated analgesia.

Of significant historic and clinical interest is the phenomenon of the placebo effect. First demonstrated (and propounded as an essential control mechanism in prospective trials) by Dr. H. K. Beecher at the Massachusetts General Hospital, the placebo effect has subsequently been shown to be a manifestation of endorphin activity within the PAG (Fig. 2.2) [10–12].

At the level of the spinal cord, endorphins/MOR ligands act in several ways to attenuate pain transmission. First, within the dorsal horn (and more specifically Rexed laminae I, II, and V), endorphins/MOR ligands act directly presynaptically (on the first-order pain afferent traveling from the periphery) to reduce substance P and other tachykinin release, which serve as the primary pain neurotransmitter at this level. This inhibition is thought to occur via suppression of N-type voltage-gated calcium channel activity necessary for the release of substance P [13, 14]. Secondly, endorphins/MOR ligands inhibit the presynaptic release of glutamate, reducing excitatory neurotransmission [15]. Thirdly, endorphins/MOR ligands may act to reduce calcitonin gene-related peptide (CGRP) release from primary afferents. Until recently, this activity had been demonstrated in vitro but in vivo studies consistently refuted the effect [16]; however, newer assaying techniques have shown that CGRP inhibition does occur in a mouse model [17]. Fourthly, MOR ligands at supraphysiologic (and supratherapeutic for most agents) have been shown to directly inhibit voltage-gated sodium channel action potential propagation in a

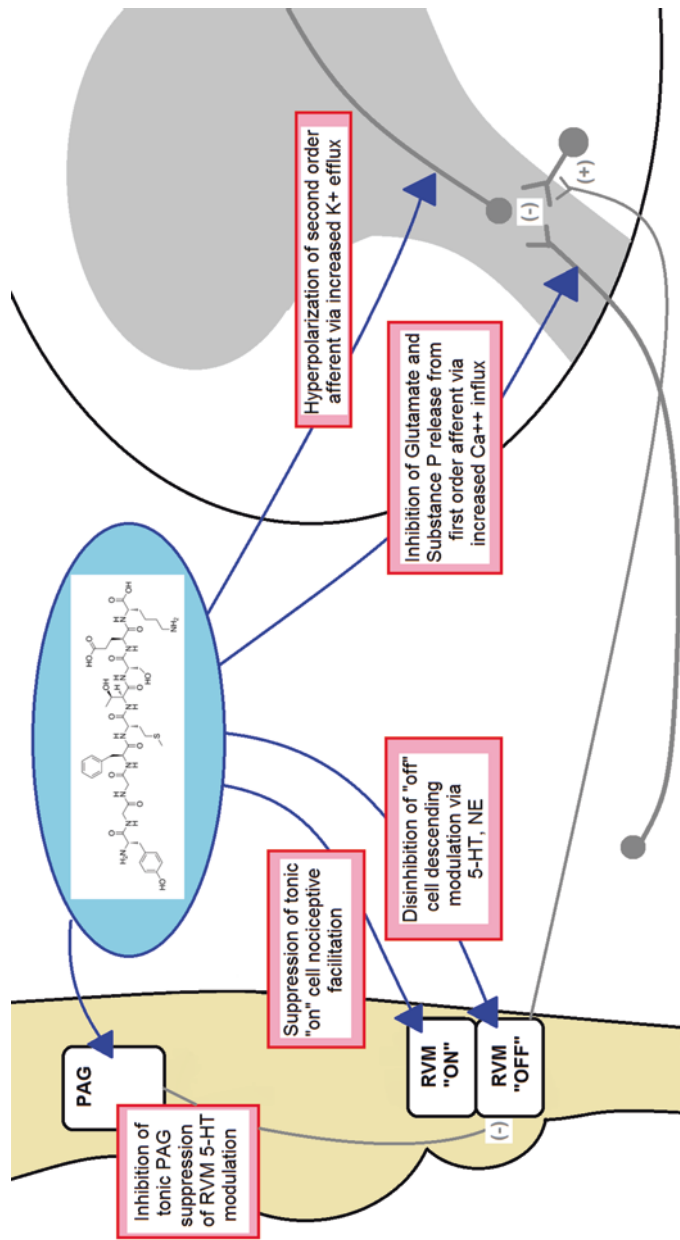


Fig. 2.1 Supraspinal and spinal mechanisms of actions of opioids

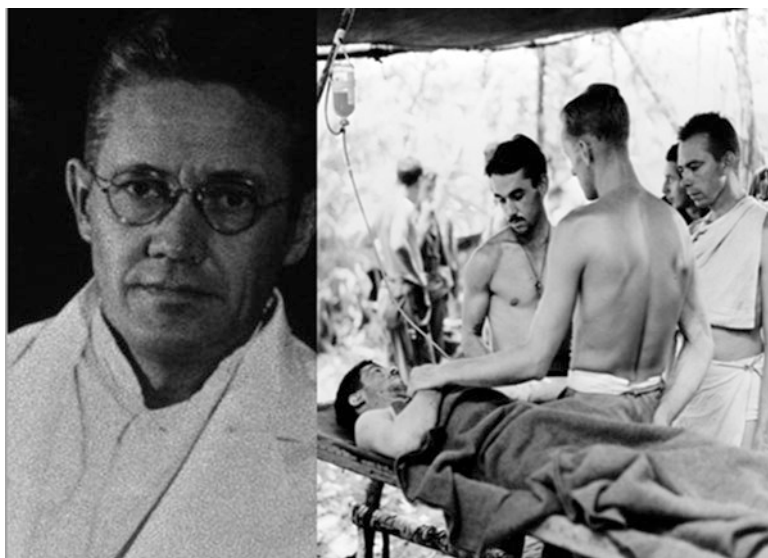


Fig. 2.2 Dr. Henry Knowles Beecher, 1904–1976, Professor Emeritus at the Harvard Medical School, was an anesthesiologist whose observations on psychological effects on pain perception during his World War II service in North Africa led him ultimately to propose what we now know as placebo-controlled trials. Other notable achievements include his groundbreaking 1966 article *Ethics and Clinical Research*, which led to the concept of informed consent and the academic Institutional Review Board system; he also trained Danish anesthesiologist Dr. Bjorn Ibsen, who later pioneered positive-pressure ventilation during a 1952 poliomyelitis outbreak and created the first intensive care unit

manner analogous to local anesthetic action [18]. Fifthly, at a postsynaptic level, endorphins/MOR ligands activate potassium channels on the second-order neuron, leading to hyperpolarization and reduction of transmission [19]. Sixthly, the activity of endorphins/MOR ligands upon both nicotinic and muscarinic acetylcholine receptors within the spinal cord have been shown to contribute significantly to analgesic effects of these compounds [20]. Finally, endorphins/MOR ligands act indirectly on the spinal cord via the aforementioned PAG/RVM descending modulation system.

Opioid receptors exist in the periphery but have not been shown to mediate any meaningful analgesic effects under normal circumstances. In states of local inflammation, however, administration of various opioid receptor ligands (μ , δ , and κ) have all shown efficacy in reducing inflammation and pain when applied peripherally to hyperalgesic tissue [21]. It is unclear if these data are relevant to physiologic situations and endogenous opioids.

Endomorphins, first described by Zadina in 1997 [22], are powerful and apparently highly selective MOR ligands whose precursor molecule has yet to be identified. Their selectivity for the MOR is 4000 times greater than their affinity for the DOR and 15,000 times greater than their affinity for the KOR [23]. They are known to be more resistant to enzymatic degradation than the other three classes

of endogenous opioids and also display vasodilatory activity via activation of nitric oxide upregulation [24]. Synthetic analogs of endomorphins have shown potent analgesic effects with significantly reduced psychomotor retardation and also addictive potential [25, 26] and may evolve as very useful clinical opioids.

