Analysis of Physicochemical Properties and Mechanisms of Action of Analgesic Drugs: A Focus on Opioid and Non-Opioid Pathways

Yuze Li [1, *]

[1] Chengdu Shishi High School, Chengdu, 610041, China

* Corresponding Author Email: Liyuze7969@qq.com

Abstract. One of the most difficult and significant aspects in clinical pharmacology is the issue of pain management. Opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and adjuvant analgesics are a large group of drugs that have various physical and chemical characteristics that influence their pharmacokinetic activity and pharmacodynamic response. This paper is an extensive overview of the structural features, physicochemical data (such as lipophilicity, pKa, protein binding, and permeability of the blood-brain barrier), and molecular action of some examples of analgesic agents. Special attention has been given to the opioid subgroup, where the example of oxycodone was used as a model case study in which minor structural changes, namely the 3-methoxy group and 14-hydroxy substitution, resulted in different metabolic pathways (CYP3A4- and CYP2D6-mediated), greater oral bioavailability, and unique kinetics of receptor-binding when compared to morphine. In addition to the discussion of non-opioid analgesics such as COX inhibitors and voltage-gated ion channel modulators, the structure-activity relationships are discussed. Moreover, the effects of drug-drug interactions on analgesic therapy of analgesia, pharmacogenetics (e.g., poor metabolizer phenotypes of CYP2D6), and new approaches to the optimization of analgesic treatment were also considered. This compilation will be helpful in providing a structured source of information about how therapeutic effects are determined by the properties of physicochemical properties and what should be done next to develop drugs.

Keywords: Analgesic drugs, Oxycodone, Opioid receptors, Pharmacokinetics, NSAIDs.

1. Introduction

Pain is a painful sensory and emotional response to the presence of real or potential tissue injury that can be both an important signal of the body, as well as a widespread clinical condition. Inadequately treated acute pain may become chronic, in which case there will be central sensitization, neuroplasticity, and other maladaptive processes of the nervous system, and life quality will be deteriorated significantly. The epidemiological researches have revealed that about 20-30 percent of the adult population of the world suffers from chronic pain, and its frequency increases dramatically in the aging population [1]. Pain has been a socioeconomic issue regarding healthcare costs, lost productivity, disability, and therefore, attempts have been made to improve analgesic pharmacotherapy.

The clinical categorization of analgesic drugs is traditionally divided into three types, i.e., NSAIDs, opioid analgesics, and adjuvant agents (anticonvulsants and antidepressants) to relieve neuropathic pain. The NSAID drugs like aspirin and ibuprofen are known to have an action by inhibiting the production of prostaglandins through cyclooxygenase (COX). Nevertheless, it has been shown that long-term consumption of NSAIDS causes well-known gastrointestinal erosion, renal failure, as well as increased cardiovascular risk [2]. Opioid analgesics, in turn, continue to be the mainstay in treating moderate-to-severe pain, especially when dealing with perioperative, oncological, and palliative care. Their effects are based on agonism at the receptors of mu-opioid receptors (MOR), delta-opioid receptors (DOR), and kappa-opioid receptors (KOR), which are G protein-coupled receptors (GPCRs) that are found in both the central nervous system and the peripheral nervous system. Although opioids are effective, they also come with a high cost of side effects such as respiratory depression, constipation, tolerance, physical addiction, and even abuse and addiction [3].

The physicochemical properties of analgesics, which are often overlooked, can be critical determinants of clinical behaviour. Lipophilicity (log P), pKa, plasma protein binding and molecular weight all contribute to oral bioavailability, volume of distribution, half-life and BBB penetration. Fentanyl, with a log P4similar-to4\sim{P}4, penetrates the BBB very quickly to deliver rapid onset analgesia, whereas morphine is more hydrophilic (log P0.9similar-to0.9\sim{P}0.9) and has slower central penetration and poor oral bioavailability (2030%similar-toabsent2030percent\sim 20-30%) as a consequence of significant first-pass metabolism [4]. These distinctions have implications for onset, duration, and the balance of risks and benefits in certain clinical situations.

