TechFest STEM Next Essay Competition 2024

Question #2: How do opioids work? Discuss the risks and benefits associated with this group of drugs.

– Chemistry & Biological Sciences –

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Section #1: Introduction

1.1 Topic & Aim of Research

Opioids are a class of drugs that are derived from natural substances of the opium poppy plant. When consumed, they start functioning in the brain producing various effects. These effects range from pain relief to substance intoxication. This means that medical professionals can prescribe opium as pain medicine, while at the same time, it can be prescribed as an illegal drug for some people. Legal prescription by a doctor with proper, directed usage allows opium to relax the patient's body and severe pain. It is specifically effective in treating chronic pain, trauma, disease, and post-surgical pain. On the other hand, opioids can easily pose risks, sometimes even under a professional's prescription. When taken at a higher or more frequent dose than suggested, it can restrict the patient's ability to breathe or may even lead to a fatal overdose (JH Medicine, 2022).

These conflicting effects of opium cause controversy over whether it is a risky or beneficial type of drug. It is crucial to acknowledge the potential effects of both the upsides and the downsides before utilizing opium to treat a certain type of disease; accordingly, this report focuses on spreading awareness of the usage of opium. To provide more information and support for the development of using opium specifically as a medical treatment mechanism in a scientific aspect, the research question states: "**How do opioids interact with the human body on a chemical and biological level, and what are the associated risks and benefits of their use?**"

1.2 Opioids

Opioids, often referred to as narcotics, are medications commonly prescribed by doctors to manage persistent or severe pain. These drugs are consumed by individuals suffering from chronic pain, providing relief to those whose daily activities are affected by continuous discomfort. Patients recovering from surgical procedures also may benefit from opioids, as such medications help mitigate the intense pain that often follows major operations. Additionally, individuals who experience symptoms associated with cancer heavily rely on opioids for their analgesic properties, which improve their quality of life during treatment (Made for this Moment, 2021).

Beyond these uses, opioids are crucial in pain management for both adults and children who have sustained injuries. For example, athletes who have hurt themselves while playing sports may be prescribed opioids to cope with significant pain caused by their injuries. Similarly, individuals who have been seriously injured in accidents such as auto accidents, falls, or other traumatic incidents often depend on these medications to alleviate acute pain throughout the recovery process (NJDE, 2018). Thus, opioids are capable of serving a broad range of patients, offering essential pain relief in challenging pain.

1.3 Chemistry of Opioids

Opioids, with the molecular formula $C_{55}H_{70}N_4O_7$, are a diverse group of compounds including alkaloids and peptides, with their natural alkaloids known as opiates. Morphine and codeine are examples of natural alkaloids, directly coming from the opium poppy. On the other hand, synthetic derivatives enclose a broader spectrum of drugs such as heroin, hydromorphone, methadone, fentanyl, and buprenorphine. These often mimic or enhance the pain-relieving properties of their natural counterparts. Opioids are recognized for their potent analgesic effects, making them capable of managing severe pain of any type. However, this potency is followed by a significant risk, as opioid consumption is prone to dependency and abuse (Pathan and Williams, 2012).

The chemical structure shown in Figure 1 below is based on the morphinan skeleton, which is common among many opioids, including morphine and codeine. Morphinan is characterized by a phenanthrene ring system with a nitrogen-containing piperidine ring, represented by the nitrogen in the molecular formula. Opiums also have multiple substituents that include ester groups and additional rings that contribute to their high potency. The hydroxyl groups, which can participate in hydrogen bonding, contribute to the solubility and receptor binding. The nitrogen atoms contribute to the molecule's basicity and allow the molecule to interact with acidic sites on opioid receptors. Lastly, the oxygen atoms in ester and hydroxyl groups form additional interactions with the receptor sites, ensuring the drug is completely bound, functioning properly (PubChem CID 126961754).