First to be identified among the endogenous opioids, but least well studied, are the *enkephalins*, found primarily within the CNS (the name indicates the observation that these substances exist and act primarily within the brain). The proenkephalin molecule is cleaved into two main peptides, met-enkephalin and leu-enkephalin, both of which are rapidly degraded within the bloodstream and various tissues [27, 28]. The enkephalins are considered to be the primary endogenous ligands of the [delta-opioid receptor](#) (DOR) [29], although they also possess some mu-opioid receptor activity as well. They are thought to be related to the processing of pain sensation beginning at the level of the dorsal horn and spinal trigeminal nucleus and to limbic modulation of these sensations by the amygdala, hippocampus, and frontal cortex [19]. Due to the relative paucity of our understanding of the DOR system, and the very short half-life of enkephalins, no lasting efforts to harness this family for therapeutic use have been undertaken.

Dynorphins are better studied than the enkephalins, but perhaps even less well understood due to their complex and confusing interactions with various pathways. These powerful compounds have been shown to be regulated in part by the stress response with release being modulated by corticotropin-releasing factor [30]. They are found primarily in the central nervous system (hypothalamus, medulla, pons, midbrain, and spinal cord) and exert their effects primarily through the [kappa-opioid receptor](#) (KOR). The name (from the Greek root for “power”) indicates the potency of these endogenous ligands; they have been shown to be six to ten times more potent as an analgesic than morphine [31, 32]. However, there is evidence that dynorphins may also be pronociceptive via bradykinin activity stimulation [33]; dynorphin levels within the spinal cord have also been shown to be elevated in chronic pain states [34]. Further complicating their biology (and clinical relevance), dynorphins have been shown to be intricately involved in KOR-mediated dysphoria and the complex neuropsychobiology of addiction [35–37]. The latter has been the major focal area of research on dynorphins and will likely continue to be so as the phenomenon of opioid addiction increases in clinical and public health significance.

Opioid Receptors

Opioid receptors belong to the ubiquitous superfamily of *G-protein-coupled receptors* (GPCRs), which mediate the known actions of most neurotransmitters and hormones. GPCRs are cell membrane-bound proteins with seven helices arranged spanning the membrane, with three intracellular and three extracellular loops forming a pocket for their ligand(s) to bind (Fig. 2.3). The GPCR is coupled to a separate regulatory protein (the G protein) that binds guanosine diphosphate (GDP) in its

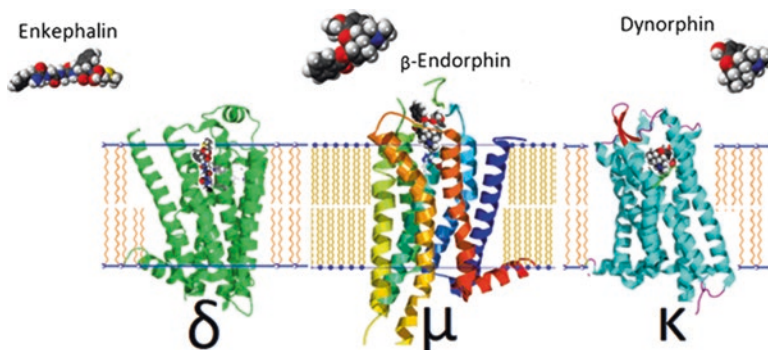


Fig. 2.3 Opioid receptors and their endogenous ligands

resting state. Upon activation by its ligand, the GPCR undergoes a conformational change that causes the G protein to exchange GDP for GTP and undergo dissociation of its component subunits which then effect a number of downstream changes. In the case of opioid receptor activity, some of these effects include inhibition of adenylyl cyclase (which reduces cyclic AMP levels), activation of potassium channels, and inhibition of voltage-gated calcium channels; the net effect of these changes results in hyperpolarization of the cell. In the case of neurons, reduction of neurotransmitter release as well as action potential propagation may result.

One feature of GPCRs that may confer clinically relevant effects is their ability to form oligomers or complexes of multiple receptors, whether homogenous (e.g., MOR-MOR dimer) or heterogenous (e.g., MOR-DOR dimer). Such multimer formation has been proposed as one possible explanation for a variety of unpredictable laboratory and clinical effects, including incomplete cross-tolerance to different therapeutic opioid drugs [38].

The *mu*-opioid receptor (MOR) is the receptor best-studied and most utilized therapeutically. All clinically used opioids today are agonists of the MOR (with varying agonist activities and in some cases antagonist activity at other opioid receptors). Located extensively throughout the central nervous system and also within the peripheral nervous system, gut, and various immune system cells, the MOR is responsible for the majority of therapeutic opioid-related activity (analgesia) as well as several of the more serious and acute adverse effects, such as respiratory depression and constipation/ileus. Mu-receptor subtypes have been proposed by various groups, but have not been accepted as definitive due to very incomplete evidence confounded by multiple alternative explanations (e.g., receptor oligomerization) for the disparity in biologic effects from different ligands [38]. Nonetheless, the mu-1 receptor subtype is suggested to confer analgesia and physical dependence; the mu-2 receptor, euphoria, respiratory depression, ileus, pruritis, miosis, and physical dependence; and the mu-3 receptor, vasodilatation.

The *delta*-opioid receptor (DOR) is currently an area of intense investigation, as its properties may prove to be uniquely useful in modulation of chronic pain and addiction. Located primarily within the cortex and basal ganglia in humans [39],

there is a considerable degree of interspecies heterogeneity in terms of peripheral distribution; among primates, DOR seems to be primarily located in small- and medium-sized afferents [40]. As with MOR, subtypes have been proposed, including DOR1 and DOR2. Its natural ligands, as discussed above, are thought to be the enkephalins. Early studies showed somewhat confusing and contradictory effects on CGRP release [41] and substance P release [42]. More recent evidence suggests that complicated interactions between the MOR and DOR (as well as other factors influencing the expression of at least the DOR in various pathologic states) including heteromerization are responsible for the difficulties in assigning clearly defined “effect profiles” for these receptors. Nonetheless, there is some suggestion that DOR agonism may confer superior neuropathic pain control, reduced respiratory depression, constipation, and physical dependence, compared to pure MOR agonism [41, 42]. Alternative roles for DOR agonists including antidepressants and cardiac myocyte ischemic preconditioning agents have also been suggested but have not yet borne fruit clinically [39, 40, 43].

The *kappa-opioid receptor (KOR)* is distributed widely throughout the brain (hypothalamus, periaqueductal gray, and claustrum), substantia gelatinosa, and in peripheral nerves. It is also represented in significant proportion throughout the viscera. Putative subtypes for this receptor have also been proposed. As discussed above, its endogenous ligands include the dynorphins. Other naturally occurring KOR ligands include menthol and the hallucinogen salvia. A disproportionate amount of adverse psychiatric effects seems to be mediated by the KOR (dysphoria/depression, dissociation and hallucinations); however, it has been suggested that this activity may confer a “natural addiction control mechanism.” Of clinical interest is the observation that buprenorphine, a partial agonist at the MOR and an antagonist at the KOR that is used primarily in addiction management, seems to possess antidepressant qualities unique to the opioid family. Numerous investigations have demonstrated the superiority of KOR agonists in alleviating pain and discomfort from visceral sources [44]; however, given the high rate of adverse effects, no clinically useful drug has yet been developed.

The *nociceptin/orphanin FQ receptor (NOR)* is a recently discovered opioid receptor “cousin” demonstrating significant interactions with both the classic opioid systems and also a highly diverse array of other physiologic functions. First isolated in 1994, the NOR was initially named opioid receptor-like 1 (ORL1) and shares a little over 50% homology to the “classic” MOR, DOR, and KOR but does not bind any of the known endogenous opioid ligands (other than dynorphin A). Its natural ligand has been independently named nociceptin (reflecting its pronociceptive activities) and orphanin FQ (the most common acronym in the literature, N/OFQ references both titles). As with most things opioid-related, it turns out the N/OFQ system is exceedingly complex, and it is found in tremendous dispersion throughout the CNS, including the cerebral cortex, thalamus, hypothalamus, hippocampus, habenula, amygdala, locus ceruleus, substantia nigra, periaqueductal gray, ventral tegmental area and raphe complex, and both dorsal and ventral horns of the spinal cord; in addition, the system is found throughout the intestinal and other visceral organs and also on many leukocytes [45, 46]. Besides facilitating both pronociception and

antinociception (discussed in greater detail below), the widespread activities of this system reflect its ubiquitous distribution and include effects on cognitive functions such as learning and memory; emotional functions related to stress and anxiety; feeding behaviors; respiratory, cardiovascular, and renal function; and immune function [45–48].