Over the past few years, structural biology and pharmacology have revealed the structure of opioid receptors at the atomic level and enabled the development of selective agonists that are biased to different functions of opioid receptors [5]. In addition, a series of studies have been conducted on the polymorphisms in the genes involved in the metabolism of analgesics (CYP2D6, CYP3A4) and their binding sites (OPRM1), which can be used to select the most appropriate drug based on the genotype of patients [6]. However, there is still no clear picture of the differences between various types of analgesic drugs in terms of the mechanism of action and other characteristics.

Considering this background, the paper attempts to carry out a systematic literature-based study of the physicochemical properties, pharmacokinetic values and molecular processes of representative analgesic agents. A special chapter is devoted to oxycodone (a semi-synthetic thebaine derivative) as a prototypical example to illustrate how particular chemical modifications influence metabolism, receptor binding and clinical efficacy. The review also covers non-opioid pathways such as COX inhibition and ion channel modulation, which provides a comparative framework. Finally, this book aims to explain the inherent relationships between chemical structure, physicochemical behavior, and therapeutic action, hence providing a conceptual basis for rational drug design and personalized pain management.

2. Opioid Analgesics

2.1. Chemical Constitution and Physicochemical Properties

Opioid analgesics are a very different group of substances, both natural and semi-synthetic (morphine, codeine) as well as synthetic (fentanyl, methadone, tramadol). Most clinically applied opioids have in common the pharmacophoric framework that is a rigid aromatic ring system attached to an amine atom which is protonated at physiological pH, allowing ionic contact with the conserved aspartate residue in the third transmembrane helix of opioid receptors.

Morphine, the gold-standard compound, is a pentacyclic molecule with a phenolic hydroxyl group in position 3 and an alcoholic hydroxyl in position 6. It has a pKa of about 8.0, which means that it can be partially ionized (about 70 to 80 percent) at the physiological pH (7.4), hence the limited ability to permeate the membrane passively and the limited central nervous system effect. Morphine has a low log P value of approximately 0.9, and this is the reason why its systemic action requires larger amounts of the drug and why it takes longer to take effect when taken orally (30-60 minutes). Moreover, morphine is metabolized by the liver into two major products, morphine-3-glucuronide (M3G, inactive) and morphine-6-glucuronide (M6G, active and more powerful than the original drug) through an extensive first-pass glucuronidation process, mostly mediated by UGT2B7. This pathway leads to the fact that the oral bioavailability of morphine is around 20 to 30 per cent [7].

On the other hand, a semi-synthetic opioid is oxycodone (C18H21NO4), which is structurally optimized and synthesized based on thebaine. It has been chemically identified as 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one. The two main changes in the structure with respect to morphine are (i) the phenolic hydroxyl group at position 3 is replaced by a methoxy group (-OCH3), and (ii) the hydroxyl group is introduced at the 14-position, and the double bond at 7,8 is saturated (Figure 1, conceptual). These changes radically change its physicochemical character: Oxycodone is a moderately lipophilic drug with a log P value of about 2.2-2.5 that greatly increases gastrointestinal absorption and BBB passage. Its pKa is approximately 8.5-8.6, similar to that of morphine, but this

compound has a lower first-pass metabolism due to the presence of the methoxy group, which means an oral bioavailability of 60-87% compared to morphine [8]. In addition, the plasma protein binding of oxycodone is also low (approximately 45%) and can be estimated.

The metabolism of oxycodone is mainly mediated by hepatic cytochrome P450 enzymes. Oxycodone is N-demethylated to noroxycodone by CYP3A4, and O-demethylated to oxymorphone by CYP2D6. Oxymorphone is a potent \mu-opioid agonist that is 10-14 times more potent than oxycodone. However, the contribution of CYP2D6-mediated oxymorphone formation to the overall analgesic effect of oxycodone is dependent on the genotype of the patient. In extensive metabolizers, oxymorphone formation contributes significantly to pain relief. However, in poor metabolizers (510%similar-toabsent510%\sim 5-10% of Caucasians), oxycodone is the main active component [9]. This example demonstrates the importance of considering both physicochemical design and pharmacogenetics for achieving appropriate dosing.