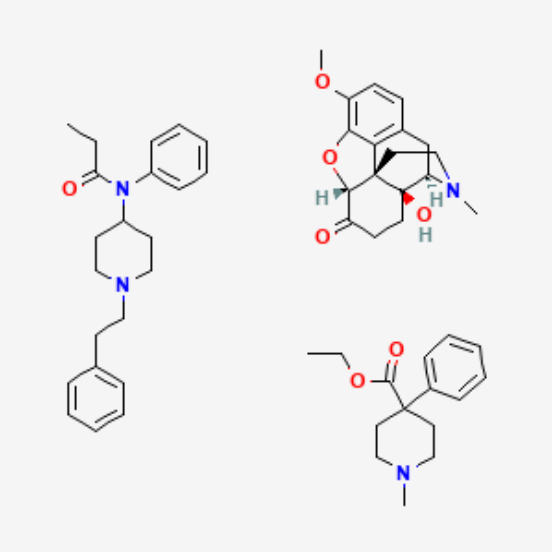

Figure 1: Chemical Structure of Opioid (PubChem CID 126961754)

The mechanism of action for opioids involves receptors known as opiate receptors, designated as μ (mu), κ (kappa), and δ (delta). They are predominantly found in the central nervous system, especially in the brain and spinal cord (Al-Hasani and Bruchas, 2011). However, they can also be found in other tissues such as the vascular system, lungs, gut, and cardiac cells. When opioids bind to these opioid receptors, they trigger a cascade of intracellular signals. This signaling involves the inhibition of adenylate cyclase, decreased opening of calcium channels, activation of protein kinase C (PKC), and increased potassium currents. The culmination of these pathways leads to a significant reduction in cell excitability and neurotransmission. This is the primary mechanism behind the analgesic effect of opioids (Kosten and George, 2002).

Additionally, when opioids bind to the receptors, the body produces endogenous opioid peptides, its natural ligands for these receptors. All naturally modulating pain and stress responses, these include enkephalins, endorphins, and endorphins. The interaction of opioids, whether endogenous or exogenous, with their receptors, is vital for their ability to treat pain but also highlights the potential for addiction and abuse due to their profound impact on the patient's central nervous system (Valentino and Volkow, 2018).

Section #2: Risks of Opioids

2.1 Common Risks

As opioids are a group of drugs that are prone to various side effects, they pose several risks. The most common risk is addiction caused by an overdose of opium. Euphoria is one of the effects individuals experience when consuming opioids, which then leads to repeated use and a high risk of addiction, even with prescription drugs. Using opioids for this effect significantly increases the risk of developing substance use disorder and may cause death. Nonmedical use of opioids includes inhaling, swallowing, or injecting the drug, with using the needle raising the risk of infection or other diseases too. About 75% of the people in the United States who became addicted to heroin are known to have started with opioids, often due to the cheaper and more accessible availability of drugs (JH Medicine, 2022). This is because opioids activate areas of our brain associated with craving, which is a strong desire that eventually results in loss of sensitivity due to the dose of opioids.

Mr. Andrea Rogolino, a professional chemist mentioned that “Opioids stimulate regions of our brain responsible for the so-called "reward-seeking" behavior, such as the hippocampus. The biochemical mechanisms are fairly complex, but they essentially all proceed via the transmission of electrical gradients through the channeling of charged molecular species, such as acetylcholine or glutamate,” revealing the link of biochemistry in the risks of opioid usage (Mr. Andrea Rogolino, personal communication, 2024).

2.2 Opioid-induced hyperalgesia (OIH)

All other disadvantages aside, one of the most severe risks associated with the use of opioids is Opioid-induced hyperalgesia (OIH). OIH is defined as increased nociceptive sensitivity due to overwhelming opioid exposure. This condition involves paradoxical reactions where patients on opioids for pain management tend to become more sensitive to certain painful stimuli. The type of pain might mirror the original pain the patients had, or may even differ from it. Numerous observational, cross-sectional, and prospective controlled trials have investigated the manifestation of this risk and clinical importance in humans. Studies were conducted including former opioid addicts on methadone maintenance, perioperative opioid exposure in

surgical patients, and healthy volunteers undergoing acute opioid exposure with experimental pain testing. The exact molecular mechanism of OIH is not fully understood, but previous research has shown progress in understanding the mechanisms further from a scientific perspective (Lee et al., 2011).