Finally, at one time, a proposed *sigma-opioid receptor* was widely accepted (the author remembers memorizing it and its effects, most of which are adverse, in second-year medical school pharmacology class) but has since been shown to be completely structurally unrelated to opioid receptors and is no longer considered to be one.

Opioid-Modulating Systems

As early as the 1980s, it was becoming apparent that endogenous “anti-opioid” systems exist within the CNS. A growing body of evidence supports the hypothesis that the body possesses its own “check and balance” system regulating the pain-modulating effects of endogenous opioids and possibly protecting us against disadvantageous phenomena such as tolerance and dependence.

Adenosine has been studied for decades as an analgesic in its own right and has been shown to undergo opioid-related release in the spinal cord, and the A3 receptor subtype is an area currently undergoing active research for possible therapeutics [49].

The *cholecystokinin (CCK)* system was among the earliest endogenous neuropeptide opioid modifier studied and is generally regarded as an opioid-inhibitory system in addition to its inherent pro-inflammatory action. At the level of both brain and spinal cord, CCK has been shown to both block opioid activity and enhance opioid-induced hyperalgesia [29]. CCK however has been shown to exert both suppressive and potentiating effects upon opioid analgesia that has been proposed to be dependent upon competing actions of subtypes of CCK (CCK-A vs. CCK-B) upon enkephalin effects at the MOR vs. the DOR [29]. Differential and possibly dose-dependent effects of CCK on RVM “ON” and “OFF” cells have been invoked to explain differential supraspinal activity [50, 51]. CCK-opioid interactions are exceedingly complex and display responsiveness to stress and anxiety states as well as other endocrine perturbation [52–54].

The *neuropeptide FF (NPFF)* system is another opioid-modulating peptide system with effects that include attenuation not only of anti-nociceptive effects of opioids but also psychological reward [54–57]. This system may play an important role in the iatrogenic phenomenon of opioid-induced hyperalgesia [57].

The *neurokinin-1 receptor (NK1R)* is the main receptor in the tachykinin receptor family, whose main ligand is the neurotransmitter known as *substance P*. While initially thought to be primarily a pain neurotransmitter active primarily within the dorsal horn, it is expressed widely by multiple cell types including neurons, glia, endothelia, fibroblasts and other poietic cells, and leukocytes as a primary inflammatory mediator and also plays an important role in initiating a

number of “constructive” processes as well including hematopoiesis, wound healing, and cell survival [58, 59]. The modulatory effects of NK1R upon opioid activity are not well characterized, but one study showed that activation of NK1R co-localized with MOR in striatal cells prevented MOR endocytosis (which finding was in contradiction to previous studies showing an increase in MOR endocytosis/inactivation) [60].

Perhaps the best-studied of the endogenous opioid-modifying systems is the *N-methyl-D-aspartate* (NMDA) system. The NMDA receptor (NMDAR) is a glutamate (one of the major excitatory neurotransmitters) receptor widely distributed throughout the CNS that is tonically inactivated by the presence of a magnesium ion within its channel. When bound by glutamate (and a co-ligand such as serine or glycine) and when the neuron undergoes depolarization, magnesium then dissociates from the channel, and various cation traffic (primarily calcium influx) results in downstream effects via calcium-sensing proteins and other mediators including G-protein complexes that result in long-term potentiation and other synaptic plasticity events [61, 62]. NMDA activity is increasingly shown to play a role in a number of physiologic events (e.g., learning) and pathophysiologic states (e.g., depression, schizophrenia, autism spectrum disorders, chronic pain states). Of relevance to opioid pharmacology is the fact that since the early 1990s, we have known that NMDA activity results in rapid development of tolerance to opioids and conversely NMDA antagonism prevents or reduces such development of tolerance. One mechanism for NMDA-opioid interactions at least at the level of the periaqueductal gray has recently been shown to be disruption of normal MOR-NMDAR coupling by binding of ligands to either receptor, which activates protein kinase C (PKC) or protein kinase A (PKA) both of which effect tolerance perhaps by internalization of the MOR [63].

The recently discovered *nociceptin/orphanin FQ* (N/OFQ) system demonstrates significant bidirectional modulatory relationships with the classic opioid receptors; depending on species and specific stimulation patterns, ligand dosing, location and chronicity, and a host of other variables, N/OFQ may exert pronociceptive or antinociceptive effects [45–47, 64]. It appears that supraspinal actions may be more complex in terms of pain responses, whereas spinal actions more consistently demonstrate analgesic tendency [46, 47]. Multiple studies have shown heterodimerization of NOR with the classic receptors, adding to the complexity of interactions between these cousins [46]. Furthermore, the pro-inflammatory effects of the NOR system effected by its neuroimmune activities and the stress/anxiety-mediated effects of the NOR system effected by limbic and hypothalamic-pituitary-adrenal axis activities confer additional layers of real-life complexity surrounding NOR modulation.

Activation of the *platelet-derived growth factor receptor type-beta* (PDGFR- β) has been shown in animal models to be activated among other things by MOR activity, and PDGFR- β activity in turn results in opioid tolerance [65]. The mechanism of action is not clear and is furthermore confounded by the fact that PDGFR- β activity inhibits NMDAR [66] which should according to our understanding of that receptor’s activity decrease opioid tolerance.

Synergistic effects of α_2 -adrenoreceptor (α_2 -AR) activity with that of opioids have been known for decades and intrathecal administration of clonidine has been commonplace by anesthesiologists for many years. Both α_2 -AR and opioid

receptors A118G variant (DOR in particular) have been shown to co-localize at the terminus of the primary afferent, and α_2 -AR are also abundant on interneurons in the substantia gelatinosa; however, the exact mechanism of this cooperative activity remains unknown. The formation of opioid-adrenoreceptor heteromers has been suggested as one potential explanation [67].

Finally, a fascinating area of research involves the bidirectional relationship of opioids and neuronal support cells (astrocytes, microglia). Long thought to be fairly devoid of any activity other than supporting neurons, our understanding of this dynamic cell population has grown exponentially over the past decade, and we now know that glia are actively involved in neurotransmission, regulating neuronal activity, remodeling synapses, and many other functions. Glia are also very active in modulating the pain response and can function to amplify and perpetuate neuronal signaling by pro-inflammatory means (including cytokines, chemokines, prostaglandins, and other mediators), alter neurotransmitter release and receptor expression, and even actively participate in signaling [68, 69]. Opioid receptors have been demonstrated on glia [49, 69], and activation of these receptors results in inflammatory mediator released/increased pain sensitivity and also opioid tolerance. A distinct innate immune receptor on glia named the *Toll-like receptor 4 (TLR4)* is activated by both stress/inflammatory signals and also by opioids and has been shown to be intricately involved with the development of opioid tolerance, dependence, psychological reward, and also opioid-induced hyperalgesia [68–70].

Overview of Non-analgesic Opioid Effects and Interactions

No twenty-first-century discussion of opioid pharmacology is complete without at least salutatory reference to the vast body of research indicating what appears to be “the most extensive and diverse peptidergic transmission system... widely involved in various pleiotropic functions” [43]. Multiple physiologic processes from the cellular to the organ level are influenced by the opioid system, and while a rigorous discussion of such interactions is well beyond the scope of this book, it bears mention that both endogenous and therapeutic applications of opioids have widespread effects upon the organism as a whole that are just now beginning to be elucidated [43, 69]. Adverse effects of opioids are discussed in a later section.

Opioid Pharmacology

Opioid Pharmacodynamics and Pharmacokinetics

Pharmacodynamics is sometimes defined as “what the drug does to the body” and is concerned with mechanisms of action of drugs and effects produced. Conversely, pharmacokinetics is described as “what the body does to the drug” and is concerned with the processes of absorption, distribution, metabolism, and excretion of drugs.