Other opioids have clinical significance and their physicochemical properties are unique. Fentanyl (log P 4.0, pKa 8.4) is a very high lipophilic drug, which can be absorbed transdermally or transmucously within minutes of intravenous delivery. Methadone (log P ~3.9, pKa 8.3) is an opioid drug with high protein binding (greater than 85%) and extremely long half-life (15-60 hours), as it binds to the tissue extensively and excretes slowly in the liver by CYP2B6 and CYP3A4. These different physical chemical profiles explain why there are so many uses of the drugs in clinical practice: acute sedation of procedures (fentanyl), chronic pain therapy (methadone), and treatment of opioid addiction.

2.2. Mechanisms of Action: Receptor Binding and Signal Transduction

Opioid receptors are members of the class A (rhodopsin-like) GPCR superfamily which has three main subtypes, namely: mu (MOR, OPRM1), delta (DOR, OPRD1), and kappa (KOR, OPRK1). These receptors have around 6070% sequence homology in their transmembrane regions but different ligand selectivity, tissue distribution and downstream signaling effects. MOR is the most common target of most clinically used analgesics and is highly expressed in the periaqueductal gray, rostral ventromedial medulla, dorsal horn of the spinal cord, and peripheral sensory neurons.

When the agonist binds to opioid receptors, it causes a change in their shape that facilitates the release of G-protein heterotrimers into two components of the protein which are G-alpha and G-beta-gamma. The subunit alpha i/o of the G inhibits adenylyl cyclase function, decreasing cyclic AMP (cAMP) levels within the cell; as a result, the activity of protein kinase A (PKA) is also reduced. At the same time, the dimer of Gb and g directly engages with the voltage-sensitive calcium channels (in particular, N-type and P/Q type), preventing the influx of calcium and hence diminishing the secretion of neurotransmitters in the presynaptic terminals. Also, the subunits of the Gbeta/gamma induce potassium efflux and hyperpolarization of the membrane by activating inwardly rectifying potassium channels (GIRKs), thus increasing the threshold of firing neurons. These actions together inhibit the release of excitatory neurotransmitters (glutamate, substance P, calcitonin gene-related peptide) by the primary afferent neuron and consequently prevent pain signal transduction at the level of the spinal cord and supraspinal [10].

Notably, it is also possible to use opioid receptors in the process of signaling through the mechanism of -arrestin. The internalization and desensitization of the receptor are facilitated by the recruitment of 2 -arrestins which inhibit G-protein signaling. But on the other hand, the MAPK cascades are activated by beta-arrestin2 as well, which has been associated with tolerance to opioids and, controversially, respiratory depression. The bias of the G-protein signaling, i.e., a preference of certain ligands towards the activation of the pathways of G-proteins rather than the recruitment of the beta-arrestin, has become one of the main issues of analgesic drug design: it is assumed that the agonists of the G-protein biased (e.g., oliceridine) would be able to relieve pain without causing any side effects [5].

When it comes to the receptor pharmacology of oxycodone, there are a good number of nuances. Even though oxycodone is an agonist in MOR, its binding affinity with MOR is about 30-40 times

less than morphine and also slightly higher than morphine in KOR. Such activity at KOR can be attributed to the difference in the subjective effects and decreased histamine release, which results in less pruritus and allergic reactions as compared to morphine [11]. Notably, oxycodone is not as much as recruiting beta-arrestin2 as morphine, which means that there are some levels of G-protein biasing, which may explain why oxycodone has been found to have a positive effect on respiratory depression when used in specific clinical situations. Nevertheless, this predisposition is quite small and does not prevent high-dose severe respiratory depression.

Moreover, it is known that oxycodone activates MOR in the spinal cord and supraspinal areas but new findings suggest that it also affects peripheral opioid receptors of inflamed tissues to cause local analgesia without central side effects. This peripheral part is especially applicable to postoperative pain and inflammatory pain conditions where tissue acidosis increases opioid receptor expression and agonist activity [12].

2.3. The Oxycodone Case: Bridging Structure, Metabolism, and Clinical Response

The clinical course of oxycodone is an example of the revolutionary effect of medicinal chemistry on analgesic therapy. It was developed in Germany in 1916 as a semi-synthetic derivative of thebaine and remained a relatively minor prescription opioid until the 1990s, when controlled-release formulations (OxyContin) were introduced. Its subsequent widespread use, and the associated epidemic of misuse, has unfortunately overshadowed its genuine therapeutic utility when prescribed judiciously.