Opioid chemistry involves complex interactions within the central nervous system (CNS). One significant aspect is the central glutamatergic system and the activation of N-methyl-D-aspartate (NMDA) receptors as a part of OIH. glutamate is the primary excitatory neurotransmitter in the CNHS, playing a crucial role in OIH. Excessive glutamate activity leads to heightened pain sensitivity, leading to overactivation of NMDA. When these receptors are activated, calcium ions enter neurons, triggering various downstream effects. The influx of calcium ions activates protein kinases and other signaling molecules, increasing neuronal excitability and pain sensitization. Protein Kinase C (PKC) is one of the kinases activated by calcium, a vital component of the process. This further modulates NMDA receptor activity and contributes to maintaining neuronal hyperexcitability (Wilson et al., 2021). Another factor in OIH is spinal dynorphins, where dynorphins are endogenous opioid peptides that typically help modulate pain. However, in OIG, dynorphin levels become unnaturally elevated, where high levels of dynorphins bind to kappa opioid receptors and other receptor sites as well. This paradoxically increases pain sensitivity rather than alleviating it (Podvin et al., 2016).

Furthermore, neuroinflammation is another crucial part of OIH. opioid use may at times activate glial cells, including microglia and astrocytes in the CNS. The resident immune cells of the CNS, microglia, transform into an activated state when chronic opioid exposure is detected. This activation is characterized by changes in the cell morphology, and increased production of factors such as cytokines, chemokines, and other inflammatory molecules. Once activated, these cells release pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines enhance pain signaling by increasing the excitability of nociceptive neurons, promoting further glial activation. The pro-inflammatory cytokines mentioned above increase neuronal excitability and sensitize pain pathways, where they can upregulate the expression of ion channels and receptors involved in pain transmission. These also promote the release of other inflammatory mediators, creating a feedforward loop that

perpetuates neuroinflammation and pain sensitivity (Sampaio-Cunha and Martins, 2022). A visual representation of this stage is seen in the figure below.

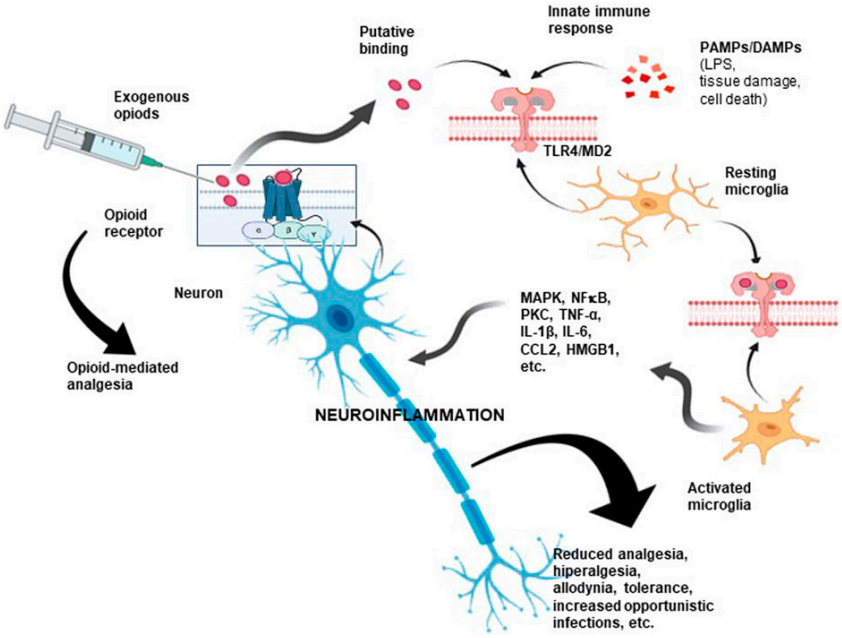

Figure 2: Neuroinflammation in OIH (Echverria-Villalobos et al., 2023)

Overall, the chemical and biological aspects of OIH are multifaceted, involving various mechanisms and processes. Understanding these complex interactions is essential for developing more effective treatments for pain and mitigating the adverse effects associated with opioid therapy.