Simple dose-response curves describing the effects of a drug as invariably correlated with the amount administered or the concentration of the drug are a gross oversimplification increasingly complicated by our expanding understanding of the effects of genetic differences, drug-drug interactions, and dynamic factors such as mutable expression or function of transporters, receptors, and post-receptor mechanisms (e.g., second-messenger systems). Tolerance, for example, discussed in its own subsection below alters pharmacodynamics with almost individual-level variance and is a phenomenon with tremendous clinical impact on opioid therapy.

Beyond the complex issues inherent within the opioid “system” proper, an ever-increasing body of evidence bears witness to the possibly unparalleled diversity of interaction between endogenous or exogenous opioids and their receptors and multiple other physiologic processes from ionic homeostasis, hypoxic/ischemic protection, and cell proliferation at the microscopic level to organ-level alteration of cerebral, respiratory, cardiac, immune, endocrine, and gastroenterologic systems [43, 71]. These interactions are frequently “two-way streets,” with complex signaling and reciprocal feedback/control mechanisms that are not fully understood but likely have their basis in dynamic receptor alterations including oligomerization, uncoupling, and endocytosis.

Similarly, the simplicity of basic pharmacokinetic concepts taught for decades (such as zero vs. first-order kinetics, single or two-compartment models) is increasingly challenged by our expanding understanding of phenomena such as pharmacogenetics, epigenetics, drug-drug interactions, induction and inhibition, and other such pharmacodynamic factors that influence metabolism. Disease states also have profound effects on pharmacokinetics (and pharmacodynamics).

It should also be noted that pharmacodynamic and pharmacokinetic principles/processes are occurring simultaneously within the body, and though they are phenomena without innate intelligence, they can be conceptualized as being at odds with each other. The drug “desires” to exert an effect on the body (pharmacodynamics), while the body “desires” to be rid of the drug (pharmacokinetic). For continuity of understanding the biological and biochemical processes involving these molecules from administration to elimination, this discussion will of necessity progress to some extent back and forth from topics within the categories of pharmacodynamics and pharmacokinetics. We will begin our examination of opioid pharmacology with processes that fall under the rubric of pharmacokinetics, such as absorption and distribution. We will then proceed to examination of endogenous opioid ligands and opioid receptors and their pharmacodynamics. Natural opioid-modifying systems will be reviewed next, followed by a brief survey of non-analgesic activities resulting from opioid receptor activation. The pharmacokinetic function of metabolism, and a brief survey of pharmacogenetic factors affecting both opioid pharmacology, and finally a review of the important phenomenon of opioid tolerance will follow before progressing to discussion of individual therapeutic agents. Therapeutic and adverse effects of opioids, evidence-based guidance for use, and alternatives will be discussed in Sect 3.

Absorption and Transport

The vast majority of clinical opioid use is oral, and after ingestion/digestion, the drugs first enter the portal circulation from the intestines via both simple diffusion and also by active transport mechanisms such as the solute carrier (SLC) superfamily of influx transporters, which in conjunction with the ATP-binding cassette (ABC) superfamily of efflux transporters regulates in part net uptake of molecules through the mucosa into the bloodstream [72, 73]. Hepatic uptake is also governed in large part by these transporters. The relatively recent development of controlled-/extended-release technology, which retards the rate of dissolution within the alimentary canal, does not alter any of these fundamental biologic mechanisms.

The drug then undergoes immediate (“first-pass”) metabolism as described in more detail below in the pharmacokinetics section—the body is already trying to degrade and eliminate the drug. Parenterally administered drugs of course are not subject to first-pass metabolism but still experience hepatic metabolism every time they circulate through the organ.

In some cases, the drug taken is a relatively ineffective precursor agent that the liver “unwittingly” alters into an active or more potent state. In either case, after running the gauntlet of the liver, the agent (or altered agent) exits the portal circulation and enters the systemic venous circulation for left-heart distribution to the rest of the body.

Distribution is a pharmacokinetic concept that will be explored in slightly more detail below; “macrodistribution” by the cardiovascular system and subsequent “microdistribution” by diffusion and active transport mechanisms into tissues and organs are both encompassed in this phase. Within the latter category, an intermediary system of opioid transporters (the SLC and ABC superfamilies) again exerts either facilitatory or inhibitory effects respectively upon the agent to ferry it across to or restrict its access to the CNS wherein lies the main arena of opioid effects. Continuous active efflux of drugs by ABC superfamily transporters within the vascular luminal endothelium may comprise the major hurdle within the blood-brain barrier for opioids and other psychoactive drugs [74, 75].

Distribution and Metabolism

Distribution of a drug to target organs and receptors, as well as inert tissues such as the muscle, bone, and fat, occurs immediately following entry of the agent to the systemic circulation. Several factors influence the transport and transfer of these molecules, including protein binding and lipophilicity.

Plasma proteins such as albumin and alpha-1 acid glycoprotein (AAG) may bind a drug and prolong its circulation within the bloodstream/retard its uptake by tissues and also retard hepatorenal elimination. The proportion of protein-bound drug varies widely among opioids, from roughly 30% for morphine to 90% for alfentanil

(an intravenous opioid). This percentage may be dynamic, however, as competition for plasma protein binding sites, and various metabolic conditions (e.g., hypoalbuminemia or acid-base disturbances) may influence binding. Furthermore, AAG is an acute phase reactant with significantly increased plasma presence during inflammation, which may alter opioid pharmacokinetics.

Lipophilicity is another variable with significant pharmacokinetic effect. As a general rule, the more lipophilic a substance, the more readily it is able to diffuse through cell membranes, which of course are composed of a lipid bilayer. This is particularly important in the context of the blood-brain barrier, where the agent must pass through the endothelial membrane, both apical and basal (all the while undergoing efflux transport back out of the cell into the bloodstream) on its journey to the CNS. There is significant variation in lipophilicity among the opioids, ranging from fairly hydrophilic molecules such as morphine to highly lipophilic molecules such as fentanyl and sufentanil (an intravenous opioid with ten times the potency of fentanyl). Discussions of these characteristics have generally been relegated to the realm of parenteral opioids, as lipophilic distribution considerations significantly impact spinal and epidural administration. However, these issues are not without relevance to the outpatient world as well, as agents with a high degree of lipophilicity (generally presented in pharmacologic textbooks as the octanol: buffer partition coefficient) also store up in adipose tissues, and in obese individuals, this can yield a volume of distribution significantly larger than anticipated. In the case of fentanyl, for example, a significant reservoir of drug can accumulate in the obese individual and wind up contributing to far greater plasma levels than would be expected from a given transdermal dose.

Infrequently discussed in the opioid literature, but commonly taught in pharmacology classes and anesthesiology residency programs is the concept of vessel-rich and vessel-poor compartments, and these theoretical compartments complicate the simple pharmacokinetic concept of half-life [76]. The so-called vessel-rich compartment is comprised of organs and tissues that are highly perfused, such as the brain, heart, lung, liver, and kidney. An intermediately, perfused group is often taught as well, comprising primarily the muscle. Finally, the vessel-poor group consists of the adipose and bone. The apparent reality of this multicompartmental model significantly complicates the simplistic concept of half-life ($t_{1/2}$), which describes the amount of time required for plasma levels of an agent to fall by 50%, and has been described for first-order kinetics as a constant (with a linear downslope of the logarithm of concentration) for virtually all medications and toxins in classic pharmacology textbooks. In a multicompartmental model, there are multiple half-lives reflecting not only elimination kinetics, but distribution kinetics as well. In the simplest form, $t_{1/2\alpha}$ refers to distribution half-life and has in general a steeper downslope, at least for agents that readily leave the bloodstream, i.e., are not highly protein-bound nor markedly hydrophilic. In this model, $t_{1/2\beta}$ refers to elimination half-life and assumes equilibrium between plasma and the compartments.