From a physicochemical viewpoint, the 3-methoxy-group is the single most important determinant of the superior oral bioavailability of oxycodone. While morphine is extensively glucuronidated, metabolism of oxycodone is dependent on cytochrome P450, with a resultant more predictable linear pharmacokinetics over the therapeutic dose range. The 14-hydroxy-group provides additional hydrogen bonding capacity to stabilize the receptor-ligand interaction, resulting in a longer duration of action (46 hours for immediate release preparations) compared with morphine (34 hours)8.

Oxycodone is clinically used to treat moderate-to-severe acute and chronic pain, such as postoperative pain, cancer pain, and non-malignant chronic pain that is not responsive to non-opioid treatment. It has a wide range of pharmacokinetic properties that enable various formulations: immediate-release tablets (onset ~30 minutes, duration ~4 hours), controlled-release tablets (steady-state within 2436 hours, duration ~12 hours), and combination products with acetaminophen or ibuprofen in synergistic multimodal analgesia.

However, oxycodone is a CYP3A4/CYP2D6 drug and this may lead to the occurrence of significant interactions between the two drugs. The use of potent inhibitors of CYP3A4 (ketoconazole, clarithromycin, grapefruit juice) also causes a high plasma concentration of oxycodone which can result in respiratory depression and sedation. On the other hand, the analgesic effect can be diminished by CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort). It is important to mention that polymorphism of the CYP2D6 gene: poor metabolizers are 1.5-2 times more likely to be exposed to oxycodone than extensive metabolizers; thus, dose adjustment might be necessary. In contrast, ultra-rapid metabolizers (with numerous copies of the CYP2D6 gene) will convert oxycodone into oxymorphone more effectively, so at the same doses they have greater analgesia and adverse reactions [9].

Notably, the glucuronide of oxycodone is not active and does not result in accumulation of an active metabolite like morphine (M6G) that accumulates in the body when a patient has renal failure. This would make it a better choice to use in patients with impaired kidney function, but one should consider reducing the dose. The moderate lipophilicity of the drug allows the oral, sublingual and transdermal administration of the drug which are good bioavailability options of the drug, especially in cases where the patient cannot swallow the drug orally.

The story of oxycodone is a good example of the close relationship between the chemical composition, physicochemical parameters, metabolism, and receptor pharmacology. The passive absorption of this compound has not only been increased by the presence of methoxy, but also it has

shifted the process of its metabolism to oxidative processes instead of glucuronidation which has completely changed the clinical pharmacokinetic paradigm. Such principles can be used as an example in the rational design and choice of opioids in patients.

3. Non-Opioid Analgesics

3.1. NSAIDs

Non-opioid analgesics are the most used drugs in this category, including non-selective COX inhibitors (aspirin, ibuprofen, diclofenac, naproxen) and selective COX-2 inhibitors (celecoxib, etoricoxib). They act by competitively inhibiting the cyclooxygenase enzyme which is responsible of converting arachidonic acid to prostaglandin G2 and PGH2. The latter compound is then converted into thromboxanes, prostacyclines, and prostaglandins. The constitutive expression of COX-1 in most cells and tissues is associated with homeostatic activity such as the protection of the gastric mucosa, platelet aggregation, and blood flow regulation in the kidney. The other type is COX-2, which is induced by inflammatory response (cytokines, endotoxins), and it has a role in pain, fever, and inflammation.

Physicochemically, the majority of NSAIDs are weak organic acids with pKa values between 3.5 and 5.5. They are mainly in the unionized, lipophilic form at gastric pH (~1.52.0), which allows them to diffuse passively through the gastric mucosa. After absorption, increased systemic pH (7.4) facilitates ionization trapping the drugs in the plasma compartment and inhibiting further passive distribution. This effect of ion trapping is one of the causes of gastrointestinal irritation caused by NSAIDs because the unionized form is accumulated in the cells of gastric epithelium and damages the integrity of membranes. To address this, COX-2 selective inhibitors were developed to retain anti-inflammatory activity but minimize gastrointestinal toxicity, a compromise that was partly met at the expense of cardiovascular safety (thromboxane/prostacyclin imbalance).