Section #3: Benefits of Opioids

3.1 Common Benefits

Although opioids are associated with several risk factors, opioid analgesics encompass a series of medicinal products that effectively alleviate pain. By acting on the mu-opioid receptors, a major analgesic receptor widely expressed throughout the nervous system, opioid analgesics act efficiently to treat patients. These opioids vary significantly in chemical structure, methods of administration, absorption, distribution, elimination rates, and affinity for opioid receptors. Some are designed for ultra-short durations of action, making them ideal for balanced anesthesia in surgeries, while on the other hand, others have extended durations of action due to either the opioid's inherent properties or its pharmaceutical formation, which allows a predictable release into the body. The clinical use of opioids is further enhanced by the availability of its dosing methods, including oral, intravenous, transdermal, intranasal, epidural, and intrathecal routes. Opioids have for a while been effective in managing postsurgical and postprocedural pain, proving more effective than placebos for nociceptive and neuropathic pain. It has been reported that opioids can reduce chronic non-cancer pain by about 30%, with 30-50% of carefully selected patients reporting pain relief (Phillips et al., 2017).

Professional chemists also mention that opioids are excellent at mitigating pain because they can strongly and specifically bind to receptors in the human body responsible for the transmission of electric signals to the brain associated with pain. The major benefit is managing pain, it is said that this is especially useful for pains such as anesthesia (Mr. Andrea Rogolino, personal communication, 2024).

3.2 Managing Chronic Pain

Opioids are especially effective in managing chronic pain. Chronic pain is a long-lasting pain that goes beyond the normally expected recovery period or occurs at the same time as an existing chronic health condition. It may be there for a while and then disappear, or it can be continuous for a certain period. It usually starts from an illness or injury with remaining pain, causing the pain to be ongoing for a while (JH Medicine, 2023). The G-protein-coupled receptors (GPCRs) found in the brain, spinal cord, and other regions of the body are associated with

managing this type of pain. Especially, the mu receptors are the primary targets for most opioid drugs and are essential to their analgesic effects. When opioids bind to mu receptors, they inhibit the release of neurotransmitters. This blocks the transmission of pain signals, effectively reducing pain perception. The delta receptors, adding on, also contribute to the effects of the mu receptors, playing a role in both pain relief and the regulation of mood and emotional states (Wang et al., 2017).

The inhibition of neurotransmitter release is the key component to be focused on that highlights the upsides of opioid usage. When opioids bind to their receptors, they trigger an intracellular signaling pathway involving G-proteins, which ultimately inhibit the release of neurotransmitters such as substance P and glutamate, which are both involved in pain transmission (Vaughan et al., 1997). The hyperpolarization of neurons is another crucial point. Activating opioid receptors eventually opens the potassium channels and closes the calcium channels, resulting in an outflow of potassium ions from the neuron and a reduction in calcium influx. This hyperpolarization then decreases the neuron's ability to fire, reducing the transmission of pain signals (Johnson and North, 1992).