As a side note, this multicompartmental model has clinical significance also in terms of unanticipated reservoirs. As mentioned previously, fentanyl, due to its very high lipophilicity, will store preferentially in adipose. Adipose is also very poorly

perfused, and while it takes a long time for stores to build up in this tissue, the converse is also true; due to very limited blood flow, the rate of egress back into the circulation and out the hepatorenal system is very slow. This phenomenon is perhaps even more well recognized clinically with methadone, which has a lipophilicity roughly an order of magnitude less than fentanyl, but two orders of magnitude greater than morphine.

Again, it should be kept in mind that all of these processes described are not occurring sequentially, but rather simultaneously. Elimination begins with first-pass exposure to the liver for orally administered agents, even before distribution.

In basic terms, the vast majority of pharmacologic compounds (including naturally occurring substances such as opium) despite therapeutic benefit are “considered toxins” by the organism and undergo alteration, degradation, and elimination (as opposed to nutrients and vitamins, etc. which are incorporated into cells and tissues for sustaining and improvement of the organism). After initial alteration by gastric acid and upper gastrointestinal enzymes (in the case of enteral administration), metabolism classically is described as beginning in the liver, where the drug undergoes transformation to render it capable of excretion by the kidneys. Opioids, like many drugs, are for the most part rather hydrophobic, which facilitates their passage into the CNS. Hepatic processes therefore alter the structure of the drug to a more hydrophilic state such that glomerular filtration and excretion can occur. As described above, oral medications undergo immediate hepatic “first-pass metabolism” upon absorption from the intestines; for parenterally administered medications (e.g., sublingual, transdermal, intravenous) “first-pass metabolism” does not apply; nonetheless, the circulating drug burden must still eventually and repetitively pass through the liver and will eventually undergo transformation by these same processes.

These hepatic processes are classified into so-called Phase 1 and Phase 2 metabolism. Both are catalyzed by enzymes, and Phase 1 is generally facilitated by the *cytochrome P450* family which will be discussed in greater detail below. In this phase, one of these “CYP” enzymes acts to modify the structure of the drug by a variety of means, such as oxidation (the most common reaction) but also by reduction, hydrolysis, and cyclization/decyclization reactions. Phase 2 is facilitated by enzymes such as *uridine diphosphate glucuronosyltransferase (UGT)* and consists of the addition of another hydrophilic moiety such as glucuronate (or sulfate, glutathione, glycine, or sulfate). The addition of these large anionic groups renders the molecule more polar as well as larger, with resultant reduction in both diffusion and active transport across cell membranes. The conjugated molecule is also much more readily excreted as discussed above.

Phase 1 metabolism, especially that performed by CYP3A4, has been shown to be highly subject to both induction (increased activity of the enzyme resulting from exposure to certain substrates) and inhibition (decreased enzymatic activity from other substrates). The CYP3A4 enzyme is thought to have at least 40 alleles and is responsible for over 50% of all drug metabolisms. CYP3A4 is responsible for the primary metabolism of fentanyl and oxycodone and is also involved in the metabolism of tramadol and methadone [77]. Many drugs or other chemicals (e.g., bergamottin in

grapefruit juice) can induce or inhibit CYP3A4 activity, yielding significant unpredictability in metabolism. Tables showing known inducers and inhibitors of CYP3A4 are ubiquitous and as such are not reproduced here; commonly used inducers include many statins, anticonvulsants, and antiretroviral agents. Commonly used inhibitors include estrogens, cimetidine, amiodarone and quinidine, many calcium channel blockers, many antibiotics, many of the antidepressants, and most of the antiretrovirals. In addition, as so many drugs are metabolized by this pathway, it is conceivable that polypharmacy may effect competition for this enzyme.

Exceptions to this basic pattern exist; for example, remifentanyl, an intravenous opioid commonly used in operative anesthesia, is degraded by enzymes within the bloodstream itself (RBC esterase) and as such has an extremely short half-life. Intravenous, subarachnoid and epidural, and peripheral parenteral administration of opioids is not discussed within this volume.

Pharmacogenetics

While technically falling under host factors and therefore more applicable to the last section of this book, the effect of pharmacogenetic variance on opioid therapy will be covered in this basic science section for continuity of understanding the drugs. Pharmacogenetic factors are likely one of the major factors conferring much of the interpersonal variability seen with both therapeutic effects and misuse/abuse of opioids and can affect both pharmacodynamics and pharmacokinetics (Table 2.1).

Table 2.1 Pharmacodynamic and pharmacokinetic polymorphisms affecting opioid therapy

Enzyme/receptor	Variants	Effects
COMT (catechol- <i>O</i> -methyltransferase)	Val158Met variant	Decreased catecholamine metabolism – Increased pain perception – Reduced opioid effectiveness – Multiple other psychiatric disorders
ORM1 (mu-opioid receptor)	A118G variant	– Increased pain perception – Reduced opioid effectiveness
CYP2B6	Reduced activity	Reduced S-methadone metabolism with increased risk of torsades de pointe
CYP2D6	“Poor metabolizer”	Decreased plasma levels/efficacy of prodrugs (e.g., codeine, hydrocodone) Reduced metabolism of tramadol, oxycodone, methadone
	“Ultrarapid metabolizer”	Increased plasma levels/efficacy of prodrugs (e.g., codeine, hydrocodone) Increased metabolism of tramadol, oxycodone, methadone
UGT2B7	Reduced activity	Reduced metabolism/increased plasma levels of morphine (hydromorphone? oxymorphone?)

Among pharmacodynamic polymorphisms, only two major genes have been studied extensively for their contribution to differences in pain perception/experience and opioid response: the *catechol-O-methyltransferase (COMT)* gene and the *mu-opioid receptor (OPRM1)* gene.

COMT is an enzyme that metabolizes catecholamines (dopamine, norepinephrine, epinephrine) and thus reduces sympathetic activity. Several studies have shown that alterations of this enzyme (the most well studied of which is the Val158Met allelic variant which involves substitution of methionine for valine at position 158 of the enzyme, resulting in reduced catabolism) are associated with significant increases in pain perception and reductions in opioid responsiveness [78, 79]. Recent analyses have suggested that the Val158Met variant of COMT may only confer clinically significant alterations in chronic pain related to musculoskeletal complaints and specifically fibromyalgia and other chronic widespread pain conditions [80, 81]. However, it must be kept in mind that COMT activity is exceedingly broad, with complex effects on cognition and executive function, emotional processing, and sense of well-being, and has been implicated in the pathophysiology of depression, bipolar mood disorder, anxiety, posttraumatic stress disorder, schizophrenia, and various substance use disorders and addiction.

The OPRM1 gene manifests over 3000 known polymorphisms, and the most well studied is the A118G variant which involves a substitution of guanine for adenosine in the coding region on chromosome 6. This mutation has been shown to result in highly variable mu-receptor biochemistry among various ligands and across species with no consistent pattern yet identified [82, 83]. Clinical observations have been similarly confusing with several studies and meta-analyses suggesting that the A118G variant is associated with increased pain perception/ reported pain scores and increased opioid requirements [83, 84], while others show no significant association [79, 85, 86]. Of note, the meta-analyses favoring a clinical effect focus on the postoperative period [83, 84].

Pharmacogenetics affecting pharmacokinetics shows more consistency in effects and have been well characterized especially in regard to the CYP450 system. As mentioned previously, the majority of drugs including opioids undergo Phase 1 metabolism by this hepatic family, and alterations herein result in significant effects upon activation of prodrugs and inactivation of drugs. Commercially available assays for several enzymes within this family (especially CYP2D6, CYP2C19, and CYP2B6) are beginning to show some utility in guiding pharmacotherapeutic choices for a number of psychoactive drugs including opioids, benzodiazepines, and antidepressants, and the narrow therapeutic window of many of these substances coupled with increased access to the assays may eventually render pharmacogenetic testing standard of care.

The *CYP3A4* enzyme is thought to have at least 40 allelic variants and is responsible for over 50% of all drug metabolisms. CYP3A4 is responsible for the primary metabolism of fentanyl and oxycodone and is also involved in the metabolism of tramadol and methadone [77]. The effects of polymorphisms at this locus have not been well characterized; alterations (e.g., CYP3A4*1G, a common variant in Asians) have been reported but have not shown any consistency in clinical effect

[84]. Of much more significance are the effects of drug-drug interactions involving induction or inhibition of this enzyme as discussed above in the section on pharmacokinetics.