NSAIDs are structurally categorized as acetic acid derivatives (diclofenac, indomethacin), propionic acid derivatives (ibuprofen, naproxen, ketoprofen), enolic acid derivatives (piroxicam, meloxicam), and fenamates (mefenamic acid). These subcategories have different levels of selectivity in COX-1/COX-2 and pharmacokinetics. The log P ~3.5, pKa ~4.4, and the oral bioavailability over 95% of ibuprofen are examples, and it has a half-life of around 2 hours. It can be used to treat acute pain due to its quick absorption and short action time, and naproxen which is taken twice daily with half-life of about 12 -14 hours. The protein binding of NSAIDs is usually more than 90 percent, and diclofenac is even more than 99 percent, thus leaving the free fraction that will exert the pharmacological effect reduced and displacing other drugs that bind highly to proteins (e.g., warfarin) [13].

Other NSAIDs have also been found to be effective in the suppression of pain besides COX inhibition. The voltage-gated sodium channels and calcium currents are suppressed by celecoxib at high concentrations, which is an additional ion channel effect of the drug. Nevertheless, it is not clear whether these side effects of the drugs are clinically relevant and the major therapeutic advantage is definitely associated with the prostaglandin inhibitory action.

3.2. Adjuvant Analgesics: Gabapentinoids and Sodium Channel Blockers

Adjuvant analgesics are drugs that have their main indications beyond pain management but have clinically significant analgesic effects in certain pain conditions, especially neuropathic pain. Gabapentinoids (gabapentin and pregabalin) have become prominent among them. Both of these substances are structural analogs of the inhibitory neurotransmitter -aminobutyric acid (GABA), but they do not bind to GABA receptors. Rather, they attach with high affinity to the 2 -1 and 2 -2 subunits of voltage-gated calcium channels (especially Cav2.1 and Cav2.2), which inhibits calcium entry into the cell and consequently lowers the release of excitatory neurotransmitters (glutamate, substance P, noradrenaline) by presynaptic terminals in the spinal cord and brain.

Gabapentin is a small zwitterionic molecule that is physicochemically water soluble and lipophilic (log P ~ -1.1). It is taken in the small intestine through the large neutral amino acid transporter (LAT-1), which leads to bioavailability that depends on the dose (60% at low doses, and decreases to 30% at high doses). The structural modification of pregabalin with a branched side chain makes it more lipophilic (log P ~0.5), as well as having more predictable linear pharmacokinetics, and oral bioavailability above 90% throughout the dosing range. Both drugs are excreted renally without alteration, requiring dosage adjustment in renal impairment. The clinical effectiveness of gabapentinoids in postherpetic neuralgia, diabetic neuropathy and fibromyalgia has been proven but their application is limited by sedation, dizziness and peripheral edema depending on the dose [14].

Lidocaine (local anesthetic), mexiletine, and the new ones (e.g., lacosamide) are sodium channel blockers. They can bind to the voltage-gated sodium channel (Nav) inactivated state to extend its refractory time and lower the hyperexcitability of the neuron. Local anaesthetics such as lidocaine are considered prototypical local anaesthetics with log P ~2.9, pKa ~7.9 and are usually administered by intravenous injection or patch on the skin to treat localized neuropathic pain. The analogue of oral mexiletine has similar effects of blocking channels but the only drawback is that it has a small therapeutic index and is prone to cardiac arrhythmias, which restricts its use to cases where it is resistant to treatment by specialists.

4. Comparative Analysis and Clinical Optimization Strategies

4.1. Structure-Activity-Property Relationships Across Analgesic Classes

It is possible to see the following trends when the physicochemical landscape of the large groups of analgesics is compared. The opioids are characterized by a moderate and high level of lipophilicity (log P 0.9 to 4.0) and they can easily cross the BBB, but the NSAIDs are characterized by a variety of lipophilicities (log P -1.0 to 4.5) and they are usually acidified in order to be taken orally. Gabapentinoids are hydrophilic zwitterions that are absorbed through active transport that requires saturation at varying levels of dosage and bioavailability.