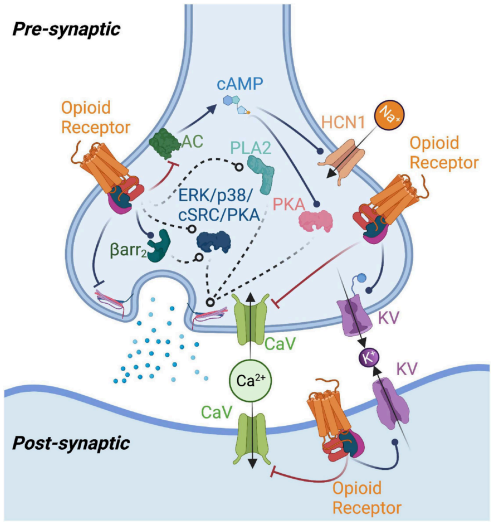

Figure 3: Hyperpolarization caused by Opioids (Reeves et al., 2022)

From a chemical perspective, opioids possess chemical structures that enable them to bind to opioid receptors specifically. Morphine, a naturally occurring opioid, has a chemical

configuration that allows it to bind to mu receptors effectively. Another opioid, codeine, is a prodrug that is metabolized into morphine in the body, eventually exerting its analgesic effects. Synthetic opioids other than natural ones such as fentanyl are designed for high potency, binding strongly to mu receptors. Semi-synthetic opioids, lastly, like oxycodone and hydrocodone are derived from naturally occurring opioids and are further engineered to offer effective pain relief with specific pharmacokinetic properties (Dhaliwal and Gupta, 2023).

In summary, opioids have as many upsides as downsides that benefit the world. Opioids provide potent pain relief through their interaction with opioid receptors and their ability to inhibit pain signal transmission, hyperpolarize neurons, and after pain perception, reducing the pain of patients. Their chemical design supports their effectiveness, allowing them to bind specifically and effectively to receptors, as described by biological evidence. Thus, opioids are indispensable tools in managing pain, especially chronic pain.

Section #4: Evaluation & Conclusion

4.1 Evaluation

As seen in the previous sections, opioid is a group of drugs that may cause both good and bad. On the good side, they are effective in managing pain, particularly chronic pain that occurs after surgery. They work by binding to specific receptors in the brain and spinal cord, blocking pain signals and allowing pain relief. On the contrary, one of the most critical issues at hand is the high potential for addiction, not only when abused for the wrong purpose but also even when taken as prescribed. Addictions led after proper prescription may lead to misuse and dependency, making the patients abuse opioids in the wrong way.

As time passes, the human body develops tolerance, requiring higher doses to achieve the same effect. This means that in the beginning, pain is easily controlled with only small doses of opioids, but in the long run, patients may have to take higher doses to achieve the same effect, further increasing the risk of overdose. Opioid overdose can be fatal, primarily due to respiratory depression. In such ways, a benefit may lead to a risk in the case of opioids.

In the same interview, Mr. Andrea Rogolino mentioned that “the prescription of opioids can be easily avoided for less severe conditions, while it may become necessary for patients under strong physical stress as a result of highly impairing diseases” (Mr. Andrea Rogolino, personal communication, 2024). Accordingly, many scientists suggested that opioids should not be used unless in the case of extreme pain that is highly challenging for patients to tolerate to prevent the risks of opioid addiction and further disadvantages (Dowell et al., 2022).

4.2 Conclusion

Rather than considering opioids as either a risk or benefit factor for treating pain, it is better to come to a conclusion that allows effective use of opioids as well as spreading awareness of the potential risks associated with the use of opioids.

Alternatives to opioids have been put into use often recently. For instance, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or cortisone have been used for decades as

alternatives for opioids. This type of drug decreases the potential risks while maintaining the advantages of opioids, ensuring safety for patients better than opioids do (Dey and Vrooman, 2022). Such as NSAIDs, better options for treating mild pain can be used to decrease the risks of opioid disadvantages. Along with that, finding a proper use of opioids such as in severe pain management will support the medical community to conclude opioids.

The research question "**How do opioids interact with the human body on a chemical and biological level, and what are the associated risks and benefits of their use?**" is therefore answered. The chemistry behind opioids and OIH, as well as the biological mechanisms behind the use of opioids as treatment for pain, was revealed. Despite the existing information given, the scientific scope of opioids should be expanded to delve deeper into the science behind all the causes of the risks. Overcoming or finding solutions to the risks will allow safer use of opioids, allowing patients to become more comfortable with using opioids as a type of medication.

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