The *CYP2D6* enzyme is primarily responsible for the metabolism of codeine and hydrocodone and partially responsible for the metabolism of tramadol, oxycodone, and methadone. *CYP2D6* is responsible for the metabolism of far fewer drugs overall and thus is less subject to induction and inhibition by other substances. *CYP2D6* however has over 100 known allelic variants [84], and this heterogeneity has shown much more significant clinical effects than has *CYP3A4s*. Four phenotypic categories resulting from these variances have been proposed: poor metabolizers (the result of homozygous nonfunctional alleles), intermediate metabolizers, extensive metabolizers, and ultrarapid metabolizers (the result of multiple functional allelic copies or promoter mutations) [78]. Intermediate and extensive metabolizers have not been shown to exhibit significant variability in clinical effect and may be considered baseline or normal subjects. Poor *CYP2D6* metabolizers will show increased plasma levels and prolonged effects (both of which may confer toxicity) of drugs that rely primarily on this pathway for degradation; conversely, they will show decreased plasma levels and effects of prodrugs such as codeine and hydrocodone that rely on transformation by the cytochrome enzyme to a more active and potent form (e.g., codeine to morphine, hydrocodone to hydromorphone). Conversely, ultrarapid *CYP2D6* metabolizers will show reduced plasma levels and shorter duration of action of active drugs and greatly increased plasma levels of active metabolites of prodrugs that may confer significant toxicity. A tragic and well-reported incident involving the death of a neonate due to maternal ultrarapid *CYP2D6* activity occurred in April 2005; postmortem analysis revealed that the infant's plasma morphine levels were sevenfold higher than morphine levels in infants prescribed morphine, due to maternal breast milk morphine levels that were one to two orders of magnitude higher than that normally seen [1]. The US Food and Drug Administration subsequently issued a warning highlighting the dangers of postpartum codeine prescriptions in 2007; the same caution must of course apply to any opioid or toxic substances metabolized through the *CYP2D6* pathway. *CYP2D6* polymorphisms have not shown consistent clinical effects with regard to tramadol nor oxycodone [84]; however, it should be noted that this enzyme converts oxycodone to oxymorphone.

The *CYP2B6* enzyme is one of many that metabolize methadone; however, it is the main enzyme that degrades the S-enantiomer of methadone [87], which is the isomer conferring that agent's N-methyl D-aspartate (NMDA) blockade and also the isomer associated with QT interval prolongation [88]. Individuals deficient in *CYP2B6* activity are thus at higher risk for torsades de pointe and may warrant more frequent/intensive ECG monitoring and lower doses.

The *UGT2B7* enzyme is the predominant mediator of Phase 2 metabolism of morphine, which does not undergo substantial Phase 1 metabolism. It also conjugates glucuronide to hydromorphone and oxymorphone. Allelic variants of this enzyme have been demonstrated among various populations [78, 79] and decreased activity results in increased plasma levels of morphine, as would be expected.

Tolerance

Many drugs used clinically demonstrate a phenomenon of inducing tolerance with repeated use; while our understanding of underlying mechanisms is far from complete, drug tolerance is conceptualized as occurring largely due either to increased metabolism and elimination of the drug (so-called pharmacokinetic tolerance) or due to a decreased response to the drug at its site of action (so-called pharmacodynamic tolerance).

Pharmacokinetic tolerance is thought to occur primarily due to upregulation of degradative function in the liver, with “induction” (increased activity) of cytochrome P450 enzymes. Many drugs induce their own metabolism, and the more of a substance the organism is exposed to, the more actively it works to eliminate the substance.

The mechanisms underlying pharmacodynamic tolerance are more complex and are not fully understood and involve a number of alterations at the level of the receptor, its downstream effects, and also other modulatory systems. Early observations of alterations in both second messenger function (such as hyperactivity of the adenylyl cyclase system) and in transmembrane ion flux and polarization were followed by discoveries that other pathways (most notably the NMDA system) are very involved in the development or prevention of opioid tolerance [89]. More recent advances in the understanding of G-protein-coupled receptor signal attenuation across the family indicate that the initial step in the development of desensitization involves phosphorylation of the receptor (by G-protein receptor kinases) that serves to prepare the activated receptor for binding by proteins called arrestins which then initiate the process of receptor endocytosis. The endocytosed receptors are held within the cell until a recycling process of cell membrane reinsertion occurs [90]. Receptor oligomerization is currently being invoked to explain a number of phenomena involving the complex and still mysterious details underlying the opioid system, and some investigators have proposed that MOR-DOR heteromerization in particular may occur in the context of chronic ligand exposure with resultant functional alteration [91].

A mechanistically different process contributing to the “diminishing returns” with chronic opioid use is an actual upregulation in pain sensitivity known as opioid-induced hyperalgesia (OIH) which is discussed in more detail in Chap. 3. As alluded to briefly in the endogenous opioid-modulation section above, native processes involved in the “check and balance” system related to opioid analgesia are likely involved in OIH. In addition, however, compensatory upregulation of non-opioid-influenced nociceptive pathways in the CNS could be responsible (in part) for both OIH and tolerance [92]. Teleologically, both phenomena perhaps represent a common means for preserving the ability of the organism to detect threats (by means of nociception).

Finally, it should be mentioned that although the situation is almost certainly the exception rather than the rule, a decrease in therapeutic efficacy of long-term opioid use may be the result of progressive “organic” pathology. Cancer grows and spreads,

and autoimmune inflammatory conditions progressively destroy more tissue. However, our understanding of the interactions between nociception and endogenous modulation of pain is expanding as discussed above in limited detail, and there is growing evidence that in the absence of modifying factors such as concurrent neuropsychological pathology (including but not limited to maladaptive neural plasticity) or OIH, even in states of aggressive tissue pathology the body (and mind) may well be capable of significantly more innate pain management than we generally give it credit for. Nonetheless, it is incumbent upon the physician to remain ever vigilant for the spread of disease within the patient, whether from the condition being treated (e.g., metastasis) or the treatment itself—such as occult bowel pathology from opioid-induced ileus/obstruction, pathologic fracture owing to opioid-induced endocrinopathy, or OIH.

Summary

The physician's safe, ethical, and effective prescription of opioids (conceptualized as the agent in classic epidemiologic paradigm) is predicated upon a thorough understanding not only of the drug class itself, which is explored in greater detail in the next chapter, but also of the biologic systems wherein/upon which they act.

Opioids are produced by the body and act as part of a comprehensive homeostatic self-preservation effort geared toward the well-being of the organism. The most salient aspect of this system is acute pain relief, but within seconds modulating and counter-regulatory effects are initiated to balance pain relief with perception of danger thus facilitating help. Different endogenous opioids exist, with primary affinity for different opioid receptors, which exert different effects toward this overall goal.

Therapeutic (exogenous) opioids exist within nature as well (e.g., opiates) and have been modified and copied pharmaceutically to harness the potent analgesic qualities of this system. Unlike the endogenous system, however, the only limitation upon exogenous opioid exposure is volitional (or imposed) discretion on the part of the consumer, and in a situation of excess exposure—whether by quantity or chronicity—both tolerance and adverse effects reduce analgesic efficacy and tip the balance of risk:benefit away from the positive. The body is prepared to some extent to reduce these potential threats by eliminating the agent metabolically. Genetic factors play an increasingly appreciated role in varying efficiency of this process from individual to individual.

Again, to date no therapeutic opioid compound (nor any known analgesic) is without limiting adverse effects which are discussed in greater detail in Chap. 3. Reducing the “virulence” of these agents must involve some degree of attenuation of not only morbid or lethal complications but also euphoria-inducing and addictive qualities, and these efforts will be reviewed in Chap. 4.