These agents have molecular weights between about 180 Da (aspirin) and 500 Da (fentanyl), which are all within the rule of five criteria by Lipinski regarding oral availability. Hydrogen bond donors and acceptors are usually restricted (less than or equal to 5 donors, less than or equal to 10 acceptors), but morphine (2 donors, 5 acceptors) and oxycodone (1 donor, 5 acceptors) demonstrate that a decrease in hydrogen bonding potential increases permeability.

In terms of pharmacokinetics, lipophilicity is a positive relationship with volume of distribution (Vd): fentanyl (Vd ~4 L/kg) has high levels in adipose tissue; morphine (Vd ~2-3 L/kg) has low levels in the central compartment. The process of elimination is also different: opioids are mainly eliminated through hepatic CYP450 and conjugation processes; NSAIDs can be eliminated both through liver metabolism and kidney excretion; gabapentinoids are excreted in an unchanged form by the kidneys. Such distinctions are the ones that determine where each type is to be used, e.g., in cases of renal failure it may be preferable to use opioid drugs, such as oxycodone (which does not have active metabolites), rather than other types, such as gabapentin or morphine.

4.2. Pharmacogenetics and Individualized Dosing

The clinical response to analgesics is quite variable, with a significant amount of this variability being genetic. The CYP2D6 phenotype is the most widely known gene in case of oxycodone. Oxycodone can be poorly metabolized (PMs) at the standard dose and the PMs can experience inadequate pain relief because they are not able to produce oxymorphone or alternatively, their bodies can accumulate the parent drug to the level that increases sedation without any proportional increase in analgesia. Also involved is the CYP3A4 genotype but the magnitude of the effect is smaller than in the case of CYP2D6. In the case of codeine which is a prodrug, it has been reported that ultra-rapid metabolism of codeine by CYP2D6 results in morphine toxicity at low doses; thus, there have been

warnings issued by regulators on the need to use codeine in children based on the genotype-based dosing.

The CYP2C9 (the enzyme that metabolizes diclofenac, ibuprofen and celecoxib) and the UGT1A6 (aspirin and acetaminophen) polymorphisms have been associated with changes in clearance of NSAID drugs as well as toxicity. Patients who are carriers of the alleles of CYP2C9 2 or 3 demonstrate a decreased rate of elimination of ibuprofen and diclofenac, which is why they need to decrease their doses to prevent bleeding in the gastrointestinal tract and renal failure. Moreover, there is evidence that polymorphism of the COX-2 gene (PTGS2) can be linked to anti-inflammatory effects of celecoxib, but the clinical significance of this type of testing has not yet been established [15].

4.3. Multimodal Analgesia and Drug-Drug Interaction Management

Since no analgesic agent can optimally cover all aspects of the pain pathophysiology, contemporary pain management is increasingly multimodal, i.e. a combination of agents with complementary mechanisms to improve efficacy and reduce individual doses and side effects of each drug. Common combinations are an opioid (e.g., oxycodone) combined with an NSAID (e.g., ibuprofen) combined with a gabapentinoid (e.g., pregabalin) in moderate-to-severe postoperative pain. This approach takes advantage of synergistic analgesia at peripheral, spinal and supraspinal levels.

Nevertheless, multimodal regimens require close observation of drug-drug interactions. Oxycodone depends on CYP3A4 and CYP2D6, which implies that the concomitant use of some antidepressants (fluoxetine, paroxetine -CYP2D6 inhibitors), antifungal drugs (ketoconazole) and macrolide antibiotics (clarithromycin) can alter oxycodone levels in an unpredictable manner. Likewise, NSAIDs and selective serotonin reuptake inhibitors (SSRIs) or anticoagulants also pose a bleeding risk due to platelet dysfunction and gastrointestinal erosive synergy when combined together. The combination of gabapentinoids with opioids is also associated with potentiation of central nervous system depression, which should be titrated and patients educated.