References

1. Koren G, Cairns J, Chitayat D. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368:704.
2. Salzet M, Vieau D, Day R. Crosstalk between nervous and immune systems through the animal kingdom: focus on opioids. *Trends Neurosci*. 2000;23:550–5.
3. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet*. 1988;19:155–7.
4. Liem EB, Lin CM, Suleman MI, Doufas AG, Gregg RG, Veauthier JM, et al. Anesthetic requirement is increased in redheads. *Anesthesiology*. 2004;101:279–83.
5. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology*. 2005;102:509–14.
6. Mogil JS, Ritchie J, Smith SB, Strasburg K, Kaplan L, Wallace MR, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet*. 2005;42:583–7.
7. Fields HL, Bry J, Hentall I, Zorman G. The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat. *J Neurosci*. 1983;3:2545–52.
8. Fields HL, Malick A, Burstein R. Dorsal horn projection targets of ON and OFF cells in the rostral ventromedial medulla. *J Neurophysiol*. 1995;74:1742–59.
9. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. *Brain Res Rev*. 2009;60:214–25.
10. Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. *Nature*. 1984;312:755–6.
11. Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. *Prog Brain Res*. 2000;122:245–53.
12. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*. 2009;63:533–43.
13. Heinke B, Gingl E, Sandkühler J. Multiple targets of μ -opioid receptor-mediated presynaptic inhibition at primary afferent A δ - and C-fibers. *Neuroscience*. 2011;31:1313–22.
14. Takasusuki T, Yaksh TL. Regulation of spinal substance p release by intrathecal calcium channel blockade. *Anesthesiology*. 2011;115:153–64.
15. Kumamoto E, Mizuta K, Fujita T. Opioid actions in primary afferent fibers-involvement in analgesia and anesthesia. *Pharmaceuticals*. 2011;4:343–65.
16. Cesselin F, Benoliel JJ, Bourgoin S, et al. Spinal mechanisms of opioid analgesia. In: Stein C, editor. *Opioids in pain control: basic and clinical aspects*. Cambridge: Cambridge University Press; 1999. p. 70–95.
17. Baillie LD, Schmidhammer H, Mulligan SJ. Peripheral mu-opioid receptor mediated inhibition of calcium signaling and action potential-evoked calcium fluorescent transients in primary afferent CGRP nociceptive terminals. *Neuropharmacology*. 2015;93:267–73.
18. Smith HS. Optimizing pharmacologic outcomes: individualization of therapy. In: Smith HS, editor. *Opioid therapy in the twenty-first century*. New York: Oxford University Press; 2013. p. 135–44.
19. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In: Brunton L, editor. *Goodman and Gilman's pharmacologic basis of therapeutics*. New York: McGraw-Hill; 2011. p. 481–525.
20. Chen SR, Pan HL. Spinal endogenous acetylcholine contributes to the analgesic effect of systemic morphine in rats. *Anesthesiology*. 2001;95:525–30.
21. Sehgal N, Smith HS, Manchikanti L. Peripherally acting opioids and clinical implications for pain control. *Pain Physician*. 2011;14:249–58.
22. Zadina JE, Hackler L, Ge LJ, Kastin AJ. A potent and selective endogenous agonist for the mu-opiate receptor. *Nature*. 1997;386:499–502.

23. McConalogue K, Grady EF, Minnis J, Balestra B, Tonini M, Brecha NC, et al. Activation and internalization of the mu-opioid receptor by the newly discovered endogenous agonists, endomorphin-1 and endomorphin 2. *Neuroscience*. 1999;90:1051–9.
24. Sarić A, Balog T, Sobocanec S, Marotti T. Endomorphin 1 activates nitric oxide synthase 2 activity and downregulates nitric oxide synthase 2 mRNA expression. *Neuroscience*. 2007;144:1454–61.
25. Varamini P, Blanchfield JT, Toth I. Endomorphin derivatives with improved pharmacological properties. *Curr Med Chem*. 2013;20:2741–58.
26. Zadina JE, Nilges MR, Morgenweck J, Zhang X, Hackler L, Fasold MB. Endomorphin analog analgesics with reduced abuse liability, respiratory depression, motor impairment, tolerance, and glial activation relative to morphine. *Neuropharmacology*. 2016;105:215–27.
27. Dupont A, Cusan L, Garon M. Extremely rapid degradation of [3H] methionine-enkephalin by various rat tissues in vivo and in vitro. *Life Sci*. 1977;21:907–14.
28. Milloy D. Enkephalins and endorphins: the endogenous opiates. *AANA J*. 1982;50:569–73.
29. Roques BP, Noble F, Fournie-Zaluski MC. Endogenous opioid peptides and analgesia. In: Stein C, editor. *Opioids in pain control: basic and clinical aspects*. Cambridge: Cambridge University Press; 1999. p. 21–45.
30. Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C. The dysphoric component of stress is encoded by activation of the dynorphin κ -opioid system. *J Neurosci*. 2008;28:407–14.
31. Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin-(1-13), an extraordinarily potent opioid peptide. *Proc Natl Acad Sci U S A*. 1979;76:6666–70.
32. Han JS, Xie CW. Dynorphin: potent analgesic effect in spinal cord of the rat. *Sci Sin, Ser B, Chem Biol Agric Med Earth Sci*. 1984;27:169–77.
33. Lai J, Luo MC, Chen Q, Ma S, Gardell LR, Ossipov MH, et al. Dynorphin a activates bradykinin receptors to maintain neuropathic pain. *Nat Neurosci*. 2006;9(12):1534–40.
34. Podvin S, Yaksh T, Hook V. The emerging role of spinal dynorphin in chronic pain: a therapeutic perspective. *Annu Rev. Pharmacol Toxicol*. 2016;56:511–33.
35. Butelman ER, Yuferov V, Kreek MJ. κ -opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. *Trends Neurosci*. 2012;35:587–96.
36. Tejeda HA, Shippenberg TS, Henriksson R. The dynorphin/ κ -opioid receptor system and its role in psychiatric disorders. *Cell Mol Life Sci*. 2012;69:857–96.
37. Wee S, Koob GF. The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. *Psychopharmacology*. 2010;210:121–35.
38. Dietis N, Rowbotham DJ, Lambert DG. Opioid receptor subtypes: fact or artifact? *Br J Anaesth*. 2011;107:8–18.
39. Peppin JF, Raffa RB. Delta opioid agonists: a concise update on potential therapeutic applications. *J Clin Pharm Ther*. 2015;40:155–66.
40. Gendron L, Mittal N, Beaudry H, Walwyn W. Recent advances on the delta-opioid receptor: from trafficking to function. *Brit J Pharmacol*. 2015;172:403–19.
41. Beaudry H, Dubois D, Gendron L. Activation of spinal mu- and delta-opioid receptors potentially inhibits substance P release induced by peripheral noxious stimuli. *J Neurosci*. 2011;31:13068–77.
42. Quock RM, Burkley TH, Varga E, Hosohata Y, Hosohata K, Cowell SM, et al. The delta-opioid receptor: molecular pharmacology, signal transduction, and the determination of drug efficacy. *Pharmacol Rev*. 1999;51:503–32.
43. Xia Y, editor. *Neural function of the delta-opioid receptor*. New York: Springer; 2015.
44. Arendt-Nielsen L, Olesen AE, Staahl C, Menzaghi F, Kell S, Wong GY, et al. Analgesic efficacy of peripheral kappa-opioid receptor agonist CR665 compared to oxycodone in a multi-modal, multi-tissue experimental human pain model: selective effect on visceral pain. *Anesthesiology*. 2009;111:616–24.
45. Schroder W, Lambert DG, Koch T. Functional plasticity of the N/OFQ-NOP receptor system determines analgesic properties of NOP receptor agonists. *Br J Pharmacol*. 2014;171:3777–800.

46. Donica CL, Awwad HO, Thakker DR, Standifer KM. Cellular mechanisms of nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor regulation and heterologous regulation by N/OFQ. *Mol Pharmacol*. 2013;83:907–18.
47. Mallimo EM, Kusnecov AW. The role of orphanin FQ/nociceptin in neuroplasticity: relationship to stress, anxiety and neuroinflammation. *Front Cell Neurosci*. 2013;7:1–18.
48. Boderá P, Stankiewicz W, Kocik J. Interactions of orphanin FQ/Nociceptin (OFQ/N) system with immune system factors and hypothalamic-pituitary-adrenal (HPA) axis. *Pharmacol Rep*. 2014;66:288–91.
49. Trang T, Al-Hasani R, Salvemini D, Salter MW, Gutstein H, Cahill CM. Pain and poppies: the good, the bad and the ugly of opioid analgesics. *J Neurosci*. 2015;35:13879–88.
50. Heinricher MM, McGaraughty S, Tortorici V. Circuitry underlying antiopioid actions of cholecystokinin within the rostral ventromedial medulla. *J Neurophysiol*. 2001;85:280–6.
51. Heinricher MM, Neubert MJ. Neural basis for the hyperalgesic action of cholecystokinin in the rostral ventromedial medulla. *J Neurophysiol*. 2004;92:1982–9.
52. Hebb AL, Poulin JF, Roach SP, Zacharko RM, Drolet G. Cholecystokinin and endogenous opioid peptides: interactive influence on pain, cognition and emotion. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:1225–38.
53. Lovick TA. Pro-nociceptive action of cholecystokinin in the periaqueductal grey: a role in neuropathic and anxiety-induced hyperalgesic states. *Neurosci Biobehav Rev*. 2008;32:852–62.
54. Bowers ME, Choi DC, Ressler KJ. Neuropeptide regulation of fear and anxiety: implications of cholecystokinin, endogenous opioids, and neuropeptide Y. *Physiol Behav*. 2012;107:699–710.
55. Mollereau C, Roumy M, Zajac JM. Opioid-modulating peptides: mechanisms of action. *Curr Top Med Chem*. 2005;5:341–55.
56. Mouldous L, Mollereau C, Zajac JM. Opioid-modulating properties of the neuropeptide FF system. *Biofactors*. 2010;36:423–9.
57. Elhabazi K, Trigo JM, Mollereau C, Mouldous L, Zajac JM, Bihel F, et al. Involvement of neuropeptide FF receptors in neuroadaptive responses to acute and chronic opiate treatments. *Br J Pharmacol*. 2012;165:424–35.
58. O'Connor TM, O'Connell J, O'Brien DI. The role of substance P in inflammatory disease. *J Cell Physiol*. 2004;201:167–80.
59. Garcia-Recio S, Gascon P. Biological and pharmacological aspects of the NK1-receptor. *Biomed Res Int*. 2015;2015:495704. doi:[10.1155/2015/495704](https://doi.org/10.1155/2015/495704).
60. Yu YJ, Arttamangkul S, Evans CJ, Williams JT, von Zastrow M. Neurokinin 1 receptors regulate morphine-induced endocytosis and desensitization of mu-opioid receptors in CNS neurons. *J Neurosci*. 2009;29:222–33.
61. Fan X, Jin WY, Wang YT. The NMDA receptor complex: a multifunctional machine at the glutamatergic synapse. *Front Cell Neurosci*. 2014;8:1–9.
62. Vyklíček V, Korinek M, Smejkalová T. Structure, function, and pharmacology of NMDA receptor channels. *Physiol Res*. 2014;63(Suppl. 1):S191–203.
63. Rodríguez-Munoz MR, Sanchez-Blazquez P, Vicente-Sanchez A, Berrocoso E, Garzón J. The mu-opioid receptor and the NMDA receptor associate in PAG neurons: implications in pain control. *Neuropsychopharmacology*. 2012;37:338–49.
64. Toll L, Bruchas MR, Calo G, Cox BM, Zaveri NT. Nociceptin/orphanin FQ receptor structure, signaling, ligands, functions, and interactions with opioid systems. *Pharmacol Rev*. 2016;68:419–57.
65. Wang Y, Barker K, Shi S. Blockade of PDGFR- β activation eliminates morphine analgesic tolerance. *Nat Med*. 2012;18:385–7.
66. Valenzuela CF, Xiong Z, MacDonald JF, Weiner JL, Frazier CJ, Dunwiddie TV, et al. Platelet-derived growth factor induces a long-term inhibition of N-methyl-D aspartate receptor function. *J Biol Chem*. 1996;271:16151–9.

67. Chabot-Dore AJ, Schuster DJ, Stone LS, Wilcox GL. Analgesic synergy between opioid and α 2-adrenoreceptors. *Brit J Pharm.* 2015;172:388–402.
68. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The “toll” of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. *Trends Pharmacol Sci.* 2009;30:581–91.
69. Hutchinson MR, Shavit Y, Grace PM. Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. *Pharmacol Rev.* 2011;63:772–810.
70. Hutchinson MR, Bland ST, Johnson KW. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. *Sci World J.* 2007;7:98–111.
71. Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y. Current research on opioid receptor function. *Curr Drug Targets.* 2012;13:230–46.
72. Klaassen C, Aleksunes L. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol Rev.* 2010;62:1–96.
73. König J, Müller F, Fromm M. Transporters and drug-drug interactions: important determinants of drug disposition and effects. *Pharmacol Rev.* 2013;65:944–66.
74. Shen S, Zhang W. ABC transporters and drug efflux at the blood-brain barrier. *Rev Neurosci.* 2010;21:29–53.
75. Tournier N, Declèves X, Saubaméa B. Opioid transport by ATP-binding cassette transporters at the blood-brain barrier: implications for neuropsychopharmacology. *Curr Pharm Des.* 2011;17:2829–42.
76. Buxton ILO, Benet LZ. Pharmacokinetics: the dynamics of drug absorption, distribution, metabolism, and elimination. In: Brunton L, editor. *Goodman and Gilman’s pharmacologic basis of therapeutics.* New York: McGraw Hill; 2011. p. 17–39.
77. Smith HS. Opioid metabolism. *Mayo Clin Proc.* 2009;84:613–24.
78. Smith H. Variations in opioid responsiveness. *Pain Physician.* 2008;11:237–48.
79. Sadhasivam S, Chidambaran V. Pharmacogenomics of opioids and perioperative pain management. *Pharmacogenomics.* 2012;13:1719–40.
80. Kambur O, Männistö PT. Catechol-O-methyltransferase and pain. *Int Rev. Neurobiol.* 2010;95:227–79.
81. Tammimäki A, Männistö PT. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. *Pharmacogenet Genomics.* 2012;22:673–91.
82. Krosiak T, LaForge KS, Gianotte RJ, Ho A, Nielsen DA, Kreek MJ. The single nucleotide polymorphism A118G alters functional properties of the human mu opioid receptor. *J Neurochem.* 2007;103:77–87.
83. Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology.* 2014;121:825–34.
84. Ren ZY, Xu XQ, Bao YP, He J, Shi L, Deng JH, et al. The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis. *Pain Physician.* 2015;18:131–52.
85. Walter C, Lotsch J. Meta-analysis of the relevance of the OPRM1 118A > G genetic variant for pain treatment. *Pain.* 2009;146:270–5.
86. Vuilleumier PH, Stamer UM, Landau R. Pharmacogenomic considerations in opioid analgesia. *Pharmacogenom Personal Med.* 2012;5:73–87.
87. Dobrinas M, Crettol S, Oneda B. Contribution of CYP2B6 alleles in explaining extreme (S)-methadone plasma levels: a CYP2B6 gene resequencing study. *Pharmacogenet Genomics.* 2013;23:84–93.
88. Eap CB, Crettol S, Rougier JS, Schläpfer J, Sintra Grilo L, Déglon JJ, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther.* 2007;81:719–28.

89. Cox BM. Mechanisms of tolerance. In: Stein C, editor. *Opioids in pain control: basic and clinical aspects*. Cambridge: Cambridge University Press; 1999. p. 70–95.
90. Williams JT, Ingram SL, Henderson G. Regulation of mu-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev*. 2013;65:223–54.
91. Pasternak GW, Pan YX. Mix and match: heterodimers and opioid tolerance. *Neuron*. 2011;69:6–8.
92. Goldberg JS. Chronic opioid therapy and opioid tolerance: a new hypothesis. *Pain Res Treat*. 2013;2013:407504. doi:[10.1155/2013/407504](https://doi.org/10.1155/2013/407504).

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