5. Conclusion

This review has reviewed the physicochemical properties, pharmacokinetics, and molecular mechanism of action of the main classes of analgesics, with specific focus on the semi-synthetic opioid oxycodone as an example of rational drug design. Several observations can be made from this analysis:

First, a slight chemical change in the molecule, like replacing one of the hydroxyl groups with a methoxy group in oxycodone will have a significant impact on lipophilicity, oral bioavailability and metabolism, as well as binding to receptors. The improved absorption of oxycodone (60-87% compared to 20-30%) orally and the ability to predict its metabolism through CYP450 is an example of how medicinal chemistry can be used to increase the therapeutic effects of a drug but at the same time reduce its genetic and drug interactions, which are clinically addressed.

Second, the analgesic effect is not so simple as it might seem: opioids are able to inhibit the action of neurotransmitters in the nervous system (G-alpha i/o, beta-arrestin); non-NSAIDs can prevent the formation of prostaglandins; gabapentin can cause calcium channel trafficking and sodium channel blockage. The above rationale of multimodal analgesia is based on such a mechanistic diversity because the use of the combination of the chosen ones will provide better pain relief with fewer side effects.

Third, the combination of physicochemical concepts and pharmacogenomic information is required to personalize analgesic treatment. CYP2D6, CYP3A4, CYP2C9, and OPRM1 genetic polymorphisms contribute significantly to drug response variability and adverse event profiles. Where possible, preemptive genotyping has the possibility of avoiding toxicities (such as codeine and CYP2D6 ultra-rapid metabolizers) and optimize dosing in marginal responders.

However, Current research is largely focused on single drugs or targets, with limited comparative studies and insufficient long-term safety data, while the gap between preclinical findings and clinical efficacy remains a major challenge. Future studies should prioritize safer biased opioid agonists and integrate systems pharmacology with chronobiology to optimize individualized and time-based analgesic therapy.

References

[1] World Health Organization. Global Pain Management Report 2023. Geneva: WHO Press; 2024.

[2] Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med. 1998; 104(3): 2S-8S.

[3] Pasternak GW. Molecular biology of opioid analgesia. Annu Rev Pharmacol Toxicol. 2014; 54: 1-20.

[4] McQuay HJ, Moore RA. Opioid pharmacokinetics. Clin Pharmacokinet. 1984; 9(2): 115-132.

[5] Manglik A, Kruse AC, Kobilka TS, et al. The μ-opioid receptor in a crystal form with morphinan antagonist. Nature. 2012; 485(7398): 321-326.

[6] Lötsch J, Geisslinger G, Tegeder I. Pharmacogenetics of opioid analgesics. Clin Pharmacol Ther. 2009; 85(6): 622-626.

[7] Smith HS. Opioid metabolism. Pain Physician. 2008; 11(2 Suppl).

[8] Pöyhiä R, Seppälä T. Oxycodone: pharmacokinetics and pharmacodynamics. Eur J Pain. 2008; 12(4): 407-415.

[9] Samer CF, Daali Y, Wagner M, et al. Genetic polymorphism and drug interactions that regulate CYP2D6 and CYP3A4 activities. Clin Pharmacokinet. 2013; 52(9): 773-792.

[10] Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology. 2011; 115(6): 1363-1381.

[11] Lemberg KK, Kontinen VK, Siiskonen AO, et al. Antinociceptive properties of oxycodone in neuropathic pain. Eur J Pain. 2006; 10(8): 711-721.

[12] Stein C, Machelska H. Peripheral opioid analgesia: mechanisms and clinical implications. Curr Opin Pharmacol. 2011; 11(1): 54-60.

[13] Grosser T, Smyth EM, FitzGerald GA. Anti-inflammatory, antipyretic and analgesic drugs. In: Brunton LL, ed. The Pharmacological Basis of Therapeutics by Goodman & Gilman. 13th ed. New York: McGraw-Hill; 2018.

[14] Taylor CP, Gee NS, Su TZ, et al. An overview of mechanistic theories of gabapentin pharmacology. Epilepsy Res. 1998; 29(3): 233-249.

[15] Van Booven D, Marsh S, McLeod H, et al. Cytochrome P450 2C9 (CYP2C9) and 2C19 (CYP2C19) pharmacogenomics. Pharmacogenomics. 2004; 5(8): 1097-1108.